# RESEARCH HIGHLIGHTS

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**Associate Editor**

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### Basic Research

### Ovarian Cancer Cell Proteins May Be Useful for Early Detection

Ovarian cancer, the most lethal of the gynecologic cancers, often remains undetected until it is in later stages. Proteomic technologies offer the possibility of developing an early-detection diagnostic assay. Researchers from the School of Medicine at Tufts University in Boston, MA, the National Cancer Institute in Bethesda, MD, and Northwestern University Medical School in Chicago, IL, presented the results of a study examining the serum from patients with ovarian cancer (n = 115) and unaffected women (n = 127). Mass spectrometry and Western blotting were used to identify low–molecular-mass proteins that bound to the carrier protein, albumin. An iterative searching algorithm was used to identify a proteomic pattern that discriminated between cancer and noncancer serum samples. The cluster pattern that emerged was 100% sensitive and 100% specific. Novel biomarkers were identified from the clusters. The researchers concluded that albumin is a significant source of diagnostic information. Their work suggests that science may be able to identify diagnostic markers useful for detecting early-stage ovarian cancer in women at high risk and in the general population.

### Progesterone Receptor Antagonists Prevent Carcinogen-Induced Breast Cancer in Rats

Researchers from Schering AG Corporate Research in Berlin, Germany, presented the pharmacologic characterization of a novel progesterone receptor antagonist. Progesterone is known to contribute to the proliferation of mammary tumors. The progesterone receptor antagonist demonstrated antiprogestagenic and antiproliferative activity in animal models. In human breast cancer models, the antagonist suppressed the growth of established tumors. In rats, the progesterone receptor antagonist prevented tumor growth that normally occurs in response to treatment with nitroso-methylurea and dimethyl-benzathracene. The researchers concluded that the biologic response to the antagonist does not result solely from its antiprogesterone effects. The compounds appear to be able to induce tumor cell differentiation that leads to apoptosis, suggesting a unique mechanism of action.

### High Levels of Cancer-Causing Agent Are Present in the Amniotic Fluid of Female Smokers

Researchers from the University of Louisville in Kentucky measured levels of polycyclic aromatic hydrocarbons (PAHs) in amniotic fluid from female smokers who smoked half a pack per day to more than two packs per day and nonsmokers between the 16th and 20th weeks of pregnancy. Previous work by these scientists examining serum had shown a clear correlation between maternal smoking and fetal exposure to smoke PAH carcinogens, including 4-aminobiphenyl and benzo(a)pyrene. PAHs were found in nearly all of the amniotic fluids examined. Maternal smoking levels correlated with the amount of PAHs in the amniotic fluid. For example, 1-hydroxypyrene levels ranged from 1.54 +/– 0.12 micrograms/l in nonsmokers to 11.72 +/– 0.67 micrograms/l in women who smoked more than two packs per day. This tenfold increase in PAHs also was found for hydroxylated benzo(a)pyrene derivatives, which ranged from 1.41 +/– 0.13 micrograms/l for nonsmokers to 11.56 +/– 0.59 micrograms/l for women who smoked more than two packs per day. The researchers suggest that these harmful environmental carcinogens during early gestation may place the fetus at risk for genotoxic and teratogenic events.

### Pentobarbital Inhibits Colon Cancer Cell Metastasis in Mouse Model

Nembutal® (pentobarbital, Abbott Laboratories, Abbott Park, IL) acts on gamma-aminobutyric acid (GABA) receptors to suppress the central nervous system. GABA receptors also are present in colon and ovarian cancer cells. Researchers at the University of Texas M.D. Anderson Cancer Center in Houston investigated the ability of Nembutal to suppress cancer cell growth and metastasis using a mouse model. They examined several colon cancer (KM12SM, HT29, RKO) and ovarian cancer (SKOV3ipl, HeyA8, OVCAR3, 222) cell lines for the expression of GABA receptors using Western blots. The receptors were present on all colon cancer cells lines and most ovarian cancer cell lines. Cytotoxicity assays measuring cellular respiration demonstrated that continuous exposure to 50 micrograms/ml of Nembutal for 96 hours reduced cell proliferation by 50%. KM12SM cells were injected into the cecum or spleen of nude mice, and tumor growth and metastasis were measured. In these experiments, mice were anesthetized with either methoxyflurane by inhalation or Nembutal by intraperitoneal injection (50 micrograms/ml). Primary tumors developed in the cecums of 9 of 10 mice anesthetized with methoxyflurane compared to 7 of 10 mice anesthetized with Nembutal. The mean weights of the tumors were 1.08 g +/– 0.19 and 0.38 g +/– 0.13 (p = 0.04) for the methoxyflurane and Nembutal groups, respectively. Primary tumors developed in the spleens of 8 of 10 mice in the methoxyflurane group compared to 4 of 10 mice in the Nembutal group. The mean weights of the tumors were 2.08 g +/– 0.73 and 0.53 g +/– 0.39 (p = 0.048) for the methoxyflurane and Nembutal groups, respectively. In the mice that had splenic injections, liver metastasis occurred in 80% of the methoxyflurane group and 20% of the Nembutal group (p = 0.007). The researchers concluded that this is the first evidence that Nembutal is an inhibitor of colon cancer and that this result may have important therapeutic applications.

