In the Laboratory and in Practice: Important Perspectives on Prostate Cancer

The National Cancer Institute estimates that in 2014 there will be more than 233,000 cases of prostate cancer and nearly 30,000 deaths in the United States. Scores of scientists and physicians around the country have made prostate cancer the focus of their laboratory and clinical efforts, seeking to reduce the ambiguities surrounding screening and diagnosis and clarify factors that can influence if and when to intervene.

At NewYork-Presbyterian Hospital, there has been a surge in the number and type of research endeavors in prostate cancer over the past several years, with world-renowned experts at both NewYork-Presbyterian/Columbia University Medical Center and NewYork-Presbyterian/Weill Cornell Medical Center helping to shed light on some of the more challenging decision-making aspects in diagnosing and treating this disease.

Research collaborations among these individuals and their colleagues within the Hospital and around the country — supported by major funding from the National Institutes of Health, the American Cancer Society, Stand Up to Cancer, the Department of Defense, and industry — are succeeding in expediting discoveries in the laboratory to applications in the clinical realm.

First Do No Harm: Getting the Right Patients the Right Treatment

“Prostate cancer is at a bit of a crossroads,” says James M. McKiernan, MD, Chair of the Department of Urology of Columbia University Medical Center and Urologist-in-Chief at NewYork-Presbyterian/Columbia. “It has always been a very controversial condition because there is a massive amount of confusion about how to manage patients diagnosed with the most common cancer in America.”

Much of this confusion centers on the prostate specific antigen (PSA) blood test, considered a great invention when it came on the scene in 1990. “It was the first ever blood test for cancer and it was used widely,” says Dr. McKiernan. “So we saw markedly increased numbers of people diagnosed with prostate cancer. About two years ago, the U.S. Preventive Services Task Force issued a very controversial but important report that recommended against PSA-based screening for prostate cancer, advising that it has ‘very small potential benefit and significant potential harms.’ What remained, because our screening tests are so inaccurate, is no clear official recommendation as to whether a healthy 55-year-old man should get checked for prostate cancer.”

“There are two telling statistics,” says Mitchell C. Benson, MD, Emeritus Chair of the Department of Urology at NewYork-Presbyterian/Columbia. “One is that before PSA screening, the most common presentation was a patient with metastatic disease. Secondly, metastatic disease is now rare and the death rate has been reduced by 40 percent. What we have to do is find ways of continuing to have a death rate reduced by 40 percent while not treating people who don’t need treatment.”

According to Dr. Benson, “There’s no such thing as overdiagnosis; there’s only overtreatment. I think every man, regardless of age, deserves one PSA. If that one PSA places you in a category where the chance of your dying of prostate cancer is low, then you don’t need to have biopsies and additional PSA testing. The rub here is not in the PSA; the rub is in what people do with the data.”

There are essentially three forms of prostate cancer, which Dr. McKiernan depicts as the good, the bad, and the ugly. “The good form of prostate cancer has very little chance of harming the patient...” (continued on page 2)
and does not need to be treated,” says Dr. McKiernan. “The bad form can be treated as long as we find it early enough. And then there are the patients who even when diagnosed early have the ugly, aggressive form of the disease, which is essentially incurable.”

The biggest challenge, he adds, is how to identify which patients belong in which category and then to be able to accurately advise them on what to do. “As clinicians in a tertiary or quaternary care medical center, our job is to be at the forefront of treatment. Patients who come to NewYork-Presbyterian expect the best technology in the world, the best imaging, the newest drugs and surgical techniques, but what they should also expect is someone to tell them if they need all that…or if they don’t.”

What is concerning, adds Dr. McKiernan, “is that because of the ambiguity of PSA, the number of men getting tested is declining and more patients are presenting with aggressive cancer. Eventually the mortality rate for prostate cancer – which has declined every year in the last 20 years – will start to creep up again. To address this depends on having the information to be able to get the right people the right treatment.”

In addition to the PSA assay, the PCA3 is a prostate cancer specific biomarker that is utilized in the assessment of prostate cancer risk as well as to help predict biopsy outcomes in men with elevated PSA. Given the rapidly increasing use of PCA3 in clinical practice, Dr. McKiernan and colleagues at centers across the country sought to examine the natural history and fluctuations of PCA3 scores over time in a variety of clinical scenarios. The study involved nearly 500 patients between 2008 and 2012 who underwent two or more post-prostatic massage urinary PCA3 assays. A PCA greater than or equal to 35 was considered positive.

