By Mike Fillon

Advances in prostate cancer therapies are shifting from a focus on cancer epithelial cells to targeting the tumor environment. In a review published in the September 13 issue of the Journal, researchers examined the most promising therapies for metastatic castrate-resistant prostate cancer (mCRPC)—when the disease progresses despite low levels of tumor-fueling hormones. “We study drugs for treating mCRPC because it is incurable and usually lethal,” said coauthor Paul G. Corn, M.D., Ph.D., of the department of genitourinary medical oncology at the University of Texas M. D. Anderson Cancer Center in Houston.

Although prostate cancer sometimes travels to other organs of the body and the lymph nodes, it often goes to the bone. Corn said that although researchers do not completely understand why this happens, the bone microenvironment must somehow support prostate cancer cell growth. “The more we understand about that complex interaction between cancer epithelial cells and the bone microenvironment, the more we can design new therapies,” Corn said.

In the study he cowrote, entitled “Novel Therapies for Metastatic Castrate-Resistant Prostate Cancer,” researchers focused on the “seed and soil” hypothesis: in other words, where the bone microenvironment provides fertile soil for prostate cancer epithelial cells to seed and then germinate into tumors. Corn said some of the newer drugs, in addition to killing cancer cells, seem to disrupt the ability of the bone microenvironment to act as a host for prostate cancer.

“Science is developing some very exciting drugs that seem to be very different from the two historic mainstays, chemotherapy and hormone therapies,” Corn said. “While these newer drugs can complement those, they use a completely different mechanism of action.”

For example, one category of drugs can block the signaling pathways that drive tumor growth and spread. The JNCI study divides the new drugs for mCRPC prostate cancer into three main groups.

The first group, called epithelial targeting agents, predominantly targets the cancer cell. These include cabazitaxel and OGX-011 (custirsen).

The second group, called stromal targeting agents, predominantly targets the bone microenvironment. So far, single-agent trials have demonstrated the proof of principle that candidate stromal-targeting drugs can modulate the tumor microenvironment. One example, still in clinical trials, is atrasentan, a selective endothelin receptor antagonist that inhibits osteoblast proliferation.

The third group targets both epithelial and stromal cells. The researchers divided the combination drugs into the following subgroups:

- **Antiangiogenic agents.** Corn said blocking angiogenesis to inhibit tumor growth has successfully treated a variety of different metastatic tumor types, including kidney, colon, and lung cancers. Drugs in clinical trials for treating mCRPC include bevacizumab and thalidomide. Corn said fewer studies have been done with thalidomide because of its potential toxic effects and unknown mechanism for angiogenesis inhibition. In a phase II trial expected to finish in mid-2012, mCRPC patients receive a combination of lenalidomide, bevacizumab, and prednisone.

- **Androgen-ablative agents.** MDV3100 is a new small-molecule androgen receptor (AR) antagonist that overcomes resistance to conventional antiandrogens. Like other antiandrogens, such as bicalutamide, MDV3100 inhibits AR function by blocking AR ligand binding, nuclear translocation, and DNA binding. In the past 15 months, the U.S. Food and Drug Administration approved two agents that prolong life in mCRPC patients—abiraterone (Zytiga), a drug that blocks all physiologic sources of testosterone, and cabazitaxel (Jevtana), a new taxane.

- **Targeted agents.** Dasatinib is an oral tyrosine kinase inhibitor. In a phase II trial, data suggested only modest clinical activity for dasatinib alone. However, Corn said dasatinib’s ability to modulate both the epithelial and stromal compartments prompted a phase III study combining dasatinib with docetaxel in mCRPC patients. Dovitinib and XL-184 (cabozantinib) are also in phase II trials.

- **Immunotherapy.** FDA has also approved the immunostimulant sipuleucel-T (Provenge).

Drugs for treating mCRPC might treat other prostate cancers, but determining that would require “a much more detailed analysis,” according to Corn. He is optimistic that basic science is leading to a greater appreciation for what makes prostate cancers tick. “It’s very exciting to see these abstract notions leading to the development of real practical drugs that are helping people in meaningful ways,” he said.