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DR. GEORGE WRIGHT RETIRES AFTER 37 YEARS OF SCIENTIFIC EXPLORATION CENTERED TOWARDS DISEASES OF THE PROSTATE

By Paul F. Schellhammer, M.D.

The anticipated shortage of physicians in the 1970's, specifically those involved in primary care, prompted the opening of several new medical schools throughout the country with a major focus on primary care and community service. Some of the schools were established from the ground up and others were grafted on to existing large community hospitals with active teaching and residency services. Eastern Virginia Medical School was one of the latter where a very active community physician base was dedicated to improve the level of care to their community by assembling the regulatory, financial, and personnel support necessary for such an endeavor. With the clinical personnel in place, it was necessary to search for the Basic Science base so necessary for a medical school to provide cutting edge scientific research. Dr. George Wright answered the challenge in 1973 when he joined the newly formed Department of Microbiology and Cell Biology (currently the Department of Microbiology and Molecular Cell Biology). Now enter the challenge: The newly formed community medical school did not enjoy the advantages inherent in an established medical school. There was no name recognition; there were no endowed chairs, and there was none to very little in-house funding to initiate scientific research projects. However, for those whose personalities and vision are so directed, a new school provided a platform to develop novel programs and because of an absence of hierarchy and bureaucracy to bring new ideas more rapidly to fruition. George Wright met the challenge and did all of these things. He came to a new medical school with an energy and vision. He possessed excellent scientific skills, but it was his recognition that interdisciplinary cooperation and the recognition that basic research in isolation fails its true goal of advancing the progress in patient care, that was so unique. And so I was fortunate to arrive two years later from a major medical institution, the Sloan Kettering Memorial Cancer Institute "to a collaboration that equaled any that I had experienced with before and which has endured for 28 years. Our long and successful partnership resulted in many exciting and successful research programs, eventually leading to the founding of the Center of Urologic Oncology in 1993 (what is now the Virginia Prostate Center)". The Center

continues to provide highly successful state-of-the-art basic, clinical and translational research; educational programs; and clinical care of prostate and other urological diseases to the citizens of Hampton Roads. The Center's highly successful proteomic research program is attributed to the vision and leadership of Dr. Wright.

As Chairman of the Department of Microbiology and Molecular Cell Biology, Dr. Wright established a strong and highly productive basic science department. Under his leadership (1986-2004) the department's faculty has established a strong national presence in cancer research, and has obtained the most National Institutes of Health (NIH) grants of any EVMS basic science department during his tenure. Dr. Wright has always practiced what he preached, receiving continued NIH funding each year since he accepted his first position at George Washington University in 1966. Continued NIH funding, considered the premier scientific research funding source, for more than 37 years, is a feat obtained only by a very few, elite scientists. His last National Cancer Institute (NCI) grant may have been his most gratifying because NCI had finally recognized that in order to improve methods for early detection of cancer, it would be necessary to identify patterns of genetic alterations in cancer cells, and not to focus on single events; something Dr. Wright had been preaching for years. This three million dollar grant made it possible for Dr. Wright and his scientific team to explore novel approaches to identify the signature "fingerprints" that accurately could distinguish cancer patients from healthy individuals. The application of proteomic mass spectral technology by EVMS scientists, led by Dr. Wright, has opened up a very promising and exciting new approach for the early detection and diagnosis of prostate and other cancers. (Details of this research have been reported in previous Newsletters [Winter 1999 and Winter 2001]; also see Dr. Semmes this issue, page 3.)

After 30 years at EVMS, Dr. Wright decided to retire to pursue other interests, including spending more time with his wife Yolonda and family, "who gave up much so that I could pursue my career", said Dr. Wright. He plans to spend more time at their farm in Appomattox and with his woodworking and painting hobbies. "Most importantly will be having more quality time to spend with our two



Dr. George Wright

children, Julie and Chris, and their families, especially our three grandchildren Megan, Jackson, and Austin, and with my 97-year-old Dad, a retired dentist", said Dr. Wright. But before he could feel comfortable about retiring, he needed to find a quality scientist who could continue the internationally recognized cancer program he started. With good fortune and funds from the Beazley Foundation, Dr. Wright successfully recruited Dr. O. John Semmes, a Cancer Molecular Biologist from the University of Virginia. (See Summer 2001 issue). Dr. Semmes has assumed the leadership of the NCI Early Detection Research Network Grant, the prostate cancer program, and the role of Scientific Director of the VPC (all roles previously held by Dr. Wright). "Dr. Semmes is an outstanding and remarkable cancer scientist who has in just three short years made major advancements in our effort to develop better tools for early detection of cancer", said Dr. Wright. "We got a winner when we recruited Dr. Semmes. I have no doubt that he will take our cancer proteomic program to new and exciting levels". (See Semmes, this issue). Dr. Wright will continue to advise and consult as his experience, collaborative interactions, reputation and recognition on an international scale, makes him an invaluable resource to the department, the medical school, the Virginia Prostate Center, and most critically, patients who look towards science and healthcare to ease the burden of cancer.