“We found that similar to PSA, PCA3 values appear to vary over a relatively short period of time,” notes Dr. McKiernan. “More importantly, more than 20 percent of patients converted from positive to negative, or vice versa, on repeat testing. These results suggest that serial PCA3 testing may be valuable for confirmatory and trending purposes, but prospective evaluation of PCA3 values over time is warranted to better define test variability and clinical implications.”

In an ongoing national trial, Dr. McKiernan and his colleagues at Columbia have harnessed the power of modern molecular biology to investigate the utility of exosomal RNA – a non-invasive method of sampling high-integrity genetic material in voided urine. This new technique may provide a non-invasive method to examine known and novel prostate cancer-related gene signatures and potentially yield information regarding underlying disease prior to a prostate needle biopsy.

The researchers prospectively collected voided urine samples without prostatic massage from patients scheduled to undergo prostate biopsy for an elevated PSA. “An EXO106 score that was elevated was considered suspicious based on our predictive models,” says Dr. McKiernan. “We found that urinary exosome-derived mRNA expression of three prostate cancer-related genes can outperform PSA and PCA3 expression as a predictor of harboring prostate cancer on biopsy.”

Based on their results, the researchers believe that this non-invasive diagnostic test holds promise in evaluating which men with an elevated PSA are at highest risk of having a positive biopsy result. If adopted, this may spare patients the discomfort and variability associated with prostatic massage and broaden the role of exosomes in future diagnostic cancer testing, including the differentiation of clinically indolent from aggressive disease.

**Stratifying Risk at the Molecular Level**

For the past decade, Mark A. Rubin, MD, Director of the Institute for Precision Medicine at Weill Cornell Medical College and NewYork-Presbyterian/Weill Cornell Medical Center, has pursued the development of molecular biomarkers capable of distinguishing indolent from aggressive prostate cancer with a goal to improve prognostic ability and risk stratification. His groundbreaking research led to paradigm-shifting work, demonstrating that over 50 percent of prostate cancers harbor recurrent gene fusions involving an androgen driven promoter, TMPRSS2, and an ETS family member transcription factor. These findings have been validated worldwide and invigorated a new line of research trying to establish a molecular classification of prostate cancer. The discovery has important translational implications. These fusions are virtually 100 percent prostate cancer specific and are now being developed into diagnostic and prognostic clinical tests to supplement PSA testing.

Building on their crucial discovery of a fusion gene, Dr. Rubin and his team more recently showed that the presence of the ERG protein in biopsied prostate tissue substantially increases the likelihood that cancer will develop – findings that may help clinicians decide which men with an aberrant biopsy need repeat...
biopsies or other types of monitoring. Their findings, reported in the *Journal of Clinical Oncology*, are the first to quantify, in the setting of a clinical trial, the increased risk of prostate cancer development from ERG.

The investigators found that 53 percent of men whose prostate biopsies showed expression of ERG protein developed invasive prostate cancer, compared to 35 percent of men whose biopsies were ERG-negative. All of the biopsies were classified as having high-grade prostatic intraepithelial neoplasia (HGPIN), which are lesions that may or may not morph into cancer.

“This means that potentially thousands of men a year — those with ERG-positive HGPIN biopsies — may benefit from increased surveillance and early treatment of prostate cancer, while those whose HGPIN biopsies come back ERG-negative may be able to avoid unnecessary future biopsies,” says Dr. Rubin, the study’s senior investigator. “This study is the largest ever conducted that focuses on looking at HGPIN and ERG in a systematic way. We learned that more than half of patients with these biomarkers go on to develop prostate cancer, and that is a significant finding, which we now want to test in a prospective clinical trial. When confirmed in larger studies, testing for ERG in these precancerous lesions may change clinical practice in how men are evaluated with abnormal biopsies and may lead to earlier cancer detection.”

The search for molecular signatures of indolent and aggressive prostate cancers is also taking place in earnest at Columbia by Cory Abate-Shen, PhD, Director of Research in the Department of Urology, Michael M. Shen, PhD, Professor of Medicine, and her research team have provided reason for optimism. In their studies, testing for ERG in these precancerous lesions may change clinical practice in how men are evaluated with abnormal biopsies and may lead to earlier cancer detection.

