Researchers find molecule that prevents Type 1 diabetes in mice

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Researchers at the University of Colorado School of Medicine have found a specific molecule that can prevent the development of type 1 diabetes in mice and has a similar effect on human cells from diabetic patients.

The findings, published in the latest edition of The *Journal of Immunology*, signal a new and promising direction in the fight against type I diabetes along with other autoimmune disorders like rheumatoid arthritis, multiple sclerosis and celiac disease.

Aaron Michels, MD, an assistant professor of pediatrics and medicine, working with George Eisenbarth., MD, Ph.D., executive director of the Barbara Davis Center for Childhood Diabetes at the CU School of Medicine, tested a series of molecules before finding one that stopped diabetes from developing in mice bred to get the disease.

"We found that when you put specific molecules into specific structural pockets you can block the formation of diabetes," said Eisenbarth. "We are basically throwing a monkey wrench into the machinery."

The researchers were looking for small molecules capable of occupying pockets along a protein binding groove. Some of the molecules got into these pockets and inhibited the presentation of insulin to immune cells while others enhanced it.

Type 1 diabetes is characterized by the body's inability to manufacture

insulin because its own immune system is attacking it. The incidence of the disease has doubled in each of the last two decades.

Michels and Eisenbarth found that the compound Glyphosine enhanced insulin presentation and prevented diabetes in mice genetically modified to develop type 1diabetes. It had the same effect on human cells. The mice remained disease-free as long as they received daily injections of the compound. It was not as effective on mice that already had diabetes.

The molecules used in the research were obtained with the assistance of the University of Florida College of Medicine in Gainesville.

"Our role was to screen a large chemical library to identify drug candidates for prevention of type 1 diabetes," said David Ostrov, Ph.D., associate professor of pathology, immunology and laboratory medicine at the University of Florida. "We developed a novel screening method that pinpoints very specific areas of a protein that is genetically associated with type 1 diabetes."

Using a supercomputer, Ostrov's lab ran tests on 139,735 drug candidates to see which were most likely to bind on the four critical pockets of the protein.

"Not only does this provide a new way to change specific immune responses in a manner that is beneficial for diabetes, this shows that we may be able to modify specific immune responses for other autoimmune diseases," Ostrov said. "This is also relevant to cancer and infectious diseases where it would be beneficial to modify specific immune responses rather than in a general way."

Michels said that based on the two and a half year study, it would be feasible to genetically screen individuals likely to develop type 1 diabetes and begin a therapy regimen using these compounds to prevent

the onset of the disease. Right now, doctors can predict who will get type 1diabetes about 90 percent of the time.

"This technique would also apply to other autoimmune disorders like arthritis and celiac disease," Michels said. "The principals are the same."

The next step is to focus specifically on human cells to try and develop new therapies for clinical use. That could be at least five years away.

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