We thank Dr. Wright for his many contributions and wish him and family much happiness and good health in the retirement years ahead. ■

VALIDATION OF A PROMISING NOVEL DIAGNOSTIC TEST

By O. John Semmes, Ph.D.

The numbers of individuals affected by cancer continues to rise as our life expectancy increases. In fact, the incidence for both prostate and breast cancer continue to climb with each successive year of life, making these the most common cancers affecting men and women and the second leading cause of cancer death. Over the past 20 years intensive efforts in discovery aimed at end-point therapeutics has been largely unsuccessful. Indeed the concept of a single genetic "correction" has lost favor in place of the accepted multi-genetic and multi-factorial component of cancer. As our understanding of disease development matures it is likely that new treatment options will emerge. However, given current technology, detecting many cancers earlier would result in an immediate realizable improvement in mortality and quality of life. This benefit from early detection would be expected to continue even as new therapies are developed. The detection of operable cancers earlier, the identification of indolent cancer for wait and see and the avoidance of unnecessary biopsies are all promises of better molecular-based early detection efforts. Recognizing this critical medical situation, NCI established the multi-institutional EDRN in 1999, to focus on identifying biomarkers to improve the early detection of cancer. Detection of early cancer has been identified as an area of extraordinary opportunity for research investment in the NCI 2004 bypass budget. Indeed the application of novel emerging technologies, such as those that would arise from the studies conducted by the Virginia Prostate Center, to the field of early detection is a high priority in the NCI's strategic plan for reducing mortality from cancer.

Proteomic techniques aimed at biomarker discovery have been centered on identification of differentially expressed proteins following gel or liquid chromatographic separation. The candidate biomarker is then evaluated by immunoassay for population-wide sensitivity and specificity for early detection. This two step approach has proven to be effective and has been greatly enhanced by the sequencing of the human genome and concomitant improvements in mass spectroscopy. However, a significant number of the biomarkers initially identified using this approach will fail in the population studies. Two-dimensional gel analysis has been the proteomic tool of choice, with systems now routinely analyzing 10s of gels simultaneously. However, in addition to the need for high-throughput, there is a tremendous need for improved ability to "mine" the full depth of the proteome.

Methodology that can accommodate higher-throughput with the ability to observe high volume of protein events are needed to advance clinical proteomics. Currently, many systems that couple robotic handling of samples in the front-end to a mass spectrometer are being evaluated for clinical utility. In terms of discriminating accuracy, the most successful of these has been a modification termed Surface Enhanced Laser Desorption/Ionization-TOF (SELDI). The advantages of these systems are that they can serve as powerful discovery tools leading to protein identification, but they also can develop protein expression profiles or patterns that can be used to distinguish one group from another, i.e. cancer vs. non-cancer. Our group was the first to introduce and pioneer the concept of using the SELDI as a diagnostic tool for cancer detection based on protein expression profiling (previously reported in detail in the Fall 2002 VPC Newsletter). Using this approach, we have been able to achieve 80-95% accuracy in distinguishing cancer from non-cancer individuals for prostate, breast, head and neck, and several other cancers. Even with these exciting results, the full potential and application of protein profiling as an early detection diagnostic tool is still in its infancy. The next major step in the maturation of this conceptual approach, before its full clinical potential, can be realized, is to determine if other institutions and laboratory can obtain the same results.

