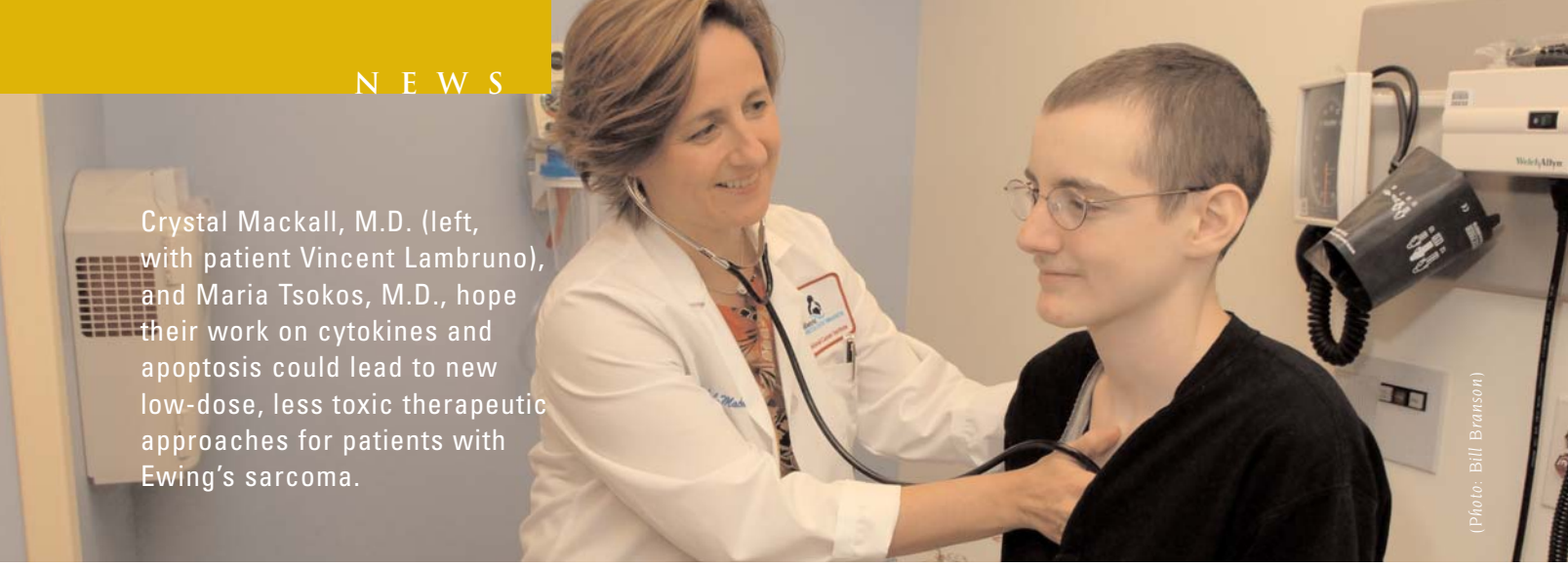

Crystal Mackall, M.D. (left, with patient Vincent Lambruno), and Maria Tsokos, M.D., hope their work on cytokines and apoptosis could lead to new low-dose, less toxic therapeutic approaches for patients with Ewing's sarcoma.

(Photo: Bill Branson)

Jump-Starting Treatment for Relapsed Ewing's Sarcoma

The outlook for patients with Ewing's sarcoma—the second most common bone tumor in children and adolescents—has improved markedly over the past several years. Now an international team of clinicians, including CCR physicians, hopes to extend that improved status to the children who relapse with this sarcoma.

Successful treatment for Ewing's sarcoma is aggressive, combining dose-intensive chemotherapy with surgery, radiation, or both. With these tools, clinicians are able to attain cure rates approaching 70 percent. But survival itself comes at a price. Current standard therapies are highly toxic and leave many cured patients with lifelong therapy-related effects.

Intensive research is under way to identify new and less toxic approaches to treating Ewing's sarcoma. Researchers at Germany's University of Freiburg are working with CCR clinicians to pursue a promising new low-dose therapy that they hope will prove effective for both primary and relapsed tumors. The international collaborators' optimism is reflected in experimental findings reported in the June, 2007, issue of the *American Journal of Pathology*.

A protein called tumor necrosis factor apoptosis-inducing ligand (TRAIL, also called Apo-2L) stimulates cancer cells to self-destruct via apoptosis, or programmed cell death, but leaves normal cells untouched. Maria Tsokos, M.D., of CCR's Laboratory of Pathology, and Crystal L. Mackall, M.D., of CCR's Pediatric Oncology Branch, teamed up with German colleagues to study the activity of TRAIL in tumor samples from 47 Ewing's sarcoma patients. They discovered that when TRAIL successfully triggers apoptosis in a cancer cell, it does so in the presence of high levels of an enzyme called caspase-8. Interestingly, Ewing's sarcoma cells from patients who relapse or resist therapy often have unusually low levels of caspase-8.

This unresponsiveness to TRAIL is not permanent, however. Tsokos, Mackall, and colleagues found that treating resistant Ewing's sarcoma cells with interferon-gamma, a protein normally produced by the body's immune system, can stimulate them into producing more caspase-8, re-sensitizing them to TRAIL's apoptotic influence. A Phase I clinical trial to assess the safety and effectiveness of a TRAIL-receptor agonist—a compound functionally and structurally similar to TRAIL—is currently under way in CCR's Pediatric Oncology Branch. With her young patients in mind, Dr. Mackall explains, "Once we complete the safety testing, we hope to combine our new TRAIL-like agonist with interferon-gamma and attempt to clinically induce cell suicide in resistant or relapsed Ewing's sarcoma. These studies suggest that such an approach may help even more children."