BASIC RESEARCH

Technology for Describing Tumor Profiles May Lead to Patient-Specific Therapies

Investigators from the U.S. Food and Drug Administration and National Cancer Institute’s Clinical Proteomics Program examined individual tumor and normal epithelial breast cells from patients and, using molecular technologies, were able to distinguish protein pathways that are inhibited only in patients who responded to treatment. The new technology combines Laser Capture Microdissection, which permits the capture of single cells from patient tissues, and reverse phase microarray, which allows researchers to analyze thousands of proteins on a single slide.

Genetic mutations underlie most cancers and result in signaling defects in cancer cells. Defective proteins either fail to suppress cell growth or stimulate uncontrolled cell proliferation. The Clinical Proteomics Program currently is investigating the effects of trastuzumab (Herceptin®, Genentech, Inc., South San Francisco, CA) followed by paclitaxel (Taxol®, Bristol-Myers Squibb Oncology, Princeton, NJ). Examination of cells from 20 patients showed that those who responded to trastuzumab demonstrated inhibition of the protein Akt, which is important in signaling apoptosis suppression. This inhibition was not found in patients who were nonresponders. Paclitaxel treatment leads to apoptosis; however, in nonresponders, prosurvival pathways remained functional. By determining individual patient tumor profiles, therapies can be directed toward the protein pathways involved in cancer signaling.

New Technology May Improve Treatment of Bladder Cancer

Researchers from FeRX Inc. in San Diego, CA; University of California, Los Angeles; and Wayne State University in Detroit, MI, presented a preclinical study demonstrating the feasibility of using magnetically targeted carriers (MTCs) for the treatment of bladder cancer. Transitional cell carcinoma of the urothelium is sensitive to direct intravesicular chemotherapy delivery. MTCs have been designed to further concentrate chemotherapeutic agents at the tumor site and potentially reduce toxicity. MTCs are 0.5–2.0 micron particles of metallic iron and activated carbon. Doxorubicin is absorbed to the carbon component MTC-DOX, and the metallic portion then can be used for directed delivery of the drug under a magnetic field. In the study reported at the American Association for Cancer Research meeting, MTC-DOX was delivered via Foley catheter directly into the bladders of six swine (dose range 10–80 mg doxorubicin on 300–800 mg MTC). Serum levels of doxorubicin were assessed prior to treatment and 15 and 30 minutes after treatment. At 30 minutes, plasma levels were found to be less than the limits of the detection assay. Histopathological examination showed MTCs primarily in the bladder wall at the targeted site. This study suggests that targeted MTC therapy is feasible for bladder cancer and may be associated with minimal adverse systemic effects.

Tyrosine Kinase Inhibitors Plus Paclitaxel Reduce Bone Metastases

Researchers at the University of Texas M.D. Anderson Cancer Center in Houston presented a study indicating that the combination of tyrosine kinase inhibitors PKI166 and STI571 (Gleevec™, imatinib mesylate, Novartis Pharmaceuticals, East Hanover, NJ) plus paclitaxel (Taxol®, Bristol-Myers Squibb Oncology, Princeton, NJ) reduces angiogenesis and the size of bone tumors in mice. The tyrosine kinase inhibitors target receptors for growth factors that stimulate tumor cell proliferation. Tyrosine kinase inhibitors PKI166 alone or in combination with farnesyl transferase inhibitor SCH66336 sensitizes imatinib mesylate-resistant leukemic cells.

Farnesyl Transferase Inhibitor SCH66336 Sensitizes Imatinib Mesylate-Resistant Leukemic Cells

A study presented by researchers at Tokyo Medical University in Japan showed that the tyrosine kinase inhibitor Gleevec™ (imatinib mesylate, Novartis Pharmaceuticals, East Hanover, NJ) has synergistic or additive effects in combination with farnesyl transferase inhibitor SCH66336 in leukemic cells. Farnesyl transferase inhibitors target ras genes known to trigger tumor growth in 30% of human cancers. When cells overproduce ras proteins, cell proliferation is uncontrolled when diagnosed with prostate cancer; however, no standard effective chemotherapy exists for this disease. This study suggests a possible combination chemotherapy that may improve survival for these patients.