The NCI-EDRN recently awarded \$1.6 million to the VPC to conduct a multi-institutional collaboration, directed by Dr. O. John Semmes (VPC Scientific Director), to validate the utility of SELDI for the early detection/diagnosis of prostate cancer. The VPC Biomarker Development Laboratory will also serve as the center for the evaluation of all SELDI profiling conducted by EDRN investigators. Many of you will recall that the seminal proof-of-principal study that SELDI-TOF-MS combined with a decision algorithm achieved accurate discrimination of prostate cancer was conceived and led by George L. Wright, Jr. (See Newsletter Summer 2001). The validation study will be conducted in three Phases. Phase I will examine the reproducibility and portability of the SELDI assay platform. Phase II will provide a validation of the ability of SELDI to detect cancer in samples from many clinical centers including John Hopkins University, University of Alabama, University of Pittsburgh Cancer Center, Walter Reed and UTHSSA. The final Phase III will demonstrate the ability of SELDI to detect cancer earlier and assess the

performance with respect to PSA. As of this date we have successfully passed all criteria for Phase I. Phase II will begin in early May of this year and is predicted to take eight (8) months. The final Phase III is designed to be accomplished in the following year.

Despite our promising initial studies, there is a great deal of confusion and controversy as to whether or not the use of high throughput proteomic techniques such as SELDI can improve the early detection of prostate cancer. Also issues as to whether or not SELDI detects equally well both high grade (Gleason score ≥ 7) and low grade (Gleason score ≤ 6) cancers of the prostate remain to be determined. Similarly, a very important comparison will be the use of SELDI in the early detection of prostate cancer compared to the use of modifications of the assays for PSA.

It is the goal of this collaborative validation project - EDRN-Prostate-SELDI Investigational Collaboration (EPSIC) - to use state-of-the-art protein profiling technology to develop and validate high throughput screening methods for the early detection of prostate cancer. A successful validation study of SELDI protein profiling would demonstrate that the same diagnostic protein peaks identified previously by the VPC-EVMS group can be detected by other investigators as being important in separating prostate cancer from non-cancer individuals. We will provide updates as each step of this rigorous validation process is completed. ■

PSA ANXIETY

(Part I)

By Dr. Paul Schellhammer

PSA, the acronym for prostate specific antigen, is a test familiar to many men whose acquaintance with it has been an emotionally charged experience. That's because PSA is a marker of prostate cancer. In fact it is the best cancer marker available in today's practice of medicine. Since half of all American men over 60 and more than three-quarters of those over 80 harbor some cancer cells in their prostate gland, it's easy to understand the impact PSA may have.

But, as important as it is as a tumor marker in the detection and treatment assessment of prostate cancer, PSA reading can create problems if not kept in perspective. First, the PSA level does not reflect all the factors which affect the course of prostate cancer.

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PSA ANXIETY

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Furthermore the PSA number is a constant reminder of disease status that can work on the minds of prostate cancer patients. Men who have low PSA's after treatment and high hopes for a cure can crash psychologically when the number begins to increase because a PSA rise points to recurrence of disease. Those with high PSA levels, although they feel physically well, must endure the dark clouds and distress generated by the threat of progressing cancer.

Simply stated, prostate cancer patients tend to evaluate their quality of life, even life expectancy, on the PSA number. It tends to become a Holy – or Satanic – Grail rather than just one component of the diagnosis and evaluation of treatment of prostate cancer.

Over the years, I have learned that most patients tend to place great importance on their PSA levels. When I visit such a patient, introducing myself with "How are you?" the inevitable rejoinder was "How's my PSA?" If I was able to provide a good number – zero or low and stable – there was an obvious sigh of relief. If the number was not what would be considered a safe range, extensive reassurance and explanation became necessary. It was clear that the patient's attitude and assessment of his treatment was overwhelmingly influenced by his PSA number. I did not truly realize how much this was the case until PSA numbers became part of my life.

Some background information about PSA is in order. PSA is used to identify men at risk for prostate cancer; after diagnosis and treatment it is used to identify the success or failure of the treatment applied. I believe strongly that the routine assessment of PSA during periodic health checks called PSA screening, will identify cases of prostate cancer earlier so that treatment can decrease prostate cancer mortality. This opinion is not yet supported by the necessary clinical studies, however. (Such investigations are currently underway in both Europe and America.) Despite this opinion that I hold that PSA screening is beneficial, I also recognize that many patients will receive the diagnosis of prostate cancer and be treated in order to rescue only some from death from disease. Indeed, treatment is not necessary for certain patients, specifically those who harbor a slowly growing tumor that will not cause problems for the remainder of their lifespan. This may seem counterintuitive, but prostate cancer is a disease of many stripes akin to a barnyard analogy of turtles (slow moving) and birds (fast flying) and other animals in between.

