DNA 'reverse' vaccine reduces levels of immune cells believed responsible for Type 1 diabetes

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A clinical trial of a vaccine, led by Stanford University School of Medicine researchers and designed to combat type-1 diabetes, has delivered initially promising results, suggesting that it may selectively counter the errant immune response that causes the disease.

Several important findings of the multicenter, randomized, double-blind trial will be published June 26 in *Science Translational Medicine*. First, levels of a blood-borne proxy of insulin production were maintained—and in some cases increased—over the course of the 12-week dosing regimen. This indicates that those getting the vaccine may have suffered less ongoing destruction of beta cells, which produce and secrete the peptide hormone insulin after a meal, than those given placebo injections. (A peptide is a very short protein sequence.)

Second, blood levels of a specific group of immune cells that inappropriately home in on and destroy a protein found only on beta cells appear to have been selectively depleted in patients receiving the vaccine. No adverse effects, serious or otherwise, that could be attributed to the vaccine were observed.

"We're very excited by these results, which suggest that the immunologist's dream of shutting down just a single subset of dysfunctional immune cells without wrecking the whole immune system may be attainable," said Lawrence Steinman, MD, professor of

pediatrics and of neurology and neurological sciences at Stanford. Steinman is a renowned immunologist and multiple sclerosis specialist who treats patients at Lucile Packard Children's Hospital. "This vaccine is a new concept. It's shutting off a specific immune response, rather than turning on specific immune responses as conventional vaccines for, say, influenza or polio aim to do."

The results must be confirmed in larger trials of longer duration, cautioned Steinman, who holds the George A. Zimmermann Professorship. To date, no DNA vaccine has ever been approved for human use, and any likely application is several years off. The vaccine's observed beneficial effects began to drop off a few weeks after the 12-week vaccine-dosing schedule was discontinued, the study reports.

Type-1 diabetes is an autoimmune disease in which, for reasons that aren't completely understood, the immune system mounts an attack on beta cells. Insulin's job is to alert all of the body's cells to the presence of sugar and other nutrients in the blood.

Type-1 diabetes affects as many as 3 million Americans. While not as prevalent as type-2 diabetes—a similar condition arising when the body's cells fail to respond adequately to insulin—type-1 diabetes typically strikes at a much earlier age and necessitates a lifetime of multiple, daily insulin injections.

"This is the first demonstration of a DNA vaccine targeting type-1 diabetes in humans," said Richard Insel, MD, chief scientific officer of JDRF, formerly known as the Juvenile Diabetes Research Foundation.

A robust immune response is vital to defending the body against infectious microbes and incipient cancer, and attempts to treat autoimmune disease by globally suppressing the immune system have met with undesirable consequences. In this study, the researchers turned

instead to a targeted approach whose goal was to suppress only a small set of immune cells believed to be a fundamental driver of the attack on insulin-producing beta cells that causes type-1 diabetes.

Different cells make different proteins, and they display small fragments (peptides) of the proteins they make on their surfaces for inspection by roving immune cells on the lookout for "foreign" or "altered" peptide fragments. These patrolling immune cells, known to immunologists as CD8 cells, largely ignore so-called "self" peptides, which reflect proteins a healthy tissue ought to be making. But when confronted with suspicious peptide fragments, CD8 cells can mount an attack on the cell displaying them.

Any given CD8 cell has the ability to recognize and attack one or, at most, an extremely small group of cell-surface features. Beta cells are the only ones in the body that make insulin, which actually begins life as a precursor protein called proinsulin. Current thinking among immunologists holds that proinsulin peptide fragments dotting beta cells' surfaces may trigger attacks by misdirected CD8 cells.

Vaccines typically deliver proteins (or groups or sections of them) in a manner intended to fire up the immune response against, say, infectious organisms to which those proteins are unique. But this one consisted of DNA containing, instead, the gene coding for the proinsulin protein. Moreover, the vaccine was designed not to beef up the immune response to proinsulin, but to shut it down. Using an approach developed at Stanford by Steinman and his colleagues, the investigators tweaked a piece of DNA containing the proinsulin gene in a way that, they predicted, would cause a special class of immune cells ingesting the vaccine to deliver an anti-inflammatory signal to CD8 cells targeting proinsulin—and to those cells alone.

The scientists incorporated the modified genetic material into rings of

DNA and administered weekly intramuscular injections of the resulting candidate vaccine for 12 weeks to 80 patients who had been diagnosed with type-1 diabetes and were receiving insulin replacement therapy injections. They gave four different doses of the vaccine to four patient groups and placebo injections to a fifth. (After the course of weekly injections concluded, placebo recipients had the option of undergoing a 12-week regimen of weekly dosing with the vaccine.)

The investigators didn't measure resulting blood levels of insulin, which spike widely and can lead to spurious measurements. Instead, they measured levels of C-peptide, a chunk of proinsulin that gets chopped off when insulin is carved out of the proinsulin molecule. C-peptide remains in circulation far longer than insulin, so it serves as an excellent proxy for insulin production by pancreatic beta cells. There are also hints in the medical literature that C-peptide may have beneficial effects in staving off or reducing some of the long-term consequences of diabetes, such as damage to the eyes, kidneys and peripheral nerves.

Patients' C-peptide levels and other blood components of interest were evaluated at baseline and at five and 15 weeks and six, nine, 12, 18 and 24 months after starting on the vaccination regimen. Each time, blood was drawn 30, 60, 90 and 120 minutes after patients drank a modified milkshake.

Blood samples were preserved and sent to the lab of Bart Roep, MD, PhD, the study's lead author and a professor of immunology at the Leiden University Medical Center in the Netherlands. Roep used a sensitive approach for detecting small numbers of proinsulin-targeting immune cells in the blood. This method was based on a technique pioneered in the 1990s by Mark Davis, PhD, professor of microbiology and immunology and director of Stanford's Institute for Immunity, Transplantation and Infection. Roep found that levels of proinsulin-targeting CD8 cells—but not other CD8 cells or other types of immune

cells in patients' blood—were substantially depleted in patients getting doses of the vaccine, compared with those getting placebo injections.

"Individuals with preserved C-peptide are at lower risk of long-term eye, kidney and nerve complications," said JDRF's Insel. "So it's intriguing that in this study, C-peptide levels were preserved or, at times, increased while patients were receiving the vaccine." Although Insel wasn't directly involved in the trial, JDRF helped to fund it and at one point held a royalty position in the vaccine. (Another funding source was the Iacocca Family Foundation.)

More information: "Plasmid-Encoded Proinsulin Preserves C-Peptide While Specifically Reducing Proinsulin-Specific CD8+ T Cells in Type 1 Diabetes," by B.O. Roep, *Science Translational Medicine*, 2013.

Provided by Stanford University Medical Center

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