

# Sylvester researchers identify protein target that might ease graft versus host disease

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In a new study published in *Science Translational Medicine*, Robert Levy, Ph.D., along with graduate student and first author Cameron Bader and colleagues, have shown that inhibiting the STING protein pathway could

protect certain patients from graft versus host disease, the most serious complication from bone marrow (stem cell) transplants.

"This pathway is very important in allogeneic (donor) [stem cell transplants](#)," said Dr. Levy, professor of microbiology and immunology at Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine. "We found that, in preclinical models of transplants which mimic those performed between HLA ([human leukocyte antigen](#)) matched patients, we would want to interfere with the STING pathway to minimize graft versus host disease and the complications associated with this disorder."

Allogeneic bone marrow transplants, in which patients receive new blood-producing cells from a donor, are often a major component in leukemia and lymphoma treatments, as aggressive chemotherapy is used to destroy the patient's own marrow cells. However, the donated cells can also generate their own immune response, pitting the grafted cells against their new host. Graft versus host disease (GVHD) can cause skin rashes, nausea, diarrhea, and liver damage, and is the major non-relapse cause of mortality in these patients.

In the paper, Dr. Levy's team tested whether STING could be modulated to control GVHD. In one instance, they created an [animal model](#) that replicates an allogeneic transplant from a sibling match and found that when STING was absent, the symptoms of GVHD were reduced. However, when investigating STING in an unmatched transplant model, in which donor and recipient were not closely related, the absence of the pathway made GVHD worse.

Further investigation showed this surprising difference was caused by distinct immune system T cells. When transplanting only CD8 T cells, excluding the CD4 variety, the lab replicated the positive results in the unmatched model, reducing GVHD.

"That told us the cell populations that mediate GVHD really affect the role STING plays in these transplants," said Dr. Levy. "STING can worsen GVHD or it can provide a protective effect. We figured out that, when the CD8 T cells are present in the transplant, they get rid of the antigen-presenting cells that drive CD4 T cells. So, if you get rid of those antigen-presenting cells, and you don't drive CD4 T cells, you can also mitigate GVHD."

Dr. Levy believes inhibiting STING in matched patients could potentially reduce their risks of developing GVHD. However, there may be an added benefit: STING could also be boosted to activate T cells and promote a stronger immune response against cancer cells. In this scenario, clinicians might want to selectively inhibit and boost STING—at different times—when treating cancer patients.

"With matched siblings, like our preclinical model, we would want to block STING during the early part of the transplant to prevent serious graft versus host disease," said Dr. Levy. "Then later, we might want to go in and activate STING to help generate tumor immunity against the remaining leukemia or lymphoma [cells](#)."

**More information:** STING differentially regulates experimental GVHD mediated by CD8 versus CD4 T cell subsets," *Science Translational Medicine* (2020). [DOI: 10.1126/scitranslmed.aay5006](https://doi.org/10.1126/scitranslmed.aay5006)

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