### Erythropoietin Improves Learning and Memory Outcomes After Whole Brain Irradiation in Mouse Model

Erythropoietin is a renal hormone known to be important in red blood cell production. Erythropoietin also is known to enter the central nervous system when administered systemically. Researchers from Sunnybrook and Women's College Health Sciences Centre in Toronto, Canada, presented the results of a study of the neuroprotective effects of erythropoietin in a mouse model. Experimental dose groups of 10 mice were established. Animals received 0, 2, 8, 17, or 22 Gy of whole brain irradiation. Erythropoietin doses of 1,000, 5,000, or 10,000 units/kg were given intraperitoneally one hour following radiation. Open field, hole-board,

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and dark/bright field tests were used to assess behavioral function at 3, 7, and 10 days following irradiation and at one, two, and four months. Learning and memory function using an eight-arm radial maze were assessed at two and four months. Irradiation with 22 Gy caused nearly 100% lethality. Doses of 17 Gy or less caused no significant weight loss or lethality at four months. At two and four months following 17 Gy irradiation, learning and memory were impaired significantly. However, if the irradiated animals were given 5,000 units/kg of erythropoietin, no significant impairment resulted in any of the behavioral or learning tests. The higher doses of erythropoietin did not result in neuroprotection. When erythropoietin was given in the absence of radiation, it had no effect on memory and learning. The researchers concluded that erythropoietin, when administered systemically, may protect against learning and memory impairment after whole brain irradiation. Studies are continuing in an effort to try to understand the molecular mechanisms underlying the neuroprotective effects of erythropoietin.

### New Approach to Kill Cancer Cells Uses Vascular Endothelial Growth Factor-Triggered Cell Death Receptor

The normal process by which cells reproduce and die is opposed in the growth of cancer. Tumors stimulate new blood vessel growth to acquire oxygen and nutrients, a process called tumor angiogenesis, by secreting vascular endothelial growth factor (VEGF), an angiogenic growth factor. VEGF normally works by attaching to the extracellular region of VEGF receptor 2, which activates the intracellular region of the receptor to send growth signals. Researchers from the University of California, San Francisco, presented a novel treatment approach using the tumor's own weapon against itself by forcing VEGF to act as a cell death factor instead of a growth factor. The research team created an artificial VEGF receptor, called R2Fas, in which the intracellular region of VEGF receptor 2 was replaced with a part of the Fas death receptor, which can trigger a process of cellular suicide termed apoptosis. Blood vessel cells in culture normally grow when exposed to VEGF. When the R2Fas receptor was expressed in blood vessel cells, the cells instead were killed rapidly by VEGF, showing that VEGF acted as a death factor instead of a growth factor. When the R2Fas receptor was expressed in cancer cells in culture that overexpress VEGF, the R2Fas receptor caused the cells to die by apoptosis. The researchers concluded that the ability of the R2Fas receptor to switch the function of VEGF from a growth factor to a death factor might allow a new approach to antiangiogenesis by simultaneously targeting the VEGF-producing cancer cells and the tumor blood vessels.

## Clinical Research

### Intake of Vitamin E May Protect Against Bladder Cancer

A dual study has shown that consuming vitamin E lowers the risk of bladder cancer. The results of a case-control study were presented by researchers from the University of Texas M.D. Anderson Cancer Center in collaboration with a research team at Texas Woman's University, both in Houston. The findings of this study showed that consuming vitamin E (alpha-tocopherol) lowers the risk of bladder cancer. In this study, the researchers evaluated the association between intake of vitamin E from dietary sources only, from diet and supplements combined, and from dietary gamma-tocopherol. Personal interviews were conducted with 468 patients with bladder cancer and 534 healthy, cancer-free controls using a modified version of the National Cancer Institute's Health Habits History Questionnaire. The questionnaire was modified to incorporate supplement use and ethnic dishes commonly consumed in the Houston area. A database with values assigned to the tocopherol content of foods was developed. It was based on published values and values for certain foods determined specifically for the study. The researchers found that almonds, spinach, mustard greens, sunflower seeds, and green and red peppers were excellent sources of alpha-tocopherol. However, gamma-tocopherol is the most common tocopherol in U.S. diets. This case-control study showed that the gamma-tocopherol form of vitamin E had no protective effect against bladder cancer. The researchers concluded that high intake of vitamin E from dietary sources alone was associated with a 42% reduced risk of bladder cancer, whereas high intake of vitamin E from dietary sources and supplements combined reduced the risk by 44%.

## Epidemiologic Research

### Walking Improves Rates of Breast Cancer Survival

Researchers from Brigham and Women's Hospital in Boston, MA, and Harvard University in Cambridge, MA, tested the hypothesis that physical activity increases survival rates among women with breast cancer. The researchers drew on participants in the Nurses' Health Study, reviewing data on women with stage I, II, or III breast cancer who were diagnosed from 1984–1996. In that study, leisure-time physical activity was measured in metabolic equivalent task hours per week (met-hours per week is the energy expenditure and caloric requirement at rest. One hour of walking represents three met-hours of physical activity.). The researchers looked specifically at exercise beginning two years after diagnosis, to avoid inclusion of women undergoing treatment. The cohort of 2,296 women were followed from 1986 until either their death from breast cancer or June 2002, whichever came first. The results showed that the relative risk of death from breast cancer was decreased with every level of physical activity compared with being sedentary. The risk of death from breast cancer was 19% less among women who undertook 3–8.9 met-hours per week of exercise, 54% less for 9–14.9 met-hours per week, 42% less for 15–23.9 met-hours per week, and 29% less for 24 or more met-hours per week of recreational exercise. The researchers concluded that even a moderate amount of physical activity, such as walking for 30 minutes most days of the week, improved the odds of surviving breast cancer.

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