Genetics and Development and Urology, Dr. Mitchell Benson, and their colleagues in the Herbert Irving Comprehensive Cancer Center. “The problem with existing tests is that we cannot identify the small percentage of slow-growing tumors that will eventually become aggressive and spread beyond the prostate,” says Dr. Benson.

In the past year, results of two major studies by Dr. Abate-Shen and her research team have provided reason for optimism. In their investigations seeking to identify a biomarker for slow-growing prostate cancer, the researchers focused on genes affected by cellular senescence, a natural phenomenon in which older cells cease to divide but remain metabolically active. Cellular senescence is known to play a critical role in tumor suppression and has been associated with benign prostate lesions in mouse models and in humans.

The Columbia team, led by co-senior author Andrea Califano, PhD, Chair of Systems Biology, identified 19 genes that are enriched in a mouse model of prostate cancer in which the cancers are invariably indolent. They then isolated three of these genes — FGFR1, PMP22, and CDKN1A — that together can accurately predict the outcome of seemingly low-risk tumors.

In a blinded retrospective study, the researchers tested the prognostic accuracy of the three-gene panel on initial biopsy specimens from 43 patients who had been monitored for at least 10 years with active surveillance at NewYork-Presbyterian/ Columbia. All the patients had first been diagnosed with low-risk prostate cancer. Of the 43 patients, 14 ultimately developed advanced prostate cancer. All 14 were correctly identified by the test.

“In our preliminary trial, we were able to accurately predict which patients with low-risk prostate cancer would develop advanced prostate cancer and which ones would not,” says Dr. Abate-Shen, the senior author of the study paper, which was published in *Science Translational Medicine*. “Use of this three-gene biomarker, in conjunction with existing cancer-staging tests, could take much of the guesswork out of the diagnostic process and ensure that patients are neither overtreated nor undertreated.”

Columbia urologist Sven Wenske, MD, and his colleagues are now working on a prospective trial of patients with newly diagnosed prostate cancer who may be eligible for active surveillance. “Using these three genes, we are assessing the patients to determine whether or not they are suitable candidates for active surveillance using biopsied tissue that confirms the diagnosis of prostate cancer,” says Dr. Wenske. “What we find should help us better assess the risk for patients entering active surveillance and enable us to counsel them based on more definitive information.”

More recently, the Columbia team revealed that two genes previously implicated in cancer — FOXM1 and CENPF — work together to drive the most lethal forms of prostate cancer. “Individually, neither gene is significant in terms of its contribution to prostate cancer,” says Dr. Califano. “But when both genes are turned on, they work together synergistically to activate pathways associated with the most aggressive form of the disease.”

Ultimately, we expect this finding to allow doctors to identify patients with the most aggressive prostate cancer so that they can get the most effective treatments,” adds Dr. Michael Shen. “Having biomarkers that predict which patients will respond to specific drugs will hopefully provide a more personalized way to treat cancer.”

To find the key genes that drive prostate cancer, the Columbia research team devised a novel computational approach to compare
the gene regulatory networks that drive prostate cancer in humans with those in a genetically engineered mouse model of the disease. “We were able to identify identical driver genes of malignant prostate cancer and to discover that they don’t work as individual drivers but rather together,” notes Dr. Califano. Using one of the world’s largest supercomputers in cancer research, based at Columbia University Medical Center, the analysis identified FOXM1 and CENPF as a synergistic driver pair in aggressive prostate cancer.

The research, which was reported in Cancer Cell, also showed that silencing the two genes inactivated the PI3-kinase and MAP kinase signaling pathways, both of which are known to be hallmarks of aggressive prostate cancers. “This adds additional strength to the possibility that combined therapeutic targeting of both FOXM1 and CENPF may be effective in arresting the human disease,” says Dr. Abate-Shen.

**The Value of Circulating Tumor Cells**

“One of the challenges with patients with prostate cancer, as well as other solid tumors, is that you need tissue to analyze the molecular portrait of the disease,” says David M. Nanus, MD, Chief of Hematology/Oncology at NewYork-Presbyterian/Weill Cornell Medical Center, and Associate Director for Clinical Services, Sandra and Edward Meyer Cancer Center at Weill Cornell Medical College/Ronald P. Stanton Clinical Cancer Program at NewYork-Presbyterian. “Prostate cancer circulating tumor cells [CTCs] are often found in the blood of patients suffering from metastatic prostate cancer, and CTCs have emerged as a viable alternative to the standard invasive tumor biopsy to understand its molecular characteristics and to achieve biological insights of the disease in the individual patient.”

