Highlights from the American Cancer Society’s 41st Science Writers Seminar

ACS Behavioral Research Group

Asking the fundamental question, “Can we alter our behavior to minimize cancer risk?” Charles J. McDonald, MD, President of the American Cancer Society, opened the 41st Science Writers Seminar, describing what he characterized as “one of the most innovative, and certainly the largest, studies ever performed on cancer survivors.”

He explained that although the Society’s extramural research funding activities are well known, in-house efforts have expanded over the past three years to include a behavioral component.

A Massive Project

Dr. McDonald, Professor of Medical Science and Chair of the Department of Dermatology at Brown University in Providence, RI, said that the Society’s Behavioral Research Group has designed a novel study to follow some 130,000 cancer survivors over the next 10 years to “identify the unique needs of cancer survivors” and to define and rank (in order of importance) those variables that constitute or contribute to quality of life.

Additionally, these researchers, led by Frank Baker, PhD, Director of the Behavioral Research Center, will be establishing a data base for evaluating Society programs for survivors. A final component of the study, Dr. McDonald explained, will focus on the late effects of cancer and cancer treatment, including second cancers.

Newly Diagnosed Patients with 10 Common Cancers

The first part of the ACS study will longitudinally follow newly diagnosed patients with 10 common cancers: Prostate, breast, lung, colorectal, urinary bladder, uterine, kidney, and ovarian cancers, and non-Hodgkin’s lymphoma and cutaneous melanoma. The second part will use in-depth interviews of a cross-section of long-term cancer survivors to characterize chronic effects and outcomes, as well as to elicit unmet needs.

Dr. McDonald reported that preliminary results from a pilot study indicate, for example, that 71% of 350 patients felt that fatigue was a significant problem for them after cancer treatment (see also “Resolving the Frustration of Fatigue,” on page 178 of this issue).

Twenty state cancer registries, which will contact primary care physicians to identify appropriate patient-candidates, have been approached thus far about participating in the ACS study. Four states, Iowa, Minnesota, New Jersey, and Utah, currently have contracts with the ACS to refer eligible subjects.
Remarking on the significance of behavioral research, Dr. McDonald pointed out that while basic science may succeed in revealing how to minimize cancer risk, such information is not automatically heeded. “We don’t always put into practice what we know is right,” he concluded.

Early Detection
Noting that the seven well-known early warning signs of cancer developed by the ACS decades ago actually detect mostly fairly advanced disease, Harmon J. Eyre, MD, the Society’s Executive Vice President for Research and Medical Affairs, chaired a session that included several presentations on promising research directed to earlier detection of disease. “People want simple tests to detect cancer. Molecular techniques offer that,” he said.

Ovarian Cancer
Investigators at the Cleveland Clinic Foundation, led by Yan Xu, PhD, of the Departments of Cancer Biology and Obstetrics and Gynecology, have identified a growth factor in the abdominal fluid produced by ovarian tumors that may be useful in early detection of ovarian cancer. Called “ovarian cancer activating factor,” lysophosphatidic acid (LPA) is a lipid normally produced in certain hematopoietic cells and is found in serum.

In preliminary studies conducted at the Cleveland Clinic, Dr. Xu and coworkers noted that 48 patients with ovarian cancer had much higher plasma LPA levels than did a comparable group of healthy women (p<0.0001). About 90% of patients with stage 1 ovarian cancer, and 100% of those with stages II, III, IV and recurrent cancers had elevated LPA levels (>1.3µM), whereas levels in healthy women were low or even undetectable—only five of 48 women without cancer had elevated LPA levels.

Observing that although LPA measurement seems to be much more sensitive than CA-125—which, Dr. Xu noted, tends to be associated with later stages of disease and is not ovarian-cancer specific—several issues need to be worked out before the marker might be ready for the clinic. An enzyme-based assay has recently been developed, she reported, as a necessary first step toward eventual commercialization of the test as a diagnostic.

Melanoma
Reviewing the drawbacks of imaging studies for monitoring recurrences in melanoma patients—namely, the inability of such techniques to detect micrometastases—Rishab Gupta, PhD, Head of the Division of Tumor Markers and Immunodiagnosis at the John Wayne Cancer Institute at Saint John’s Health Center in Santa Monica, CA, reported the development of an enzyme-linked immunosorbent assay (ELISA) to detect the presence of TA-90—a melanoma tumor antigen—as an immune complex of the antigen bound to anti-TA 90 antibody.

“We recently found that our TA-90 ELISA could identify patients whose primary cutaneous melanoma had started to metastasize to nearby lymph nodes or distant sites,” Dr. Gupta said. “Of 57 such patients whose melanoma had metastasized without clinical signs, 43 had a positive TA-90 assay.”

