

How Blood Cancer Research Might Help Organ Transplant Patients

Fred Hutch study suggests certain immune cells are the source of antibodies that attack donated organs.

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Each day, 13 patients awaiting transplants for severe kidney disease in the U.S. lose their lives before a compatible kidney can be found.

Frequently, it is simply that there are not enough donated organs available, but sometimes it is because the right donor is too rare. Of the [92,000](#) people in U.S. waiting this year for a kidney transplant, about one in ten will have an especially hard time finding a compatible donor.

These “highly sensitized” patients are at [higher risk of dying](#) while still on the waiting list and of rejecting a transplanted kidney if they receive one.

When blood samples are tested from that group of patients, they are found to carry immune proteins—antibodies—likely to react against most of the kidneys available from potential donors.

“Having antibodies against your potential donor is one of the fundamental reasons for rejecting a transplanted organ, which is obviously a huge issue,” said [Joshua Hill, MD](#), a physician-scientist at Seattle’s Fred Hutchinson Cancer Center. “If you are unable to receive the majority of kidneys that are out there, you are going to be stuck on the wait list for a long time, and you are probably going to die on the wait list before you can get one.”

Hope for these highly sensitized patients is being kindled by researchers like Hill, a specialist in infections and immunology, whose work seldom involves kidney disease. He and his team are primarily focused on engineering our immune systems to fight blood cancers such as leukemia, lymphoma and multiple myeloma, and also to prevent or treat viral infections in vulnerable patients.

The Culprits: Long-Lived Plasma Cells

Hill and his Fred Hutch colleagues, along with those at the University of Washington and Seattle Children’s Research Institute, have used their expertise to zero in on a type of antibody producing

cell that may be keeping donated organs out of reach for thousands of patients needing new kidneys, hearts, lungs or other vital organs.

The culprits, they suspect, are plasma cells, which are members of an antibody-making family of blood components.

At the head of this family is the B cell. Think of it as a mother ship, housing microscopic engineers who design antibodies in response to a perceived threat. Once a threat is encountered, the original “naïve” B cell spins off a variety of [more specialized descendants](#). Plasma cells are B cell descendants that have become fully specialized. They have matured into machines whose sole purpose is to churn out antibodies of a specific design.

Several different drugs are used in organ transplantation to clear out B cells that might produce antibodies potentially hostile to the donor organ. But Hill and his team contend that the role of the more specialized plasma cells in transplant rejection is underappreciated and needs a closer look.

He is lead author of a study published recently in the [American Journal of Transplantation](#), in which his team suggests that plasma cells—left untouched by common B-cell depleting therapies—may be contributing to organ rejection in highly sensitized patients.

Their paper proposes that sensitized kidney transplant recipients might be helped by therapies that strip hidden pools of long-lasting plasma cells from the immune system. Such treatments are used against [multiple myeloma](#)—a cancer marked by uncontrolled replication of plasma cells. If that strategy works, hard-to-match, highly sensitive transplant patients might qualify for kidneys that are off-limits to them today.

To make their case, Hill and his colleagues drilled down into the nitty-gritty of antibody responses, as shown in an experiment that compared antibody populations in two leading-edge, CAR T cell therapies for patients with different kinds of blood cancer.

One group of 21 lymphoma patients was treated with CAR T cells genetically modified to wipe out B cells. These CAR T cells were programmed to spot a biomarker found on the surface of most B cells — a protein called CD19 — and kill all those cells that display it.

A second group of 28 multiple myeloma patients was treated with CAR T cells modified to wipe out plasma cells, which — although they are a specialized form of B cell — do not display the telltale CD19 marker. Instead, the T cells are programmed to kill by homing in on a biomarker found only on plasma cells, called BCMA.

“The CD19 recipients are losing nearly all of their B cells, but not their plasma cells. The BCMA recipients are just getting their plasma cells knocked out,” Hill said.

Testing for Antibody Sensitivities

Prior to qualifying for highly advanced CAR T treatments, the patients in each group were given, as part of their previous cancer care, different conventional therapies designed to clear out malignant B cells in the case of lymphoma and plasma cells in the case of myeloma. The first step of Hill's experiment was to screen blood samples collected prior to CAR-T cell infusion with the same tests used to match donor and patient in organ transplantation — to see whether they had antibody sensitivities to a theoretical transplant.

Out of these two groups, the initial screens found four patients among those with lymphoma who had reactive antibodies prior to getting CAR T cell therapy, which could mean trouble for an organ transplant. In tests of blood samples collected after infusion of the B-cell targeting CAR-T cells, these antibody profiles persisted for months, providing proof of concept that even the most effective therapies targeting B cells do not adequately remove these antibodies problematic to transplants.

Among the second, larger group of patients with multiple myeloma, only one was found prior to their BCMA-targeted T cell therapy to have antibodies that might be concerning for an organ transplant. Hill said it is possible that a smaller portion of those with myeloma had reactive antibodies because the prior, conventional treatments were quite effective at clearing potentially reactive antibodies, but the numbers were too small to be conclusive.

However, for that one patient, the team was not able to obtain samples after the CAR T treatment to provide proof-of-concept data that depleting BCMA-positive plasma cells would rid the body of the problematic antibodies. A future, larger study is needed to get a clearer picture of that.

So, while the patients in these experiments did not have kidney disease and were not in need of a transplant, their cancer treatments provided a way for the scientists to evaluate two different strategies for protecting future organ transplant patients from unwanted antibody responses.

Hill said that although this experiment was too small to make any definitive conclusions about the importance of long-lived plasma cells in organ transplantation, the findings were nonetheless “hypothesis-generating.” It was enough evidence to suggest that the role of plasma cells in organ transplant rejection needs closer study through larger and more conclusive clinical experiments.

A Need to Target Plasma Cells Before Transplant for Some Patients

Given the grim prognosis for highly sensitized patients on organ transplant waiting lists, Hill stressed that the stakes involved are high. He also said that findings like his send a cautionary message about current B-cell depleting therapies used in transplants now.

For example, patients undergoing a transplant whose antibody profile shows they are at risk for rejection, or who develop rejection after transplant, may be prescribed rituximab, a B-cell

depleting drug.

“The classic approach has been to use rituximab, because that’s what’s available and it knocks out your B cells. But it does not always work that well. Maybe there are better strategies we should be using,” Hill said.

His study has shown that even when an exquisitely effective B-cell depletion method — CD19 targeted CAR T cell therapy — is used, “those B cells are gone, but the plasma cells and problematic antibodies persist.”

While the BCMA-targeted CAR T cell therapy is extremely effective in stripping out plasma cells, Hill said such complex and costly procedures are not the only way to eliminate persistent and potentially dangerous antibodies. [New therapies](#) developed to treat multiple myeloma might be used. They include drugs such as [daratumumab](#) and [elotuzumab](#), laboratory manufactured antibodies that destroy plasma cells.

Hill and his colleagues also stress in their paper that their findings — while needing further validation and larger studies — have important implications for the organ transplant community. Without targeting plasma cells, they wrote, improved techniques focused on B-cell depletion, “are unlikely to establish persistent control of donor-specific antibodies” in transplant patients.

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