

Assay Pinpoints Natural Killer Cells To Improve Transplant Outcomes

St. Jude Children's Research Hospital



A bone marrow or stem cell transplant in which stem cells from a donor (called *allogeneic*) are transplanted into a patient is often the best chance for a cure for patients with recurrent or resistant cancers such as leukemia and lymphoma.

However, of the roughly 25,000 patients who receive a stem cell transplant each year worldwide, only about half survive, according to the [Worldwide Network for Blood & Marrow Transplantation](#). And until recently, researchers could not accurately predict the outcome of the costly and high-risk transplant procedure.

[Insight Genetics](#) hopes to reduce that uncertainty — and increase the success rate of stem cell transplants — by offering a new test to help identify the optimal stem cell donor. The assay, developed by researchers at [St. Jude Children's Research Hospital](#), provides information on both the patient's cancer cells and the makeup of receptors on specialized immune cells called natural killer (NK) cells from donor candidates.

This test helps take the guesswork out of donor-patient matching for allogeneic stem cell transplants," says JonEric

Pettersson, manager of commercial development at Insight Genetics.

The researcher behind the assay is Wing Leung, M.D., Ph.D., chair of [St. Jude's Department of Bone Marrow Transplant and Cellular Therapy](#).

“The use of the new test will change the choice of stem cell donors in as many as 20,000 of the 25,000 transplants performed each year.

Wing Leung

Using the Immune System to Fight Cancer

Stem cells, which live in the spongy center (called marrow) of certain bones in the body, produce the body's blood cells — including NK cells — that play a critical role in the immune system to fight off invading germs and cancer cells. A stem cell transplant essentially recruits a whole new defense against the disease by infusing stem cells from a well-matched donor into the patient to attack the cancer.

The Stem Cell Transplant

The majority of stem cell transplants are performed on patients with cancers that originate in blood cells, including leukemia, multiple myeloma and some lymphomas, that are highly resistant to standard treatments.

The stem cell transplantation procedure (also called a *bone marrow* or *cord blood transplant*) is typically preceded by chemotherapy and radiation therapy to eliminate as much of the cancer as possible.

“The chemo and radiation are harsh, but if it is effective, you eradicate 99.99 percent of the cancer cells,” says Stephan W. Morris, M.D., chief scientific officer at Insight Genetics. “However, that leaves a tiny percentage of cells that are able in some cases to re-grow and cause a recurrence. In a successful transplantation, the donor cells seek out the latent cancer cells, eradicate them, and you have the potential for a cure.”

This desired characteristic of the donor cells is called the graft-versus-tumor (GVT) reaction.

Unfortunately, not all transplantations are a success. In some patients, the GVT reaction is robust — but in others, the effect is suboptimal. To better understand the molecular mechanisms that influence GVT in bone marrow transplants, Leung and his colleagues began studying the genetic makeup of NK cells in 2004.

Understanding Natural Killer Cells

Each NK cell has proteins extending from its surface called *killer-cell immunoglobulin-like receptors* (KIRs) that regulate the cell's activity. Before NK cells attack and eliminate foreign cells in the body, these receptors must first recognize and bind to proteins or ligands (known as *human leukocyte antigens* or HLAs) on foreign cells.

Using a specially developed molecular assay to determine the genetic makeup of KIRs, Leung discovered that a specific KIR receptor — KIR2DL1 — varies from person to person. What's more, he found that this variation in the NK cell's gene content, as well as the matching between the donor KIR and recipient HLA, affects the strength of the cells' immune response and its cancer-killing ability following transplantation.

Using the test to retrospectively analyze the outcomes of previous transplant procedures, Leung's research team determined that NK cells expressing the stronger version of KIR2DL1 destroy cancer cells more effectively than cells expressing the weaker version of KIR2DL1. In a study by Leung and his colleagues published in the [Journal of Clinical](#)

[Oncology](#), the researchers demonstrated that children with leukemia were much more likely to survive their transplant and their disease was significantly less likely to progress when bone marrow transplants came from donors whose NK cells expressed the stronger form of KIR2DL1.

“It’s a three-fold difference, which is huge,” says Leung.

When HLA ligands in the patient’s body bind to KIRs on the donor’s NK cells, the receptor sends a signal to the NK that either activates or inhibits the attack mechanism. The balance between these activating and inhibiting signals plays an important role in the ability of NK cells to mount an effective GVT response.

Leung and his team also developed a second test to determine the type of HLA ligands present in the patient. The optimal stem cell recipient does not have ligands that will inhibit the donor’s NK cells, a situation referred to as a *KIR-KIR ligand mismatch*.

Accordingly, Leung had discovered that he could match donor stem cells that express the stronger form of KIR2DL1 with recipients that were less likely to inhibit those cells in order to greatly increase the stem cell transplantation success rates.

A Friend and Partner in Insight Genetics

After filing the patents for the KIR/KIR-ligand assay, [St. Jude’s Office of Technology Licensing](#) approached Insight Genetics as they knew the company’s scientific founder well.

Morris co-founded Insight Genetics in 2007 after working as a clinician and researcher on St. Jude’s staff for 25 years — helping to discover and characterize a number of oncogenes (including anaplastic lymphoma kinase, ALK, among others) — before beginning his commercial venture dedicated to providing companion diagnostics to the increasingly personalized treatments for cancer.

“After nearly 30 years in academic medicine I finally decided to scratch my entrepreneurial itch,” says Morris, who left St. Jude and joined the company full-time as chief scientific officer in 2012.

Insight Genetics obtained exclusive, worldwide licensing rights to KIR2DL1 coding sequences and the KIR/KIR-ligand assay, including unique probe and primer designs for developing the test.

The KIR/KIR-Ligand Assay

Now 20 employees strong, the company has been refining the assay for clinical use and plans to begin processing blood samples from donor candidates in its Nashville-based laboratory, Insight Molecular Labs, during the second quarter of 2014.

Depending on demand for the assay, the company may also develop a testing kit that can be sold to individual laboratories and bone marrow registries across the country so they can perform the assay on their own.

The automated KIR/KIR-ligand assay is a quantitative real-time polymerase chain reaction (qPCR)-based test that amplifies, or makes multiple copies of, the specific molecules of interest with a fluorescent label that is detected by an instrument common to clinical laboratories. The company hopes to return test results — indicating the optimal donor based on the presence of the stronger KIR receptor and a KIR-KIR ligand mismatch — within 48 hours.

“There’s a clear utility for this assay for leukemia patients,” says Morris. “But it also has potential for other diseases that are treated with bone marrow transplants.”

Leung says that more and more physicians are referring patients for stem cell transplants earlier in the cancer treatment process, not just at the end-stage of the disease.

“The stem cell transplant has become much safer as the technology has advanced,” he says. “Plus, stem cell transplantation is curative and more patients have access to transplant centers in 42 states now.”

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