There's a saying that many men don't die of prostate cancer, they die with it. In other words, it's quite possible for cases of prostate cancer to be so slow in developing that patients live to advanced years before succumbing to other diseases. When urologists are sure that a patient has this type of problem they can adopt the 'if it ain't broke, don't fix it' approach. The problem, of course, is to determine if a case of prostate cancer really is of the slow-growing type. Is it really a "turtle", or is it more "birdlike"?

Research efforts are currently directed towards identifying with greater certainty those patients whose cancer may behave like a bird and for whom treatment and cure is necessary because of the aggressive nature of their disease. In our laboratory, we are analyzing serum and tissue from men with and without prostate cancer to measure the protein constitution of each. The science and methodology is termed Proteomics and has been discussed in prior newsletters. It is hoped that these characteristic protein signatures or profiles will be able to separate turtles and birds, and other animals, and also provide added value to PSA in the diagnostic process.

In the meantime, we work with the tools at hand, prominent among them that PSA reading. The most common treatment for PSA diagnosed cancers, is surgery or radiation therapy. Physicians directing treatment will tell the patient and his family that the measure of success of his treatment will be determined by examination, but especially the quarterly, semiannual, or annual PSA level. The desired objectives would be an undetectable PSA in the case of surgery and very low, stable PSA if radiation therapy is employed.

After surgery, which removes the entire prostate, it is anticipated that the PSA level will become undetectable. If this occurs the patient is, of course, overjoyed, and the physician will reinforce the patient's sense of pleasure and satisfaction especially against the background of disruptive changes in urinary and sexual function that the patient is likely to experience immediately after surgery. The bottom line is that his zero PSA is a significant reward for his pain, discomfort and dysfunction. Buttressed by a zero PSA, the postoperative patient's physical and mental forces become concentrated in recovering, healing, and recuperating. These are energy-consuming processes and the patient can still be considered under treatment. Being under treatment is actually quite comforting; a patient draws strength from and finds security in the

support provided by his physician and medical staff. When recovery nears completion and the discomfort and dysfunction begin to resolve, the 'under treatment' umbrella is removed which, in many patients, triggers a sense of insecurity. The patient is no longer moored closely to the pier of active therapy but finds himself adrift in a sea of some uncertainty. His only anchors are his visit to his surgeon and, more critically, a periodic PSA reading – and he awaits that PSA number with a great deal of apprehension.

Patients who undergo radiation therapy rather than surgery face a different problem with respect to their PSA readings. Successful therapy will ultimately lower the PSA to undetectable or only slightly detectable levels. Unfortunately, the fall to low numbers may take several years and, to make matters worse, the decline will not be in a straight line. It will have a sawtooth pattern, up one time, down another. Understandably, this will produce anxiety in the patient. He will worry that the decline in his PSA is too slow, or if it seems to be rising, that he needs more treatment, and so on. A physician has to exercise great patience and provide adequate counseling to allay those fears.

Studies have shown that most prostate cancer patients indicate they do not mind being otherwise sick as long as their PSA readings are good. In other words, their PSA number has become more important to them than their quality of life. This should not be the case. Physicians recognize that a rise in the PSA level, though it likely indicates disease activity, does not necessarily mean that immediate treatment is necessary. It may take months, even years, for the disease to cause symptoms, and indeed symptoms or problems may never appear! This is a difficult situation with which most prostate cancer patients feel uncomfortable, and understandably so. While we all face a ticking clock and know in the back of our minds that someday death will arrive, a rising PSA is a forceful reminder that the clock is ticking – and why it's ticking. This is disturbing and unsettling. Almost everyone has had the experience of being sick and then recovering. But this is not the same as facing a rising PSA. The increasing number places a known impediment to the quality and perceived duration of life. The clock is no longer remote. The enemy has entered the gates and there is an overwhelming desire to do something to block the PSA rise, and thrust the enemy aside. ■



VIRGINIA PROSTATE CENTER
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THE VIRGINIA PROSTATE CENTER

A Unique Collaboration of Scientists and Clinicians

The Virginia Prostate Center, a program of EVMS, was established in 1992. The idea for the Center was conceived by Dr. George L. Wright, Jr., a researcher and tumor immunologist; Dr. Paul F. Schellhammer, a urologic oncologist; and Dr. Anas M. El-Mahdi, a radiation oncologist. Although the Center is a relatively recent development, the groundwork for it was established in 1974 when the three men began a collaboration to evaluate better ways of treating prostate cancer and other urologic diseases. In 1993 the trio was joined by Dr. Donald F. Lynch, Jr. and in 1998 by Dr. Robert Given. Both have done specialized training in urologic oncology.

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