Recruited by the ULB in 2007, Mariana Igoillo-Esteve, PhD became associate professor in 2016 and created her own research group at the ULB Center for Diabetes Research (UCDR) dedicated to study the mechanisms underlying ß-cell failure in different forms of diabetes. Her team, that she is currently expanding, is composed of 1 PhD student and 2 postdoctoral fellows. She has a large network of national and international collaborators. Her work is internationally recognized and has earned her European, national, regional, and even associative funding.

Research Focus

Prof. Igoillo-Esteve studies the molecular mechanisms involved in the dysfunction and death of pancreatic ß-cells and neurons in monogenic forms of diabetes associated with neurodevelopmental or neurodegenerative features. Her main goal is to identify therapeutic targets to prevent ß-cell and neuronal loss. Unlike type 1 and type 2 diabetes (polygenic forms of diabetes), the monogenic forms of the disease are rare (they constitute between 1 and 4% of all diabetes cases) and are caused by mutations in a single gene. In some cases, these rare forms of diabetes have severe syndromic presentations in which the metabolic alterations are accompanied by extrapancreatic manifestations often affecting the brain.

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Current Research Projects

Project 1: tRNA Modifications and Diabetes

Prof. Igoillo-Esteve's research group is involved in two research projects. The first and most important one aims to study the impact of alterations in transfer RNA (tRNA) modifications and tRNA fragmentation on the development of diabetes and neuronal demise.

Essential molecules for protein synthesis, tRNAs are decorated with a large number of

posttranscriptional modifications important for their folding, stability and function. These modifications are introduced by tRNA modifying enzymes that, when mutated, cause human disease.

Prof. Igoillo-Esteve's project is based on her initial discovery: mutations in TRMT10A, a tRNA modifying enzyme, cause a monogenic form of diabetes characterized by young onset diabetes and microcephaly; what is more, the absence of this enzyme in pancreatic ß-cells results in reduced methylation of specific tRNAs, some of which are prone to enzymatic cleavage, leading to the production of tRNA fragments that induce ß-cell death. This finding unveiled a completely novel mechanism of pancreatic ß-cell demise in diabetes.

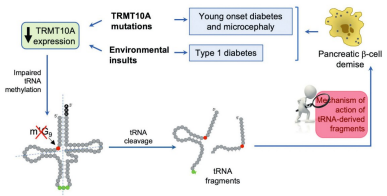
At present, Prof. Igoillo-Esteve is using different targeted and high-throughput approaches to better understand the mechanism of action of these fragments and identify the molecular pathways modulated by them to understand how exactly they cause pancreatic ß-cell demise. She is also investigating the association between TRMT10A deficiency and microcephaly to assess the impact of tRNA hypomethylation and fragmentation on neuronal differentiation, function and survival.

Therapeutically, the action of the tRNA fragments could be antagonized by the use of antisense oligonucleotides, synthetic RNA molecules designed to bind and block these fragments, that may contribute to prevent ß-cell loss and neuronal damage in conditions of TRMT10A deficiency.

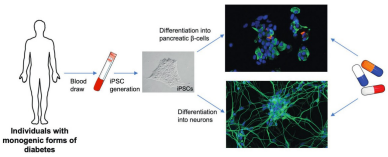
Project 2: Drug Repurposing for Monogenic Diabetes

The second research project focuses on identifying therapeutic options based on drug repurposing or newly developed drugs, to prevent or slow diabetes and neurodegeneration in certain monogenic forms of diabetes. The focus is laid upon testing therapeutic options for Wolfram syndrome with a particular focus on GLP-1 analogues, currently used for the management of patients with type 2 diabetes.

This preclinical approach involves the use of in vitro and in vivo disease models, including induced pluripotent stem cells (iPSCs) from patients generated from blood cells, that are differentiated into ß-cells or neuronal cells. This constitutes an invaluable patient-relevant model to test the effect of drug-based therapies and obtain a proof of concept for the potential use of certain drugs for the treatment of rare diseases.



© ULB Center for Diabetes Research - nactivating mutations in the TRMT10A gene result in altered methylation and cleavage of transfer RNA (tRNA): the tRNA fragments cause damage to pancreatic ß-cells contributing to the development of diabetes.



© ULB Center for Diabetes Research - Inducible pluripotent stem cells (iPSCs) from individuals with monogenic forms of diabetes (here from one Wolfram syndrome patient) are generated from blood cells and then differentiated into pancreatic ß-cells and neurons.

ULB CENTER FOR DIABETES RESEARCH

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