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Hua Li, left, and Jim DiRenzo found surprisingly high amounts of a nervous system protein in breast cancer cells.

Surprise finding suggests a new biomarker

How does nestin, a long filamentous protein found in adult stem cells in the central nervous system, wind up being an indicator for a deadly form of breast cancer?

Ask Dartmouth Medical School researchers James DiRenzo, Ph.D., and Hua Li, Ph.D. They were trying to determine whether basal epithelial breast cancer cells had the same self-renewing capacity as mammary stem cells. The latter are regenerative cells believed to be the site of breast cancer initiation. The researchers confirmed the similarities between the two types of cells but were surprised to discover high amounts of nestin in the breast basal epithelial tumors. They reported their findings in the January 15 issue of *Cancer Research*.

Triple: “It’s so amazing to detect nestin’s overexpression in a triple-negative breast cancer, which lacks almost all important diagnostic markers,” says Li.

“Triple negative” refers to the fact that basal epithelial tumors lack three important molecular targets that are used to diagnose other types of breast cancer. “In the clinic, these tumors are generally only recognized by what they are not as opposed to what they are,” explains DiRenzo. They are not positive for receptors for estrogen, progesterone, or a

human epidermal growth factor-related protein known as HER2. Since there is no direct means of determining whether tumors are the basal epithelial type, “diagnosing them became a process of elimination.”

High risk: Basal epithelial breast cancer represents between 17% and 37% of all breast cancers and is more common in premenopausal African-American women than in other demographic groups. Patients are at high risk for recurrence after treatment, according to DiRenzo.

The researchers—whose retrospective study of triple-negative breast cancer tumors showed extremely high amounts of nestin in 14 of 16 tumor samples—are trying to develop a general understanding of mammary stem cells and their role in breast cancer.

“Are they the first cell to get sick—that ultimately gives rise to the tumor?” DiRenzo muses. While scientific evidence shows that stem cells give rise to brain and prostate cancers as well as leukemias, “it hasn’t been shown to be the case yet in the breast,” he says. He hopes to prove that mammary stem cells not only initiate breast cancer but are responsible for its recurrence, too.

“Conventional wisdom is that our standard therapies are very good at shrinking and

debulking tumors to the point where they’re no longer detectable,” says DiRenzo. “But since they recur, it obviously suggests that we’re not killing all of those cells. I believe that these tumor cells that survive conventional therapeutics, and ultimately come back to cause recurrences, are a major contributor to breast-cancer death.”

He contends that traditional treatments, combined with anti-stem-cell therapy that would knock out the tumor stem cells, would reduce the risk of recurrence.

DiRenzo is more than a researcher. He is also the scientific director of the Comprehensive Breast Program at Dartmouth’s Norris Cotton Cancer Center and meets weekly with clinicians to discuss ongoing cases as well as research topics. He therefore has an appreciation for both the clinical and research sides of cancer. He’s especially interested in the question of tumor recurrence. “Is it the result of drug resistance,” he wonders, “and, if so, is that drug resistance acquired or was it always innate in these tumor stem cells? That’s an unanswered question,” he says, “but it’s a question that we’re trying to get our hands around.”

Selective: One way to answer that question would be to run small clinical trials to look at potential anti-stem-cell therapeutics as a way to limit tumors’ recurrence. With further work, DiRenzo hopes to “demonstrate that nestin is a selective marker for this type of breast cancer” and useful for diagnosis and treatment.

“I totally believe that nestin could work as a reliable diagnostic marker to distinguish this most aggressive breast cancer subtype,” says Li. He agrees with DiRenzo, however, that more work is needed to develop a means of detecting nestin in a clinical setting.

Their collaborators also included pathologist Wendy Wells, M.D., who provided tumor tissue samples. The study was funded by the National Cancer Institute, the U.S. Department of Defense Breast Cancer Research Program, and the Mary Kay Ash Charitable Foundation. LAURA STEPHENSON CARTER