“Lack of tumor tissue for molecular analyses is also a major impediment to understanding drug resistance,” adds Paraskevi Giannakakou, PhD, Director of Laboratory Research, Division of Hematology and Medical Oncology at Weill Cornell. “Circulating tumor cells give us the opportunity to look at the molecular makeup of tumor cells and how they change over time, especially in response to drug treatment.”

Drs. Nanus and Giannakakou, along with Neil H. Bander, MD, Director, Urological Oncology Research, and Scott T. Tagawa, MD, Medical Director, Genitourinary Oncology Research Program, at Weill Cornell, have been collaborating with Brian J. Kirby, PhD, Director of the Micro/Nanofluidics Laboratory at Cornell University, and have developed a microfluidic device that isolates circulating tumor cells based on size and specific antigen presentation. The technique they developed – geometrically enhanced differential immunocapture (GEDI) – is being used in concert with an antibody for prostate-specific membrane antigen for high-efficiency and high-purity capture of prostate CTCs from peripheral whole blood samples of castrate-resistant prostate cancer patients.

“Our ultimate goal is to utilize this micro device to capture and molecularly analyze tumor derived CTCs using a simple, non-invasive blood draw,” says Dr. Giannakakou, whose laboratory has also developed a number of protein assays to interrogate the biological and molecular features of the captured CTCs. “This will enable us to determine the best treatment for each patient based on the molecular make-up of their circulating tumor cells.

“Microtubules are the highly dynamic network of wires within cells and when taxanes are used the network stops moving,” adds Dr. Giannakakou. “However, despite their clinical success, not every patient responds to taxane-based chemotherapy and the development of clinical drug resistance makes patients previously sensitive to chemotherapy, insensitive. A better understanding of the molecular basis of clinical drug resistance to taxanes and other widely used microtubule targeting drugs [MTDs] is imperative in order to prolong patient survival. The therapeutic benefit of taxanes on microtubules depends on more than just stopping cell division.”

Dr. Giannakakou’s laboratory has demonstrated that MTDs – by disrupting the microtubule cytoskeleton – sequester the androgen receptor within the cytoplasm, inhibiting its subsequent transcriptional activation. This provides the rationale for why taxanes represent the sole class of chemotherapy agents that improves survival of metastatic prostate cancer patients.

At the core, this research is providing tools that can help oncologists better treat their patients. “Ideally our molecular analyses will help physicians customize therapy and make more informed decisions about treatment,” says Dr. Giannakakou.

“Through the capture of prostate CTCs, we can study molecular mechanisms of clinical drug resistance, profile individual patients’ PCTCs in order to generate personalized chemotherapeutics, and do real-time monitoring of chemotherapeutic efficacy,” says Dr. Nanus.

**Bringing Discoveries into the Treatment Arena**

Fifteen years ago, Dr. Neil Bander directed his immunotherapy research group to develop antibodies to target prostate cancer. This resulted in the development by his research group of the first series of monoclonal antibodies to prostate-specific membrane antigen (PSMA) that could bind viable prostate cancer cells. In part, as a result of Dr. Bander’s efforts, PSMA has become recognized as the most prostate-cancer specific cell surface antigen known. “Our strategy is to take advantage of monoclonal antibody technology to develop therapies that are very precisely targeted to the tumor cells so that they can be highly efficacious without causing collateral damage,” says Dr. Bander.

According to Dr. Bander, PSMA has several very valuable features that make it a particularly good target. First, he says, PSMA is present in more than 90 percent of prostate cancers. “By way of comparison,” says Dr. Bander, “in breast cancer, the HER2 target is present in only 20 percent of breast cancers. So HER2-directed therapy, while it has been transformational, is relevant for only 1 out of 5 breast cancer patients. Conversely in prostate cancer,
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if we can develop a successful therapeutic agent that targets PSMA, we would expect to have a beneficial effect in about 90 percent of prostate cancer patients. That’s very significant.”

Another important characteristic is PSMA's specificity; for all intents and purposes, the only cells that express PSMA are prostate cancer cells. “Normal cells, which are PSMA-negative, do not bind the therapeutic agent,” he adds. Furthermore, Dr. Bander's lab was the first to show that PSMA functioned as an internalizing cell surface receptor, actively internalizing antibodies that bind to PSMA as well as any payload these antibodies may carry. “The antibody-targeted therapeutic will get swallowed up by the prostate cancer cells but not by their neighboring normal cells. Lastly, because the expression of PSMA is normally suppressed by androgen receptor activity, when you treat a patient with anti-androgen hormonal therapy, it has the fortuitous effect of substantially increasing the expression of PSMA, increasing the cancer’s susceptibility to a PSMA-targeted agent.”

