Leveraging AI for genetic target identification in a chronic disease (Type 2 Diabetes) and functional validation

Conférence du Dr Benoît Hastoy

Principal Investigator, R.D Lawrence Fellow
OCDEM, Oxford Centre for Diabetes, Endocrinology and Metabolism
Oxford University, UK

Chercheur invité par Jochen Lang et Matthieu Raoux (CBMN)
(*Mobilité entrante courte du Département Sciences & Technologies pour la Santé*)

Mercredi 6 Novembre 2024 à 10h
Amphithéâtre de l'IECB, 2 rue Robert Escarpit 33600 Pessac

Insulin, the body's only hypoglycaemic hormone, is crucial for maintaining normal blood sugar levels and is secreted exclusively by pancreatic β-cells. Dysfunctions in these cells lead to impaired insulin secretion and diabetes. Genetics play a significant role in Type 2 Diabetes (T2D) risk, with about 700 genetic loci that could contribute to its onset. My work is dedicated to investigating the molecular mechanisms that regulate physiological insulin secretion and the dysfunctions caused by Type 2 Diabetes (T2D)-risk alleles [1-5]. At the Centre for Artificial Intelligence in Precision Medicine (CAIPM), we use AI to discover new genetic targets for T2D treatment, aiming to develop small molecules. Among the top 1,000 AI-identified potential targets, many are confirmed by previous Genome Wide Association Studies (GWAS), and novel ones were detected. We are now validating the roles of these targets in islet β-cells and testing in-house compounds to restore insulin secretion, laying the groundwork for further collaboration with our colleagues in Bordeaux.

Références :

[1] Electrophysiological characterization of inducible pluripotent stem cell-derived human β-like cells and an SLC30A8 disease model, *Diabetes* **2024**, *73*, 1255,

[2] Loss of ZnT8 function protects against diabetes by enhanced insulin secretion, *Nat Genet* **2019**, *51*, 1596

[3] Type 2 diabetes risk alleles in PAM impact insulin release from human pancreatic β-cells, *Nat Genet* **2018**, *50*, 1122

[4] Electrophysiological properties of human beta-cell lines EndoC-βH1 and -βH2 conform with human β-cells, *Sci Rep* **2018**, *8*, 16994

[5] A central small amino acid in the VAMP2 transmembrane domain regulates the fusion pore in exocytosis, *Sci Rep* **2017**, *7*, 2835