University of Miami
Miller School of Medicine

News

UM Researchers Awarded Grants to Find Treatments and Cure for Type 1 Diabetes

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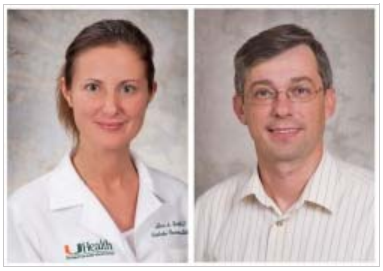

Alice Tomei, Ph.D., and Peter Buchwald, Ph.D.

Two University of Miami Miller School of Medicine researchers have been awarded funding from the Iacocca Foundation, a nationally renowned organization committed to funding innovative research in the hopes of finding a cure for type 1 diabetes.

The one-year grants were awarded to Alice Tomei, Ph.D., research assistant professor in the DeWitt Daughtry Family Department of Surgery, Division of Cellular Transplantation, and the Diabetes Research Institute (DRI), and Peter Buchwald, Ph.D., associate professor in the Department of Molecular and Cellular Pharmacology, and Director of Drug Discovery at the Diabetes Research Institute.

Type 1 diabetes, also known as juvenile diabetes or insulin-dependent diabetes, is an autoimmune disorder in which the body does not produce insulin, the hormone necessary for the body to metabolize sugar. Without insulin, sugar cannot move from blood into the cells, causing the blood sugar to rise above a safe level and leaving cells without the ability to function properly. It is a lifelong disease with many complications, and both Tomei and Buchwald are pursuing promising research to better understand, and eventually cure, the disorder.

Tomei's research aims at unraveling novel mechanisms contributing to the triggering of autoimmune diabetes, which would be an important first step in developing immunoengineered therapeutics to counteract its development. The grant will allow Tomei to study the protective role of the CCL21 lymphoid chemokine, and of tolerogenic lymphoid stromal cells when they are localized in beta cells, the main target of autoimmunity.

"In autoimmune diseases, like type 1 diabetes, immunological tolerance toward self is lost, which allows the immune system to attack and destroy organs and cells, like insulin producing cells in the pancreas in the case of diabetes," said Tomei. "Currently there are no means to restore self-tolerance in patients with autoimmune diseases, unlike in cancer where tumor cells are able to induce tolerance toward themselves. In order to exploit that strategy for type 1 diabetes and other autoimmune diseases, we need to understand what causes the tumor to build tolerance toward itself."

In earlier research published in *Science*, Tomei reported that tumor cells trigger our immune system and induce tolerance by secreting the CCL21 molecule, which is naturally present in lymph nodes and other lymphoid organs. "The tumors create a lymph node-like environment where immune cells are shifted toward a regulatory phenotype. In such an environment, tumor cells escape immune destruction and grow undisturbed. Our idea was to utilize the same strategy – engineered local secretion of CCL21 in target cells – to

prevent destruction of beta cells in type 1 diabetes," said Tomei, who credits the assistance of her mentor, Alberto Pugliese, M.D., professor of medicine, immunology and microbiology, and Head of the Immunogenetics Program at the DRI.

Tomei's background is in material and biological engineering. Her primary research at the DRI is in engineering immunoprotection of islet transplants via islet immunoisolation and local immunomodulation. Her research findings have been published in some of the most prestigious peer-reviewed scientific journals.

The corresponding work in Buchwald's research group focuses on potentially reversing recently diagnosed cases of type 1 diabetes. "Our main intention with this treatment is to prevent or revert new-onset cases in patients who have just become diabetic, or have a family history, and are very likely to become diabetic," said Buchwald.

He will be investigating the therapeutic potential of modulating Smad7, a regulator of the TGF-β pathway, using an agent that is in advanced clinical trials for the treatment of inflammatory bowel disease. In a pilot study, Buchwald and his co-workers achieved encouraging results in non-obese diabetic (NOD) mouse model, a widely used animal model of this disease. "We obtained long-term reversal in about 60 percent of the mice treated only after onset of diabetes," he said.

Now, the research will move toward more detailed exploration of the dosing and timing requirements of the potential therapeutic agent, as well as toward clarifying details of the mechanism of action.

"Ultimately, it would mean starting to treat patients as soon as they notice that they are diabetic, treat them for a few years, and then, hopefully, treatment will not be needed for their whole life, as this may be enough to restore immunological self-tolerance and prevent further destruction of insulin-producing cells," Buchwald said.

Buchwald is directing the DRI's efforts to develop safer and more effective drugs for diabetes prevention and for islet replacement therapies. He has worked in multidisciplinary fields related to drug design and development both in the academic and industrial settings and has published numerous articles in peer-reviewed journals.

Camillo Ricordi, M.D., the Director of the Diabetes Research Institute and Cell Transplant Program, said he is grateful to the Iacocca Foundation for their leadership and commitment to fund cure-focused research.

"The two projects supported at the DRI represent highly innovative approaches on the path to immunomodulation and tolerance induction, to eliminate the autoimmune condition associated with type 1 diabetes. Both proposed strategies have a high translational potential and very promising preliminary results that make us hopeful for their likelihood for success," said Ricordi, who is also the Stacy Joy Goodman Professor of Surgery, Distinguished Professor of Medicine, and professor of biomedical engineering, and microbiology and immunology. "Importantly, modulation of Smad7 is already entering Phase III trials for treatment of another autoimmune condition, Crohn's disease, with very promising results emerging from the initial clinical trials. We are obviously very excited to be able to explore the relevance of this strategy on the path to cure type 1 diabetes."