Scripps Research

Repurposed cancer drug holds potential for innovative diabetes treatment

A study led by Calibr scientists reveals that an FDA-approved cancer therapy can protect insulin-producing beta cells.

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LA JOLLA, CA – Scientists at **Calibr**, the drug development arm of Scripps Research, have found what may be the beginnings of a new approach to treating diabetes. And they found it in an unexpected place: a drug that's currently used for a form of breast cancer.

The discovery has jumpstarted efforts to refine the drug for non-cancer diseases and highlights the value of assessing approved medicines for unexpected therapeutic benefits. The study appears in ***Nature Communications***.

"The speed of the translation and early proof-of-concept in animals was perhaps the most exciting part of the project," says **Matthew Tremblay, PhD**, chief operating officer of Calibr and Scripps Research, and a senior author of the study. "We were able to find a compound very quickly that we could deploy as a tool in mouse models of diabetes. And because the drug already has FDA approval, we were able to understand its selectivity and pharmacology very readily to drive the program in a preclinical setting."

The drug, neratinib, was shown to protect insulin-producing beta cells in the pancreas. The loss of these cells is a hallmark of both forms of diabetes: type 1, an autoimmune disease that typically emerges early in life; and type 2, the adult-onset form influenced by both genetics and lifestyle. Neratinib is already widely used as a targeted drug for early stage breast cancer, with efficacy for patients whose tumors test positive for the HER2 gene.

Tremblay says the discovery came about through a collaboration facilitated by **JDRF** (formerly the Juvenile Diabetes Research Foundation), a nonprofit organization dedicated to finding a cure for type 1 diabetes. As part of a platform partnership, JDRF has introduced Calibr to researchers across the globe to translate innovative discoveries into potential new medicines.

The work described in *Nature Communications* is the result of Calibr's partnership with **Kathrin Maedler, PhD**, Amin Ardestani, PhD, and their colleagues at the University of Bremen in Germany. The team uncovered that an enzyme known as MST1, which controls cell development and survival, played a key role in activating cell signals that lead to the death or dysfunction of pancreatic beta cells.

The researchers believed that if they could find a way to block or reduce those damaging signals, they may be able to protect beta cells and stave off diabetes. Through prior work together, JDRF was aware of Calibr's unique drug-repurposing and translational capabilities.

"Dr. Maedler came to us with an actionable approach for diabetes," Tremblay says. "We brought the drug discovery tools to bear, and rapidly found a chemical inhibitor of this particular mechanism that appears to play a key role in the development of disease."

More than 422 million people globally have diabetes, according to the World Health Organization, and an estimated 1.6 million deaths were attributed to the disease in 2016. It is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation.

Calibr identified neratinib using high-throughput screening of drug compounds known as kinase inhibitors, which are often used to treat cancer but also have other therapeutic properties.

Calibr and University of Bremen found that treating diabetic mice for 30 days with neratinib markedly restored beta cell survival and function and prevented severe increases in blood glucose over time. A robust pro-survival effect was also observed in human islets, which are areas of the pancreas that contain beta cells. Prior to the study, neratinib's ability to inhibit MST1 signaling and protect beta cells was not known.

Though the research is just now being published, most of the work was completed before 2017. Calibr has since focused on optimizing neratinib's properties for diabetes and other chronic degenerative diseases. This means letting the drug's anti-cancer properties fall away and diminishing gastrointestinal side effects, among other things.

"For chronic, non-terminal diseases where treatment is prolonged, the side effect profile must be pristine," says **Weijun Shen, PhD**, Calibr's director of metabolic disease and a senior author of the study.

Notably, this project served as one of several inspirations for Calibr in 2018 to build and deploy its **ReFRAME drug repurposing collection**, an extensive library of nearly all existing, safe small-molecule drugs shown to be appropriate for direct use in humans. The collection offers great potential for finding therapies more quickly and cost-effectively.

"Repurposing of FDA-approved drugs has been a topic of great interest amidst the escalating costs of new drug development, particularly in the case of diseases with high-unmet medical need," such as type 1 diabetes, the authors say in the study.

The discovery of neratinib's ability to protect beta cells "amounts to an accelerated path to a preclinical proof of concept" and a firm basis for follow-up work on next-generation compounds that could add to the treatment options for diabetes, they conclude.

*Authors of the article "**Neratinib protects pancreatic beta cells in diabetes**," include Amin Ardestani, Sijia Li, Karthika Annamalai, Blaz Lupse, Shirin Geravandi, Aleksandra Dobrowolski, Shan Yu, Siying Zhu, Tyler D. Baguley, Murali Surakattula, Janina Oetjen, Lena Hauberg-Lotte, Raquel Herranz, Sushil Awal, Delsi Altenhofen, Van Nguyen-Tran, Sean Joseph, Peter G. Schultz, Arnab K. Chatterjee, Nikki Rogers, Matthew S. Tremblay, Weijun Shen and Kathrin Maedler.*

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