Postdoc **Jonas Borup Roland**, PhD, MSc

Place of employment University of Copenhagen, Department of Nutrition, Exercise and Sports

Principal supervisor: Master of Science Human Physiology Thomas E. Jensen, University of Copenhagen, Department of Nutrition, Exercise and Sports

Title of project: GLUT4 storage vesicle biogenesis as a universal determinant of muscle insulin sensitivity?

ABSTRACT

Rationale: One of the earliest pathological manifestations in the development of type 2 diabetes in humans is skeletal muscle insulin resistance, i.e. the impaired ability for insulin to stimulate glucose transporter (GLUT)4 translocation to the cell surface to facilitate glucose uptake. Remarkably, exercise counteracts insulin resistance and transiently increases/reestablishes the sensitivity of glucose uptake to insulin. We recently showed in humans that insulin sensitization after exercise correlates with intramyocellular redistribution of GLUT4 to insulin-responsive GLUT4 storage vesicles (GSVs) and a greater subsequent insulin-stimulated translocation of GLUT4 to the cell surface, suggesting that GSV biogenesis determines insulin-sensitization post exercise. However, neither the mechanisms regulating exercise-stimulated GSV biogenesis are known, nor has the role of GSVs in muscle insulin-resistance been studied.

Hypothesis: The content of insulin-responsive GSVs determines both insulin sensitivity and insulin resistance in skeletal muscle.

Approach: I will spearhead an international team of researchers from different disciplines and sectors, to study muscle samples from normal, insulin resistant and exercise-trained humans, as well as from three new transgenic loss-of-function mouse models of the suspected GSV regulators ULK1, Sec16A and Rab10. The state-of-the-art methods will include advanced live and fixed muscle fiber bio-imaging, real-time electrochemical glucose sensing and automated artificial intelligence-based data analysis.

Impact: This project is the first to test the novel concept that GSV biogenesis universally determines skeletal muscle insulin action, as well as the underlying mechanisms, in both insulin resistant and exercising humans and mice. These results will significantly advance our understanding of what determines insulin-stimulated glucose uptake in human skeletal muscle to inform future efforts to prevent or treat type 2 diabetes.