Engineered T cells for type 1 diabetes move closer to clinic

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Dr. Jane Buckner of the Benaroya Research Institute at Virginia Mason and Dr. David Rawlings at Seattle Children's Research Institute are leading research to develop an engineered T-cell therapy for type 1 diabetes. Credit: Seattle Children's

For much of the last decade, Dr. David Rawlings, director of Seattle Children's Research Institute's Center for Immunity and

Immunotherapies, has dreamed of developing a therapy for children with type 1 diabetes that doesn't involve insulin injections but uses a person's own immune cells to target and treat the disease.

Now, new research and a fresh infusion of funding bring this dream closer to reality, and nearer to opening a first-in-human clinical trial of an experimental therapy at Seattle Children's in collaboration with research partner Benaroya Research Institute at Virginia Mason (BRI).

"What started as a dream is now within reach," Rawlings said. "My hope is that our research will lead to a new treatment that turns off the destructive immune response leading to development of type 1 diabetes in children."

The immune system's imbalance in diabetes

The research led by Rawlings, who is also the Division Chief of Immunology at Seattle Children's and a professor of pediatrics and immunology at the University of Washington School of Medicine, along with co-investigator Dr. Jane Buckner, president of BRI, focuses on T cells, the immune system's disease-fighting white blood cells.

In type 1 diabetes, specific types of immune cells called effector T cells mistakenly attack insulin-producing islet cells in the pancreas. The job of these islet cells is to sense when glucose levels are rising in the bloodstream and to respond by releasing insulin.

The attack continues because other components of the immune system, regulatory T cells (Treg), do not function normally.

"A healthy immune system requires regulatory T cells to balance the attack of effector T cells," Rawlings said. "Regulatory T cells tell the effector T cells to calm down and limits damage to tissues like the

pancreas."

Once destroyed by the unchecked effector T cells, the islet cells can't release insulin. Glucose levels in the bloodstream then rise unabated, causing the early symptoms of diabetes such as frequent urination, unquenched thirst, insatiable hunger and extreme fatigue.

Novel engineered T cells offer a way to restore balance in the pancreas

To stop this attack, Rawlings' lab devised a way to genetically engineer a patients own T cells, so they function like normal Treg. The hope is that when transferred back into the patient, these engineered or edited regulatory-like T cells (edTreg) enter the pancreas, where they can help to suppress the overactive immune response, sustaining and protecting the function of the islet cells.

A paper published in *Science Translational Medicine* shows how the research team used gene editing techniques to target the FOXP3 gene in human T cells. By turning on FOXP3, they equipped the T cells with the instructions needed to specialize into Treg.

The resulting edTreg looked very similar to natural Treg. They also functioned like natural Treg when tested in both animal models and tissue cultures. Finally, researchers demonstrated how they could make the engineered cells antigen-specific. According to Rawlings, this feature, which is accomplished by attaching a T-cell receptor to the surface of the engineered cell, will be critical to targeting the cells to the pancreas in a diabetic patient.

Further research to validate these results will help pave the way for a phase 1 clinical trial of a type 1 diabetes cell therapy.

"This data offers the first proof that engineering by way of turning on FOXP3 is sufficient to make a functional Treg-like cell product," he said. "Not only is it a landmark research finding, but it's directly translatable to clinical use."

New funding continues promising research

Much of the research to develop the edTreg has been funded through a combination of industry sponsored agreements and generous philanthropic support from The Leona M. and Harry B. Helmsley Charitable Trust.

Most recently, the Helmsley Charitable Trust awarded a new $4 million grant to Seattle Children's and BRI to continue the diabetes research.

The grant builds on $3 million in prior funding from the Helmsley Charitable Trust and an ongoing research collaboration between the two research programs. In this next phase, the teams will work to fine tune the T-cell receptor used for the edTreg and enhance the manufacturing process used to generate the edTreg for clinical use.

"Our collaboration with BRI combines their broad expertise in finding and testing T-cell receptors from diabetic patients with our novel technology to engineer the T cells," Rawlings said.

The best T-cell receptor will direct the edTreg to the pancreas and turn on their protective activity and, ideally, will also work for the greatest number of type 1 diabetes patients.

"We want to identify T-cell receptors that will create engineered Treg that will go to and protect the pancreas. This type of therapy could then be used to stop the destruction of cells that produce insulin in the pancreas to slow the progression and ultimately prevent type 1 diabetes,"

said Buckner of BRI.

A dream within reach

Rawlings says the newly-funded studies will help them to establish the final cell product and key information required to establish a first-in-patient clinical trial.

He's optimistic that the 3-year grant will give them the opportunity to complete the preclinical studies and study design required to submit an Investigational New Drug Application to the U.S. Food and Drug Administration for the approval to open a phase 1 clinical trial at Seattle Children's and BRI.

"This is a novel technology that no other lab in the world is pursuing and that has potential major advantages over Treg therapies being studied elsewhere," Rawlings said. "I think some in the field questioned whether our approach would actually work, and so it's gratifying to not only have proof that it works, but to continue to generate data showing just how remarkably well it works."

More information: Y. Honaker el al., "Gene editing to induce FOXP3 expression in human CD4+ T cells leads to a stable regulatory phenotype and function," *Science Translational Medicine* (2020). stm.sciencemag.org/lookup/doi/ … scitranslmed.aay6422

Provided by Seattle Children's Research Institute