

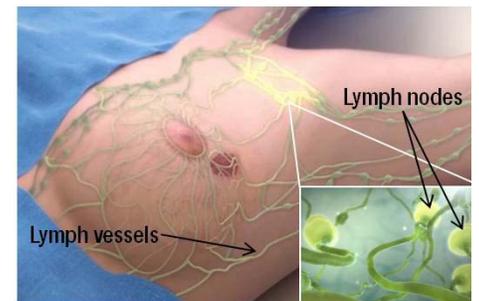
Road Map of Metastasis

Cancer that has spread beyond the breast - or metastasis - is the leading cause of death in breast cancer patients. Unfortunately, finding whether cancer has metastasized is no easy task. Today, the best method for breast surgeons to determine whether cancer has spread from the breast is to surgically remove lymph nodes - small glands that act as filters - near the tumor and examine them for the presence of cancer cells. Analyzing cancer cells found in lymph nodes can provide important information on a patient's outcome and risk of recurrence and can help identify which treatment options are best.

Current methods for identifying which lymph nodes contain cancer cells unfortunately have several drawbacks and can occasionally cause serious side effects. With the help of a Komen grant, Dr. Anne Wallace, Chief of Plastic Surgery at the University of California at San Diego, and her colleagues, have developed a new, effective, FDA-approved agent to determine exactly which lymph nodes contain cancer.

An Unfortunate Hitchhiker

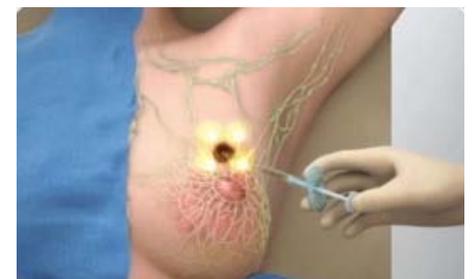
Breast cancer cells that break off from the main tumor can hitch a ride to other parts of the body by traveling primarily through the fluid of the lymphatic system - a system of vessels that connects the lymph nodes located throughout the body or the blood stream. Lymphatic fluid from the breast drains mostly into the lymph nodes located under the arm and near the collarbone. The fluid travels through lymph nodes in a step-wise fashion, so nodes 'upstream' are the first to receive the fluid as it leaves the breast. Since they act like biological filters, trapping bacteria and other cellular debris, lymph nodes are often the first place where cancer cells land once they have left the breast - an early warning sign that tumors have metastasized.



Lymph nodes are the first place that breast cancer cells travel to once they have left the breast. Photo courtesy of Navidea Biopharmaceuticals, Inc.

Finding Hitchhikers

To ensure that no cancer cells lurking in the nodes will spread after the primary tumor has been removed, surgeons need to find and remove all of the lymph nodes near the breast that may harbor cancer cells. The sentinel lymph nodes are the first to receive lymph fluid from the tumor. Using a specific method called 'sentinel lymph node mapping', surgeons can identify these nodes and remove them. Removing only the lymph nodes of concern is a delicate balance, since removing too many, unnecessarily, can lead to a significant number of temporary and permanently debilitating complications including arm and leg swelling (lymphedema) or a loss of skin sensation. Removing too few can leave lymph nodes that contain cancer, increasing the risk of metastasis or recurrence. Ideally, surgeons would like to identify and remove only the sentinel lymph nodes. If the sentinel lymph nodes are free of cancer, it is likely that other lymph nodes in that region are free of cancer and there is no need to remove any additional lymph nodes.



Surgeons can identify and remove only the "sentinel" lymph nodes by injecting a blue dye and/or radioactive tracers into the breast near the tumor. The blue dye and tracer mimic the behavior of cancer cells moving through the lymph vessels. Photo courtesy of Navidea Biopharmaceuticals, Inc.

Stuck in the 60s

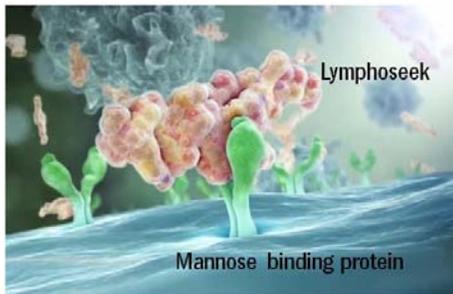
The diagnostic agents currently used to map sentinel lymph nodes have changed little since the 1960s. Surgeons inject a blue dye and/or a radioactive tracer, called Technetium 99m (T99m) - sulfur colloid, near the tumor site. Both are absorbed by the lymph system and travel through the lymph vessels to lymph nodes. The surgeon then removes the blue stained and/or radioactive nodes and analyzes them for the presence of cancer cells. Unfortunately, this procedure has drawbacks. The blue dye can drain too quickly through the sentinel lymph node and move to other lymph nodes, which could be unnecessarily removed. Or, the radioactive tracer can become stuck near the injection site and never enter the lymph system.



The surgeon locates the blue dye (blue) stained node then uses a hand held device to detect the small amounts of radioactivity (orange). Typically, one to three sentinel nodes are removed. Photo courtesy of Navidea Biopharmaceuticals, Inc. (Adapted)

Sugary Bait

Drs. Anne Wallace and David Vera wanted to improve how lymph node mapping was being performed. Dr. Vera, a chemist, and Dr. Wallace, a clinician scientist, combined their talents to create a diagnostic imaging agent that would specifically target and bind to



Lymphoseek® molecule binding to proteins in lymph nodes that are normally attracted to the sugar, mannose. Photo courtesy of Navidea Biopharmaceuticals, Inc.

lymph nodes draining from a tumor, to improve accuracy of the procedure, and enhance patient outcomes. To do this, Dr. Vera focused on a protein that is found in great abundance in lymph nodes and is attracted to a sugar called mannose. He believed that by adding mannose sugars to the radioactive tracer, the compound would stick to and stay in the lymph nodes, unlike the old dye and tracer system. Early experiments in animal models showed that it worked as they had hoped - the new sugary compound found its way quickly to the target and stayed in the lymph nodes. This imaging agent was developed further by Wallace and Vera along with Navidea Biopharmaceuticals, Inc. to become the commercial product known today as Lymphoseek® (technetium Tc 99m tilmanocept) Injection.

