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Gene Provides Clues To Development of Type 1****TAKING ANTIBODY ORALLY MAY
HELP BLOCK DIABETES**

An injected antibody already in clinical trials to prevent type 1 diabetes may offer protection if taken by mouth, researchers at Harvard Medical School have found. The discovery, made in diabetic mice, suggests that taking the compound orally could induce immune tolerance and potentially make the therapy more effective than if given by injection.

Anti-CD3 antibodies are currently being tested in several human clinical trials, some with JDRF support. In all of these studies, however, the antibody is injected into the patient like most conventional vaccines. The Harvard researchers found that feeding the vaccine to mice prone to diabetes appeared to reduce the chance of disease onset.

The study, led by Hiroki Ishikawa in the laboratory of Howard Weiner, is reported in the journal *Diabetes*.

Taking an antibody by mouth modifies a different part of the immune system, exploiting a phenomenon known as “mucosal tolerance.” When a substance is ingested, the immune system adapts to tolerate it; this is thought to be how the body avoids overreacting to harmless food proteins and bacteria. The primary interface between our bodies and pathogens such as viruses and bacteria are mucosal surfaces, and the immune system has evolved unique ways to respond to agents administered by this route.

The exact mechanisms of how the body adjusts its immune response are unclear, but some scientists think oral exposure to the substance impacts the function of regulatory T cells, which act as a brake on the immune system.

The Harvard researchers got the idea for oral administration of anti-CD3 antibodies for diabetes after discovering that this approach suppresses another immune reaction—acute experimental autoimmune encephalomyelitis—in mice. The EAE mouse is a model for human multiple sclerosis, another autoimmune disease.

The scientists think ingested anti-CD3 antibodies move quickly to the intestinal tract, where they induce regulatory T cells to proliferate. Previous studies have suggested that type 1 diabetes may be triggered partly by events in the intestinal tract, so the presence of regulatory T cells at this site could have a powerful effect.

The Harvard researchers found that giving anti-CD3 orally blocked type 1 diabetes, depending on the stage of disease progression. Therefore, oral administration of this therapy either alone or following anti-CD3 injection could potentially be used to optimize the treatment.

**STOPPING ISLET INFLAMMATION
MAY BE KEY FOR TYPE 1 PREVENTION**

JDRF-funded researchers in Boston have developed a therapeutic cocktail that blocks the autoimmune attack in mice and also prevents islet inflammation. Use of this treatment may increase the effectiveness of therapies aimed at preventing type 1 diabetes in newly diagnosed patients.

Researchers have succeeded in modifying the immune response—first in mice and now in human clinical trials—and slowing the progression of diabetes, with the use of anti-CD3 antibodies, among other compounds. But they have failed to restore normal blood sugar control, even in mice, with this treatment alone. One reason is that islet inflammation resulting from the autoimmune attack seems to impair the ability of the body’s tissues to use insulin properly.

Because of this, some scientists conclude that a more successful prevention strategy may be to induce immune tolerance while simultaneously suppressing inflammation. This multi-pronged approach requires a combination therapy of several agents working together.

The JDRF researchers, led by Maria Koulmanda in the laboratory of Terry Strom at Harvard Medical School, used a “triple therapy” regimen on nonobese diabetic mice, an animal model for type 1 diabetes. The therapy consisted of three agents (rapamycin, IL-2.Ig, and mutIL-15.Ig) working in combination.

Rapamycin is a potent immunosuppressive agent, and IL-2.Ig and mutIL-15.Ig are engineered “fusion proteins” designed to promote the destruction of the T cells that attack islets. The addition of mutIL-15.Ig to the cocktail is innovative, as it is thought to reduce inflammation indirectly by blocking the effects of a signaling molecule that spurs another molecule to promote inflammation.

This three-drug cocktail halted the autoimmune destruction of insulin-producing cells and restored normal blood sugar control in the mice. There was no increase in beta cell mass or insulin levels in the blood, suggesting that the absence of inflammation was a significant factor in restoring control of glucose levels.

The study is published in *Proceedings of the National Academy of Sciences*.

GENE PROVIDES CLUES TO DEVELOPMENT OF TYPE 1

JDRF-funded researchers in the U.K. and Florida have found a correlation between a type 1 diabetes susceptibility gene and lower concentrations of a biomarker in the blood of people with type 1 diabetes. The discovery will help researchers clarify a possible mechanism causing the autoimmune attack leading to diabetes.

The finding, based on a large-scale analysis of samples from people with type 1 diabetes, strengthens the evidence that risk for the disease is tied to the gene controlling IL2RA, a receptor on the surface of immune cells that plays a vital role in proper immune functioning. The research establishes a link, in people, between type 1 risk and lower levels of the IL2RA protein, a biomarker for immune activation.

This research is an example of connecting a gene variant with the pathway it controls. The work is reported in the journal *Nature Genetics* by Christopher Lowe and Jason Cooper, and colleagues in the Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation laboratory, co-directed by Linda Wicker and John Todd, as well as collaborators from the University of Florida.

The potential mechanism for how IL2RA affects disease risk was suggested earlier this year by a study in mice. In the animal, susceptibility to diabetes is due partly to reduced production by immune T cells of the mouse form of the signaling protein that binds to the receptor mIL2RA.

The mouse study showed that when the gene for this protein, mIL-2, is defective, an essential subset of immune cells—regulatory T cells—do not develop properly and fail to perform their role of preventing autoimmune attack on the insulin-producing cells in the pancreas. Now the new research with human genes points toward the same pathway.

When the IL2RA protein on the surface of the immune cell binds the signaling protein IL-2, the receptor is released into the blood, where it can be measured by researchers. They found that people at risk for developing type 1 risk have lower levels of that protein. This suggests some versions of the IL2RA gene may produce insufficient levels of the receptor. Researchers now will try to answer the question: In humans, is there something interfering with the proper interaction between IL-2 and IL2RA that prevents regulatory T cells from developing properly?

One important aspect of the study is that it links a gene variant with an observable physical trait—in this case, IL2RA protein levels in the body. This points researchers in the right direction, allowing them to narrow their search.

“Genetics gives you an anchor to the biology,” says Marie Nierras, Ph.D., JDRF Director of Partnerships and Consortia. “Knowing that a gene is associated with a disease tells you that a pathway controlled by the gene has to be involved. You’re able to get closer to understanding how the whole thing works without getting distracted by other factors that are often changing.”