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Study validates Type 1 diabetes computer model's predictive success through lab testing

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A La Jolla Institute team, led by leading type 1 diabetes researcher Matthias von Herrath, M.D., has demonstrated the effectiveness of a recently developed computer model in predicting key information about nasal insulin treatment regimens in type 1 (juvenile) diabetes. Development of the software, the Type 1 Diabetes PhysioLab Platform, was funded through the peer-reviewed grant program of the American Diabetes Association.

The findings, which also showed the platform's ability to predict critical type 1 diabetes molecular "biomarkers," were published in the December issue of the scientific journal *Diabetes*, and further validate the importance of the new model as a valuable research tool in type 1 diabetes. The software is designed to enable researchers to rapidly streamline laboratory research through the evaluation of alternative scenarios for therapeutic strategies that show the most promise for working in humans.

"Since laboratory studies can cost hundreds of thousands of dollars, and early stage human clinical trials can cost $10 million dollars or more, predicting the right conditions to try is important," said Dr. von Herrath, director of the Type 1 Diabetes Research Center at the La Jolla Institute for Allergy & Immunology, where the studies were conducted.

"We've found that using this in silico (computer analysis) prediction platform can quicken the pace and effectiveness of type 1 diabetes research," he continued. "By allowing us to pre-test our theories in

computer models, we can ensure that the more time-intensive and costly process of laboratory testing is focused on the most promising therapeutic strategies, with the greatest chance of success."

The platform, developed by Entelos Inc., a life sciences company specializing in predictive technologies, has previously been shown to successfully predict various data from published type 1 diabetes experiments. Dr. von Herrath's team used a different approach to test the model, asking it to predict the outcome of a hypothetical experiment on nasal insulin dosing frequency in animal models that had not yet been performed. The prediction was then tested in the laboratory, where its results were confirmed.

In addition, he said, the model was able to accurately identify the particular time frame at which key type 1 diabetes "biomarkers" kicked in. Biomarkers are specific cell types or proteins that tell researchers at what point a therapeutic option is working or when it is time to start treatment. In the case of the La Jolla Institute study, the model successfully predicted the onset of biomarkers indicating beta cell protection in the NOD mouse.

"The model accurately predicted that implementing a low frequency nasal insulin dosing regimen in animal models was more beneficial in controlling type 1 diabetes than a high frequency regimen," said Dr. von Herrath, noting that the software's prediction of the biomarkers was key in this process. "These results confirmed our hypotheses on the benefits of low-frequency nasal insulin dosing. But even more importantly, the advantage of applying computer modeling in optimizing the therapeutic efficacy of nasal insulin immunotherapy was confirmed."

The results were reported in the paper "Virtual Optimization of Nasal Insulin Therapy Predicts Immunization Frequency To Be Crucial for Diabetes Protection." Dr. von Herrath was senior author on the paper

and La Jolla Institute scientist Georgia Fousteri, Ph.D., and Jason Chan, Ph.D., from Entelos' R&D group, were first co-authors.

The Type 1 Diabetes PhysioLab® Platform is a large-scale mathematical model of disease pathogenesis based on non-obese diabetic (NOD) mice. The platform was developed with input from an independent scientific team of leading type 1 diabetes experts. The research support group of the American Diabetes Association funded the work of the software's development to provide a new scientific tool for enhancing the speed and effectiveness of type 1 diabetes research.

More than 400,000 children worldwide suffer from type 1 diabetes, a chronic disease that can lead to severe complications, such as blindness, cardiovascular disease, renal disease, coma or even death.

The platform, developed over two years, simulates autoimmune processes and subsequent destruction of pancreatic beta cells from birth through frank diabetes onset (hyperglycemia). The destruction of insulin-producing beta cells in the pancreas is the underlying cause of type 1 diabetes.

Specifically, Dr. von Herrath's team employed the model to investigate the possible mechanisms underlying the effectiveness of nasal insulin therapy, using the B: 9-23 peptide. "The experimental aim was to evaluate the impact of dose, frequency of administration and age at treatment on key molecular mechanisms and optimal therapeutic outcome," he said.

Using parameters input by the scientific team, the model accurately predicted that less frequent doses of nasal insulin, started at an early disease stage, would protect more effectively against beta cell destruction than higher frequency doses in NOD mice.

Dr. von Herrath added that the positive results add credence to the idea of creating computer models for analyzing therapeutic interventions in human disease. "These results support the development and application of humanized platforms for the design of clinical trials," he said.

Provided by La Jolla Institute for Allergy and Immunology