

## Prostate Cancer Spreads to Bones – Then What?

<http://tinyurl.com/4mdtjkh>

**(MY NOTE: What is particularly of interest and importance is the knowledge that as the cancer cells migrate to bone, they can lodge and lay dormant in what is explained below as the “bone marrow niche.” There they can remain for years since one of the jobs of the niche is to keep hematopoietic stem cells from proliferating—which may be the case for cancer cells, as well. Current drugs go after cells that are proliferating, therefore miss these cells apparently being held back from proliferation. However, dormant cancer cells can eventually become active, apparently then proliferate, and “over-run” the bone marrow niche. When this occurs, it is the beginning of osteoclast activity and tumor development. As explained below, with this knowledge research now has a new target to attack these cancer cells in the bone marrow – the sooner the better - and, hopefully, serve to prevent bone metastases.)**

*PCF's Take:* Patients with advanced metastatic prostate cancer frequently have significant metastases to their bones. This can result in destruction of the bone material and result in pathologic fractures, pain requiring narcotics and other interventions including surgery and radiation to the bone. This process can be worsened by common treatments for prostate cancer such as androgen deprivation (hormone) therapies.

Research conducted by PCF-supported researcher, Matthew Smith, MD, PhD, at Massachusetts General Hospital has focused on the role of over-expression of RANK Ligand, a natural molecule that supports bone metabolism and bone integrity. Dr. Smith's studies with denusomab (Xgeva) have shown that the drug can inactivate RANK Ligand and prevent bone destruction and fractures.

Today, University of Michigan (U-M) scientists announced that they believe prostate and breast cancer cells specifically target and eventually overrun the bone marrow niche, a specialized area for stem cells that produce red and white blood cells. The cancer cells can lay dormant in these niche regions for years before reactivating and resulting in disease recurrence.

“This news from the University of Michigan represents a potentially important and targetable pathway that may someday be targeted by new drugs to stop bone

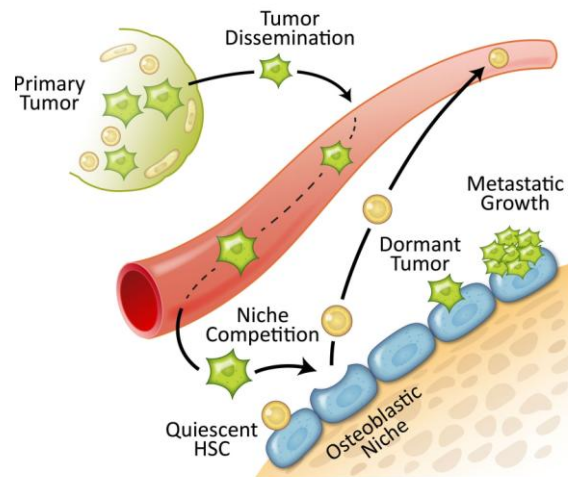
metastases before they take root,” says Howard Soule, PhD, PCF’s chief scientist. “We will continue to follow this research closely.”

Kenneth Pienta, MD, one of the study’s authors and is also a PCF-supported researcher.

*The complete U-M news release follows.*

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Thursday, March 24, 2011 (Ann Arbor, Mich.)—Like bad neighbors who decide to go wreck another community, prostate and breast cancer usually recur in the bone, according to a new University of Michigan study.



*Prostate cancer cells in the bone marrow niche.*

Now, U-M researchers believe they know why. Prostate cancer cells specifically target and eventually overrun the bone marrow niche, a specialized area for hematopoietic stem cells, which make red and white blood cells, said Russell Taichman, professor at the U-M School of Dentistry and senior author of the study.

Once in the niche, the cancer cells stay dormant and when they become active again years later, that's when tumors recur in the bone. The implication is that this may give us a window as to how dormancy and recurrence take place.

Taichman and a team of researchers looked in the bone marrow and found cancer cells and hematopoietic stem cells next to one another competing for the same place. The finding is important because it demonstrates that the bone marrow niche

plays a central role in bone metastasis—cancers that spread into the bone—giving researchers a new potential drug target.

Drugs could be developed to keep the types of cancers that likely recur in the bone from returning, Taichman said. For example, these drugs could either halt or disrupt how the cancer cells enter or behave in the niche, or keep the cancer cells from out-competing the stem cells.

Cancer cells act a lot like stem cells in that they must reproduce, so the U-M research group hypothesized that prostate cancer cells might travel to the niche during metastasis. One of the jobs of the niche is to keep hematopoietic stem cells from proliferating—which may be the case for cancer cells, as well, the researchers found.

So why does cancer recur? Say a person has a tumor and surgeons cut it out or do radiation, but it recurs in the bone marrow five years later, Taichman said. Those cancer cells had been circulating in the body well before the tumor was discovered, and one place those cancer cells hid is the niche.

"So what have the cancer cells been doing during those five years? Now we have a partial answer - they've been sitting in this place whose job it is to keep things from proliferating and growing," Taichman said.

"Our work also provides an explanation as to why current chemotherapies often fail in that once cancer cells enter the niche, most likely they stop proliferating," said Yusuke Shiozawa, lead author of the study. "The problem is that most of the drugs we use to try to treat cancer only work on cells that are proliferating."

Metastases are the most common malignant tumors involving the skeleton, and nearly 70 percent of patients with breast and prostate cancer have bone involvements. Roughly 15 percent to 30 percent of patients with lung, colon, stomach, bladder, uterus, rectum, thyroid or kidney cancer have bone lesions.

Researchers aren't quite sure how the cancer cells out-compete the stem cells in the niche. However, they do know the stem cells were displaced because when cancer cells were in the niche scientists also found evidence of immature blood stem cells in the blood stream, instead of in the marrow where they were supposed to be, Taichman said.

"Eventually the entire blood system is going to collapse," he said. "For example, the patient ultimately becomes anemic, gets infections, and has bleeding problems.

We really don't know why people with prostate cancer die. They end up dying from different kinds of complications in part because the marrow is taken over by cancer."

The next step is to find out how the tumor cell gets into the niche and becomes dormant, and exactly what they do to the stem cells when they are there. Researchers also want to know if other types of cancer cells, such as breast cancer, also go to the niche.

The study, "Prostate Cancer Metastases Target the Hematopoietic Stem Cell Niche to Establish Footholds in Marrow," appears online in the *Journal of Clinical Investigation*.

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