

Scientists develop new technique to selectively dampen harmful immune responses

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The human immune system is remarkably efficient, but sometimes its attack is misdirected, leading to allergies, autoimmune diseases and rejection of transplant organs and therapeutic drugs. Current immune suppressants have major drawbacks, but a team from The Scripps Research Institute (TSRI) has demonstrated a new technique that may lead to a better way to selectively repress unwanted immune reactions without disabling the immune system as a whole.

As a proof of principle, the study, reported online ahead of print on June 3, 2013, by the *Journal of Clinical Investigation*, focused on a problem faced by some hemophiliacs—rejection of a therapeutic replacement blood clotting protein.

One of the most common forms of [hemophilia](#), hemophilia A afflicts patients who don't have enough of a critical blood clotting protein called [Factor VIII](#). This deficiency can lead to potentially fatal, uncontrolled bleeding. Patients can take replacement Factor VIII as a biotherapeutic, but for about 20-30 percent of them, this is ineffective because their own immune systems attack the Factor VIII.

Current methods to thwart these unwanted immune attacks have severe drawbacks. One method aimed at reversing rejection of Factor VIII has been to give patients very large doses of the protein. But the treatment takes years and is prohibitively expensive. Other techniques, often used

for transplant and autoimmune patients, involve taking drugs that broadly compromise the [immune system](#).

In contrast, the new technique from TSRI selectively disables [immune cells](#) responsible for Factor VIII rejection, while leaving the rest of the immune system intact.

Harnessing B-Cells

In developing the new method, the scientists, led by James Paulson, chair of TSRI's Department of [Cell and Molecular Biology](#), exploited their knowledge of specialized cells of the immune system.

Both wanted and unwanted immune responses revolve around a few key components. An antigen—anything that the immune system detects as a problem—prompts the body to produce antibodies that will neutralize and destroy the antigen. B-cells, a type of white blood cell, are the source of these antibodies after coming in contact with specific antigens. The body has millions upon millions of different types of B-cells, each recognizing different antigens.

In addition to their role as antibody producers, B-cells also have receptors on their surfaces that recognize certain naturally occurring molecules that, when bound to the B-cells, initiate their destruction. This process, known as apoptosis, is part of a complex balancing act that allows the immune system to get rid of unneeded cells.

It's this mechanism of cell death that the team is putting to use. The researchers had been working with a specific glycan (type of sugar) that binds to a key B-cell receptor, called CD22, involved in suppressing B-cell activation and apoptosis. An earlier study in collaboration with Professor David Nemazee at TSRI showed potential for causing apoptosis of B-cells with a conjugate of the glycan to small molecule

antigens (haptens), but the method had not been applied to protein antigens.

"After we started, we realized the opportunity to exploit the receptor's natural function in ways that might be medically relevant," said Paulson.

Preventing Misguided Attacks

To explore the idea, the Paulson group worked with mice genetically altered to lack Factor VIII, which serve as a good model for hemophilia A.

Matthew Macauley, a senior research associate in Paulson's group, and colleagues treated the animals with tiny nanoparticles that included both Factor VIII and the glycan that binds with CD22. They found this combination selectively induce apoptosis in the B-cells that recognize Factor VIII. In this way, mice that had become "tolerized" to Factor VIII could be successfully treated with therapeutic Factor VIII to prevent bleeding.

By eliminating only these troublesome B-cells while leaving the vast majority of the B-cells intact, the researchers were able to prevent Factor VIII rejection without any negative side effects to the immune system.

"We're just taking advantage of a natural mechanism," said Macauley.

The team also conducted experiments that showed the technique prevented an unwanted [immune response](#) in mice for several months and may, under some circumstances, even lead to permanent tolerance. This would be a huge benefit if the technique can eventually be applied to humans.

One promising aspect of the new method is that the scaffold used to

deliver the necessary components, called liposomal nanoparticles, is already approved by the Federal Drug Administration for other uses. This means that eventual human testing could be vastly simplified. Several pharmaceutical companies have already expressed interest in the technique.

Future Research

In future studies, Paulson, Macauley and colleagues hope to extend the work, answering questions such as: Can the technique be adapted for use on individuals who have already been exposed to Factor VIII and whose "memory" B-cells have become involved in rejecting the drug? Can the researchers induce tolerance to the multiple antigens on transplanted organs that can lead to organ rejection? Is the technique applicable to more complicated conditions such as allergies and [autoimmune diseases](#) such as multiple sclerosis?

"We know that the issues are more complex," said Paulson, "But our technique, in combination with others, might work to address them."

In addition to Paulson and Macauley, authors on the paper, titled "CD22 induced B-cell tolerance prevents inhibitory antibodies to FVIII," are Fabian Pfrengle, Christoph Rademacher, Corwin Nycholat, Andrew Gale and Annette von Drygalski, all from TSRI.

More information: Antigenic liposomes displaying CD22 ligands induce antigen-specific B cell apoptosis, *J Clin Invest*.

doi:10.1172/JCI69187

Commentary: STALing B cell responses with CD22, *J Clin Invest*.

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