Dr. Bander’s group has led the way in translating these basic research findings to patients, sponsoring over a dozen clinical trials using anti-PSMA antibodies testing the antibody alone, antibody-targeted radioisotopes, and antibody-targeted drugs. These studies demonstrated that the lead antibody, designated “J591,” is capable of virtually flawlessly targeting of tumor sites wherever they are in the body. “This core PSMA antibody-targeting technology is allowing us to develop a variety of diagnostic and therapeutic agents of which ¹⁷⁷lutetium (¹⁷⁷Lu)-labeled anti-PSMA monoclonal antibody J591, or Lu-J591, is the first.”

A Phase II trial of Lu-J591, led by the Weill Cornell team with Dr. Scott Tagawa as principal investigator, was published last year in Clinical Cancer Research. It demonstrated that the majority of patients with metastatic, androgen-independent prostate cancer who took Lu-J591 showed evidence of anti-tumor activity such as a decline in PSA levels and tumor shrinkage of up to 90 percent. In addition, patients lived longer than predicted had they received traditional treatment. “Lu-J591 combines a radioactive agent bound to J591 to target PSMA,” explains Dr. Bander. “The radioactive antibody locates, radiates, and shrinks the cancer. Lu-J591 has now been licensed by a pharmaceutical company, which is conducting an international, randomized Phase II clinical trial this year with the goal of finalizing the dosing schedule, confirming the anti-tumor activity, making the therapy more widely available, and subsequently culminating in a Phase III registration trial.”

Favorable results in patients with metastatic disease has led to the initiation of a large, multicenter, randomized Phase II trial in high risk prostate cancer patients who have rapidly rising PSAs despite prior surgery and hormonal therapy, but who have not yet developed metastatic disease on imaging studies. “While these patients typically go on to develop overt metastatic disease within one to two years, the goal of this trial is to see if treatment with radiolabeled J591 can delay or even prevent the development of metastatic disease and thereby prevent death from prostate cancer,” says Dr. Bander.

Dr. Bander and Dr. Tagawa note that fundamental to the development of this antibody is that it will target all the prostate cancer cells in the body — whether they are in the prostate, the liver, or in the bone — and “you can leverage that technology to develop a wide variety of potential therapeutic and diagnostic agents based on the central ability to target the tumor cell and not the normal cell,” says Dr. Bander.

With collaborators at Memorial Sloan-Kettering Cancer Center and NewYork-Presbyterian/Weill Cornell, they have labeled the antibody with a PET (positron emission tomography) isotope enabling, for the first time, prostate cancer-specific PET imaging. “These studies showed more sensitive and specific prostate cancer imaging compared to conventional modalities, not only of metastatic disease but also of prostate cancer while it was still localized within the prostate,” says Dr. Bander. “This improved imaging offers the potential to improve the accuracy of staging the extent of disease, provide a means to rapidly determine the effect of treatment, and to diagnose the disease. These imaging applications have also been licensed to a company for development. We are leveraging the technology by collaborating with several companies that are each developing therapeutic and/or imaging agents based on our antibody. In doing so, we can catalyze the development of a series of diagnostic and therapeutic agents that offer a variety of benefits to patients at all stages of the disease.”

In addition, prostate cancer investigators at both the Weill Cornell and Columbia campuses of NewYork-Presbyterian continue to collaborate on novel therapeutics for men with advanced prostate cancer. Dr. Tagawa, in collaboration with Weill Cornell and Columbia colleagues, as well as faculty at Cedars-Sinai Medical Center, the University of Wisconsin School of Medicine and Public Health, and Yale Cancer Center, recently completed a Phase I trial evaluating a combination of drugs — docetaxel (Taxotere) and abiraterone acetate (Zytiga) — each approved for metastatic prostate cancer, but that had not previously been studied as a combined treatment strategy. “We felt they may be beneficial used together as they have complementary mechanisms of action,” says Dr. Tagawa. “The results were fairly impressive; the combination was well-tolerated, safe, and more effective than we expected than with either drug alone.”

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Reference Articles


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