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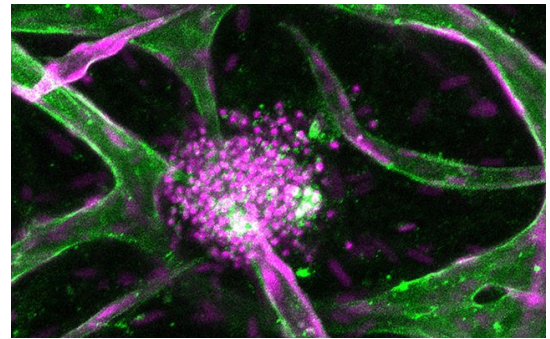
UC San Diego Receives \$9 Million in Grants to Pinpoint Cellular Cause of Type 1 Diabetes

University of California San Diego School of Medicine researchers have been awarded nearly \$9 million to fund two multi-institutional research projects that use human pluripotent stem cells, CRISPR and human organoids to dissect beta cell defects and create a human cell model of type 1 diabetes aimed at identifying the elusive cellular actions leading to disease onset.

“We are using technology that, for the first time, allows us to create human conditions that mimic type 1 diabetes in a culture dish in order to understand the mechanism or genes by which beta cells are killed,” said Maike Sander, MD, professor in the departments of Pediatrics and Cellular and Molecular Medicine at UC San Diego School of Medicine and co-principal investigator on both grants. “Our hope is that we can generate the information we need to eventually make beta cells survive in people living with type 1 diabetes.”

Two multi-year special statutory grants from the National Institute of Diabetes and Digestive and Kidney Diseases, part of the National Institutes of Health (NIH), help build on ongoing research into type 1 diabetes, an autoimmune disease that destroys pancreatic beta cells and affects more than 1 million people in the United States. Pancreatic beta cells, found in groups called islets of Langerhans, help maintain normal blood glucose levels by producing the hormone insulin — the master regulator of energy (glucose). Impairment and the loss of beta cells reduces insulin production, leading to types 1 and 2 diabetes.

A \$3.8 million grant funds work co-led by Sander and Kyle Gaulton, PhD, assistant professor in the Department of Pediatrics and the Pediatrics Diabetes Research Center, to decipher the function of genes associated with genetic risk for type 1 diabetes using a high resolution reference map of pancreatic cells. Sander, Gaulton and colleagues are designing the map after receiving an [NIH grant in 2018](#).



In a multi-institutional research project, UC San Diego School of Medicine researchers have teamed up to create a human cell model of type 1 diabetes that includes a vascularized human pancreatic islet in a dish. Pictured are blood vessels in green and islets (cell nuclei) in magenta.

“A unique aspect of this project is to determine how pancreatic beta cells are affected in type 1 diabetes through a combination of both your genes and your environment,” said Gaulton, who brings expertise in genetics and genomics of diabetes into the project. “Our goal is to identify genes that protect beta cells from immune responses that occur during the development of type 1 diabetes, and which may represent novel therapeutic targets in preventing disease onset.”

After identifying genes associated with beta cell function, the team, including Prashant Mali, PhD, assistant professor in the Department of Bioengineering at UC San Diego Jacob School of Engineering, Wenxian Fu, PhD, assistant professor in the Department of Pediatrics and the Pediatric Diabetes Research Center, and Graham McVicker, PhD, assistant professor at the Salk Institute, will use CRISPR to validate which genes are promoting cell survival and which are causing cell death.

This information can then be tested using an islet-on-a-chip (human organoid) being developed with the second \$5.1 million NIH grant to study the immune attack on beta cells in the dish. Human organoids are miniaturized, 3D versions of an organ.

In this case, human induced pluripotent stem cells (hiPSC) from persons with type 1 diabetes are converted into beta cells and supporting cells in the lab to create the human islet organoid. Sander is collaborating with Karen Christman, PhD, professor in the Department of Bioengineering, Luc Teyton, MD, PhD, professor in the Department of Immunology and Microbiology at Scripps Research, Steven George, MD, PhD, professor in the Department of Bioengineering at UC Davis, and Christopher C.W. Hughes, PhD, professor in the Department of Molecular Biology and Biochemistry at UC Irvine.

At UC Irvine, the Hughes lab has created an organ chip that allows living blood vessels to provide nutrients to tissues growing in the lab.

“We are growing human islets in culture that are supported (that is, fed) by perfused human blood vessels. All organs in the body receive their nutrients through blood vessels and we are capturing this process in the lab,” said Hughes. “Under these conditions, we expect the islets to behave much more like they do in the body than if we had grown them using standard procedures, which have not changed much in the last 30 years.”

Immune cells from the blood of the same person whose hiPSC were used to induce beta cells in the human organoid will be fed into the organoid to watch the immune system response to the beta cells.

“We will activate and deactivate genes we think are involved in whether beta cells live or die. We want to know what causes the attack on beta cells because no one has been able to identify it,” said Sander, who is also director of the Pediatric Diabetes Research Center, co-director of the Center on Diabetes in the Institute of Engineering in Medicine and a member of the Sanford Stem Cell Clinical

Center. “We recognize that people who are living with type 1 may still have beta cells. If we can rescue those cells we may be able to help with blood glucose management and provide a clinical improvement.”

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