One Door Open Leads to Many

With success in the laboratory, Drs. Wallace and Vera were ready to test Lymphoseek® in patients. In a phase I clinical trial funded by Komen in 1999, they tested the safety of Lymphoseek® in patients. The trial results, published in 2003, showed that Lymphoseek® did not cause any serious side effects and was better at identifying sentinel lymph nodes

than the blue dye and T99m -sulfur colloid. These initial results¹ opened the door for Dr. Wallace to move forward and test Lymphoseek® in more patients in larger clinical trials. ***“Komen took a chance on funding this phase I study with only preliminary animal work and was forward thinking enough to take this risk. Few funding organizations do that...,” said Dr. Wallace.***

“Without Komen funding, Lymphoseek® would have gotten nowhere,” says Dr. Wallace.

Fast Forward

Lymphoseek® has now been tested in phase III clinical trials in more than 13 different cancer centers with the same result as the phase I trial. The studies showed that Lymphoseek® not only performed as expected, it also identified more tumor-draining lymph nodes than the standard of care, blue dye. ***"This was an unexpected, surprising finding," said Dr. Wallace. "It's one thing to have a molecule in a test tube, but it's a 1 out of 1,000 chance that the thinking, planning, and testing that went into a designer molecule will not only be feasible to give to a patient, but that it would actually work better than the current method used in the clinic," added Dr. Vera.***

It's been about a 12-year journey since the results of the first phase I clinical trial in breast cancer patients were published², but it was the first of many steps forward to improve breast cancer diagnosis. On March 13, 2013 the U.S. FDA approved Lymphoseek® for use as an imaging agent for I lymph node mapping in breast cancer and melanoma patients.

What Does It Mean for Patients?

The five-year survival rate for breast cancer patients of all races diagnosed with tumors that are confined to the breast (and has not spread) is 98.6%. For those whose cancer has metastasized, that rate is as low as 23%. Improving sentinel lymph node detection could be an additional important step forward in detecting the spread of cancer earlier and contributing to the increased survival rate for patients with metastatic disease.

Lymphoseek® creates a significant advance for breast cancer patients in several different ways. Because it is designed to target specific proteins in the lymph node and stay in place for a period of time, Lymphoseek® can detect more tumor-draining lymph nodes than blue dye, and reduces the likelihood of removing lymph nodes that do not contain cancer cells. Finding the right lymph nodes that have cancer cells makes a difference in the treatment recommendation. ***"This is huge in early breast cancer," Dr. Wallace explained. "The product made a difference. [Women] will go on to adjuvant therapy that they may not have otherwise received."***

Patients whose nodes are cancer-free may be spared from unnecessary surgery, chemotherapy and potentially debilitating side effects. Lymphoseek® stays in the lymph node longer than the blue dye, up to 30 hours, increasing the chance of finding the right tumor-draining node the first time. Lymphoseek can rapidly dissolve into lymphatic fluid and is not a mix of particles like T99m-sulfur colloid, so it can quickly move away from the injection site. ***"What can take up to a couple of hours using blue dye, takes fewer than 20 minutes with Lymphoseek®. This helps the comfort level of patients and willingness to undergo this procedure," says Dr. Wallace.*** In addition, Lymphoseek® does not appear to cause allergic reactions, unlike blue dye or sulfur colloid.

And that's just the beginning. Lymphoseek® will not only be used in breast cancer and melanoma patients, but may also have value for other cancer patients in the future, including those with prostate, colorectal, thyroid and gastric cancers.

Lymphoseek® is the first new drug for lymph node mapping to be approved in more than 30 years. Currently used sulfur colloid was approved by the FDA in 1974 and isosulfan blue dye was approved in 1981.

Learn more at www.lymphoseek.com

Behind the Science

A plastic surgeon by training, Dr. Wallace generously gives her mentors and colleagues much of the credit for her current success. Fate and talent brought Dr. Wallace to breast cancer. In her daily practice as a plastic surgeon, she diagnosed a number of her female patients with breast cancer. "My UCSD colleagues recognized I had a talent for breast cancer and encouraged me to pursue additional breast surgical oncology training with the eventual goal of leading our breast surgery department. I owe a lot of my success to my colleagues and mentors with their support over the years," says Dr. Wallace.



In choosing to remain in academic medicine, treating patients and clinical research are inseparable for Dr. Wallace. *"When you decide to go into academic medicine, you commit to not only excellent patient care, but to teaching and to the advancement of science. You do not think twice about trying to do creative research and embracing opportunities [as they come up]. Therefore, I would not feel like I was doing my job completely for breast cancer if I was not involved in research."*

¹*"Lymphoseek[®]: A Molecular Radiopharmaceutical for Sentinel Node Detection," was published on June 23, 2003 in the Annals of Surgical Oncology.*

²*"Comparative Evaluation of [^{99m}Tc] Tilmanocept for Sentinel Lymph Node Mapping in Breast Cancer Patients: Results of Two Phase 3 Trials," was electronically published ahead of print on March 17, 2013 in the Annals of Surgical Oncology.*