Duplicating immunity boosting regulatory T-cells to unprecedented levels

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University of Minnesota Medical School researchers have discovered a method to quickly and exponentially grow regulatory T-cells – also known as "suppressor cells." The new process enables replication of the cells by tens of millions in several weeks, a dramatic increase over previous duplication methods. Historically, regulatory T-cells have been difficult to replicate.

The new technique will give patients a better chance of having a successful bone marrow or organ transplant, and will have profound implications for patients with autoimmune diseases such as lupus, type 1 diabetes, Crohn's disease and multiple sclerosis.

The use of the new replication technique has already shown promising effects in the treatment of acute graft-versus-host disease; a post-transplant condition in which T-cells from the donor's bone marrow recognizes a recipient's body as foreign, and tries to attack.

"When regulatory T-cells don't respond to inflammation quickly enough to suppress an immune system response, the patient's own immune response can do considerable harm after a transplant, injuring organs, joints and other tissues of the body," said Dr. Bruce Blazar, senior author of the study and Director of the Clinical and Translational Science Institute at the U of M.

Compounding the challenge is that humans have a limited supply of regulatory T-cells, Blazar said. So even if the immune system's cells

respond appropriately, there may not be enough suppressor cells to stop errant reactions in time before the immune response causes widespread tissue damage.

Researchers felt that by developing a way to replicate the cells – which have been historically challenging to coax into high rates of duplication – they could increase transplantation success rates.

Between 30-40 percent of all related bone marrow transplant patients experience graft-versus-host disease, and between 10-30 percent of kidney transplants and 60-80 percent of liver transplant recipients experience acute rejection, according to the National Institutes of Health.

About the New Method

The immunology team, led by Blazar, developed a method to extract regulatory T-cells from blood and subsequently deliver the right combination of signals to make the cells replicate up to 50 million fold. Previous methods to duplicate these cells led to only 70-fold expansion at best.

The findings are published in the May 18 edition of *Science Translational Medicine*.

"The ability to deliver such large quantities of these cells to patients before they undergo transplantation significantly reduces the chances of graft versus host disease and rejection of a transplanted organ," Blazar said.

In animal models and in human clinical trials (where smaller doses of regulatory T cells were given to patients), Blazar's hypothesis came to fruition: Animals and patients became less likely to develop severe

immune reactions that caused tissue damage.

The next step in Blazar's work is phase 1 human clinical testing headed by the U of M's Dr. John Wagner, a world renowned researcher who has been a leader in the field of blood and marrow transplantation. Wagner plans to lead a team of doctors who will administer increasing doses of regulatory T-cells before bone marrow transplants using Blazar's new expansion method.

"This is truly exciting and a major, major breakthrough with profound implications in the treatment of our patients," Wagner said. "If we can super charge patients' immune systems before we do a transplant, we hope to eliminate the chance of graft-versus-host disease or rejection of the transplanted organ. Furthermore, we hope to move these trials ahead quickly to treat autoimmune diseases which affect hundreds of thousands of people worldwide."

Alongside Drs. Blazar and Wagner, U of M assistant professor Dr. Keli Hippen, the lead investigator of the study, pushed this new technology forward.

Collaborators from the University of Pennsylvania provided the key cell lines that made the research possible. Penn scientists engineered artificial Antigen Presenting Cells (aAPCs) which massively expanded regulatory T-cells. The process by which they were replicated could be used to generate a master cell bank that could be used to treat a large number of patients, making therapy much more feasible and cost effective.

Provided by University of Minnesota