

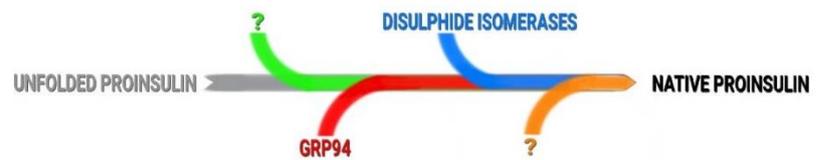


New and critical steps in proinsulin folding. Can you uncover them?

The project can be tailored to the 3-6 months ERASMUS exchange.

Emerging evidence indicates that proinsulin misfolding is an important contributor to the development of type 2 diabetes and gene variants that predispose to T2D point to pancreatic β -cell

dysfunction as a primary defect. However, the underlying mechanisms of β -cell failure caused by misfolded proinsulin are still incompletely understood. Identifying and then modifying those mechanisms may help stop the disease in its tracks or alternately could restore production and folding capacity of β -cells. We have recently identified a first chaperone, GRP94, critical in proinsulin folding and now follow with new structural and functional observations suggesting the importance of a subtle proinsulin structural adjustments and posttranslational modifications in its maturation into insulin.



Proper *in vivo* proinsulin folding: what are those unidentified new folding steps?

THE PROJECT

In this project, you will investigate folding conditions and their alterations during the period of increased insulin demand. You will perform genetic manipulation on model beta cells via CRISPR-Cas9 knock-out of genes of interest and/or creation of their mutants in cells. The new clonal cells in turn will be analyzed via a spectrum of techniques commonly used in the laboratory (below). Depending on the project requirements, you will design and express proinsulin mutants and analyze their folding.

Techniques you will learn during the project: CRISPR-Cas9 based genetic manipulation, cell transfection and transduction with Lentiviral particles, plasmid and primer design, PCR, protein analysis (reducing and non-reducing SDS-PAGE, Western blot, immunoprecipitation), ELISA, mass spectrometry, cell culture, literature search, critical analysis and presentation of the results.

THE GROUP

We are a small and dynamic research group at the Department of Biomedical Science (BMI, <https://bmi.ku.dk/english/research/proinsulin-folding/>). We are located at 12.6 in the old Panum building and we share office and lab spaces with 3-4 other groups. The project can be tailored to the interests of the candidate.

THE CANDIDATE

We are looking for a highly motivated candidate with an interest in cellular biology and/or diabetes. Ideally, the project is designed for a 10 months study. The project is suitable for a Master thesis for students of the study courses human biology, biomedical engineering, molecular biomedicine, biochemistry. If you wish to know more about this project, please contact associate professor Michal Marzec (michal@sund.ku.dk).