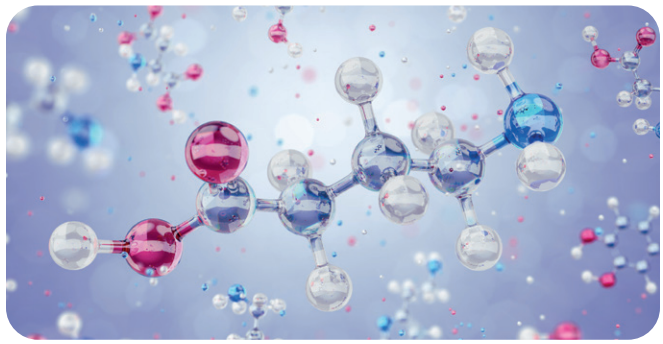
Artemisinins target $GABA_A$ receptor signaling and impair α cell identity

Type 1 diabetes is caused by autoimmune destruction of pancreatic β cells and has a profound impact on the lives of the millions of individuals worldwide who are living with the disease. Prior to the development of insulin therapy in the early 1920s, it was often fatal. Modern technology, including insulin pumps, has made Type 1 diabetes management more convenient, but it still remains expensive and oftentimes reduces quality of life.

An ideal solution would involve replenishment of the body's original pancreatic β cell mass, which could produce endogenous insulin rather than a patient remaining reliant on exogenous sources. With this goal in mind, regenerative medicine researchers have made significant progress toward the generation of new insulin-producing cells, through the discovery of transdifferentiation potential of related pancreatic cell types.

While the primary role of pancreatic β cells involves generation of insulin, which is intended to lower blood sugar, their counterpart α cells are responsible for producing glucagon. Glucagon is a glucoregulatory peptide hormone that counteracts the effect of low blood sugar by encouraging the liver to produce glucose. While the terminal roles of these two cell types are in direct opposition, they are developmentally closely related. Differentiation from their progenitor cell is governed by an identified, and newly-appreciated, transcription factor called Arx. In recent studies, loss of the Arx master regulatory transcription factor allowed conversion of α cells into insulin-producing β-like cells.



Identification of Arx as a drug target allowed researchers to discover potential drug candidates, which led to the drug class of artemisinins, a known anti-malarial drug. They are a class of small molecules with a mechanism of action involving functional repression of Arx via cytoplasmic translocation.

Animal studies involving zebrafish and rodents, as well as research using primary human pancreatic islet cells, suggests that gephyrin is a promising drug target in the journey to regenerate human pancreatic β cells. The trans-differentiation studies detailed here involved the use of artemether, of the artemisinin class, to stabilize gephyrin and thereby increase GABA receptor signaling function in pancreatic α cells. The enhanced $GABA_A$ signaling works as part of a negative feedback loop, eventually decreasing glucagon secretion and reducing extracellular glucagon levels to the point of inducing loss of α cell identity. Once this identity is lost, it is possible to encourage conversion of existing α cells into insulin-producing β-like cells.

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The first step in promoting transdifferentiation of cells involves establishing cell line models for inducible overexpression of Arx, specifically Min6. High-throughput screening was conducted on the Min6 cell line to identify functional repressors of Arx. Hits, including certain artemisinins, were chosen based on the degree of insulin intensity, visualized using immunofluorescence, while maintaining cell viability. Images were taken using the Revvity Operetta® CLS™ high-content analysis system, then analyzed using Harmony® software.

Gephyrin could be identified as the most specific interactor with artemisinins using mass spectrometry, which was then confirmed in cellular context by high-content imaging captured using the Revvity Operetta CLS system. Once expression was optimized and additional immunomarkers were quantified, artemisinin-mediated pancreatic cell differentiation was successfully trialed in zebrafish and rodent models. From there, researchers were able to assess the effects of artemether on α cells in primary pancreatic islets, again using the Operetta system to capture and analyze high-quality cellular imaging. Based on the quantification and ensuing data analysis, there is a strong case for considering the efficacy of artemisinins in inducing pancreatic cell transdifferentiation and de novo endogenous insulin production.

The recent progress toward regenerating pancreatic β cells sets the stage for continued advances in the field of endocrinology, as well as other areas of medicine and biomedical engineering. Understanding of cell behavior continues to expand, often as a result of improvements in the technology being used in research labs around the world. As instruments and experimental software become more sophisticated, so does our appreciation of the molecular mechanisms that could potentially be targeted in lifesaving therapy.

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