A patient’s TA-90 status also seemed to be a useful prognostic tool. “We found that the rate of five-year overall survival following surgical removal of a melanoma on the skin was only 63% for patients with a positive TA-90, compared with 88% for patients with a negative TA-90,” Dr. Gupta reported.

Only 2% to 3% of individuals without melanoma test positive for TA-90, he said. The ELISA has been reported to have a sensitivity of 77% and a specificity
of 76% for subclinical melanoma. “TA-90 is the first tumor marker that accurately predicts metastatic disease and survival for patients with early-stage melanoma,” Dr. Gupta said.

**BLADDER CANCER**

Utilizing the abnormal cellular and nuclear shapes of cancer cells compared with normal cells as a starting point, Robert H. Getzenberg, PhD, Director of Research at the Prostate and Urologic Cancer Center of the University of Pittsburgh Cancer Institute, and colleagues have identified several components of the nuclear matrix, one of which is called BLCA-4, that differentiate human bladder tumor cells from normal bladder cells.

Anti-BLCA-4 antibodies were generated and were found to be able to detect BLCA-4 in the bladders of individuals with bladder cancer but not in those without the disease. Normal samples from unaffected individuals did not react with the antibody, Dr. Getzenberg reported, whereas, “we have found positive BLCA-4-staining in 100% of the ‘normal’ tissues from bladders of patients with cancer.”

Importantly, BLCA-4 appears to be successfully detected BLCA-4 in all but two of 35 patients with histologically proven bladder cancer.

The BLCA-4-urine immunoassay has a specificity of 100% and a sensitivity of 95%. According to Dr. Getzenberg, “BLCA-4 appears to be the first bladder cancer specific marker to be able to distinguish, absolutely, patients with bladder cancer from those without the disease.” The assay is currently being tested by the Pittsburgh researchers in a clinical trial of individuals at high risk for bladder cancer.

**Improving Specificity of Prostate-Specific Antigen**

Observing that while detection and incidence of prostate cancer appear to have peaked in the 1990s with the availability of prostate-specific antigen (PSA) testing, Isaiah Fidler, DVM, PhD, Professor and Chair of the Department of Cancer Biology and R.E. “Bob” Smith Distinguished Chair in Cell Biology at the University of Texas M.D. Anderson Cancer Center in Houston, and chair of a session on prostate cancer, noted that mortality from the disease has not changed.
In an effort to improve the specificity of PSA measurement, as well as to simplify calculation and interpretation of the free-to-total PSA ratio, a new specific immunoassay, the “complexed PSA” was recently developed and approved for monitoring patients with established prostate cancer.

Michael K. Brawer, MD, Director of the Northwest Prostate Institute at Northwest Hospital in Seattle, noted that measurement of complexed PSA “provides quantitation of the alpha1-antichymotrypsin complex bound to PSA (cPSA) with one convenient assay.”

Using a standard total PSA cut-off point of 4.0 ng/ml results in more false positive results, Dr. Brawer said, than does the complexed PSA, which has a cut-off point of 3.75 ng/ml. Using the new assay, his team measured cPSA in 300 men, 75 of whom had prostate cancer. “Complexed PSA avoided about 25% of false positive PSA results, but did not miss any cancers,” he reported.

Reducing the rate of false positive results with complexed PSA, Dr. Brawer observed, would decrease the number of unnecessary biopsies performed to rule out malignancy.

First Differentiation Agent for Liposarcoma

Calling cancer cells “too stupid to die,” George D. Demetri, MD, Director of the Center for Sarcoma and Bone Oncology, and Attending Physician at the Dana-Farber Cancer Institute in Boston, reported that the FDA-approved diabetes drug troglitazone appears to induce differentiation and a more normal phenotype in patients with liposarcoma.

Based on laboratory research identifying a key regulatory molecule—peroxisome proliferator activated receptor-gamma (PPAR-γ)—that controls the process of differentiation in normal fat cells, Dr. Demetri, who is also an Assistant Professor of Medicine at Harvard Medical School, and colleagues made what he characterized as a “serendipitous transition from preclinical observations to clinical discovery,” when they found that troglitazone could be used to activate the PPAR-γ receptor in patients with liposarcoma, essentially reducing proliferation and inducing a more mature type of fatty cell.

As troglitazone is already an approved drug, sufficient safety data exist to warrant proceeding directly to phase II clinical studies. Despite the fact that higher oral doses of troglitazone (800 mg per day) are used in the liposarcoma patients than in the diabetes setting, Dr. Demetri observed, “Compared with what we usually use in cancer patients, any potential hepatic toxicity is minor.”