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Trials race rashly ahead for regulatory immune cells

Horror autotoxicus: lethal, ravaging autoimmunity—a terrifying fate that would await us all, were it not for the constant surveillance of a relatively small number of immune cells, whose task it is to keep the rest of the immune system under tight control.

That is the remarkable implication of a study, published in February, showing that in adult mice, depleting regulatory T cells, or 'Tregs', rapidly causes severe wasting disease, massive inflammation and death (*Nat. Immunol.* 8, 191–197; 2007).

The study is the latest to hint that Tregs play a crucial role in autoimmune diseases and that their suppressive power could be used to treat people with those disorders.

"The field of Tregs has taken off like gangbusters," says Richard Insel, executive vice president of research for the Juvenile Diabetes Research Foundation (JDRF), a nonprofit funding organization based in New York City. "Resetting the immune system with Tregs rather than using immunosuppressive drug treatment is very attractive."

There are already several trials under way, with more planned, even though there is much disagreement among scientists over how best to identify and isolate Tregs.

"There are some who are negative about using Treg cells in the clinic," says Jeff Bluestone, an immunologist at the University of California, San Francisco, and head of a JDRF-funded center for Tregs. "Maybe I'm too optimistic, but I think we'll see clinical use of Tregs to treat autoimmune diseases."

Tregs were identified more than 20 years ago, but have yielded their secrets only in the past 5 years. Loosely categorized into two types, Tregs can rapidly suppress the activity of other immune cells.

'Natural' Tregs are produced in the thymus, a tiny organ located just behind the breast bone. These Tregs express signature proteins, including CD4, CD25 and Foxp3. The second category, 'adaptive' Tregs, develop by 'conversion' of normal T cells.

Exactly how either of these types of T cells suppresses the immune system is still unclear.

One trial in Germany is evaluating natural Tregs and another in Italy is testing the adaptive type. Both trials involve individuals at risk of graft-versus-host disease after receiving bone marrow transplants.

The same individual who donates the bone marrow for the transplants—and whose immune profile is compatible with the recipient's—would provide the Tregs.

In the German trial, the Tregs are given after the transplant recipient is taken off immunosuppressive drugs. These drugs minimize the risk of rejecting the transplanted bone marrow.

Although the trial is designed to test the safety of Tregs, the donor cells are a mixture of Tregs and normal T cells. "Only about half are actually Tregs," notes Matthias Edinger, one of the trial's lead investigators.

Transferring a mix of both Tregs and normal T cells runs the risk of triggering an immune response instead of suppressing it, because normal T cells tend to become activated when they encounter foreign molecules.

Paradoxically, using a mix of T cells is likely to help the marrow to graft effectively, notes Edinger, because the normal T cells might kill any residual cells from the recipient's own marrow.

The outcome of these two trials is likely to affect plans for testing Tregs for other diseases, such as juvenile diabetes.

"We want to wait and see if the data from the trials show that Tregs are safe," says Bluestone.

Tregs used to treat diabetes would have to be highly purified because normal T cells in the mix could destroy the critical insulin-producing beta cells.

For that reason, some researchers plan to use Tregs isolated from a different source, such as umbilical cord blood.

"Cord blood has the benefit of containing Tregs but not other T cells found in the normal blood," says Bluestone. Genetically modified designer Tregs, which would be uncontaminated by other T cells, would be an even more attractive option.

Because scientists are just beginning to understand how to purify and identify Tregs, these trials also pose a challenge for regulatory agencies. The US Food and Drug Administration is consulting researchers in the field but is allowing trials to proceed.

That's not entirely surprising. The FDA has for years allowed trials for other cell-based therapies, notes Insel. "If we [JDRF] don't take the risk, who will?"

Other experts are more cautious, pointing out that there are no set criteria yet for what cells should be injected into people.

"It really matters what the cells are," says Ethan Shevach, head of the Cellular Immunology Section at the US National Institute of Allergy and Infectious Diseases. But Shevach acknowledges that these concerns are unlikely to hold back the research, given the dearth of therapies for many of the diseases.

Parents of children with juvenile diabetes, for instance, "are well aware that therapy has not changed since the introduction of insulin," Shevach notes. "Perhaps this is a risk everyone is willing to take."

Douglas Braaten, New York

Unknown entity: Scientists are still struggling to define how regulatory T cells differ from other immune cells.

US National Cancer Institute