PhD Student **Mona Sadek Ali**, MSc

Place of enrolment: University of Copenhagen, Faculty of Science

Principal supervisor: Master of Basic Science Lykke Sylow, University of Copenhagen, Department of Nutrition, Exercise and Sports.

Title of project: Determining the Impact of Breast Cancer on Skeletal Muscle Molecular Regulation and Insulin Sensitivity

ABSTRACT

Recent epidemiological studies have revealed that 60-80% of women with breast cancer (BC) develop metabolic disorders, including obesity, hyperinsulinemia, and glucose intolerance. Such disorders markedly increase BC mortality and likelihood of relapse. Despite such impact on disease progression, there is no standard of care treatment and the underlying biological mechanisms are unresolved. I hypothesize that BC-associated metabolic disorders are caused by BC-mediated molecular rewiring of skeletal muscle, causing insulin resistance and whole-body metabolic perturbations.

The specific aims of my project are to 1) determine the presence of insulin resistance in skeletal muscle in survivors of BC, 2) identify BC-associated molecular changes in skeletal muscle and plasma, and 3) establish the molecular mechanisms in skeletal muscle that might underlie BC-associated insulin resistance and metabolic perturbations.

Insulin sensitivity in BC survivors will be determined via the gold standard hyperinsulinemic-euglycemic clamp method. State-of-the-art proteomic and phosphoproteomic analyses of skeletal muscle biopsy samples from BC survivors will identify proteins and signaling mechanisms that are rewired in survivors of BC. I will undertake knockdown and overexpression of candidate proteins in L6 myotubes to screen for molecular mechanism, which could cause insulin resistance in BC. Based on the findings from my *in vitro* screening experiments, I will use recombinant adeno-associated virus to remove or overexpress the 2-3 most promising candidate proteins in skeletal muscle *in vivo* that are likely to cause BC-associated insulin resistance. The role of candidate proteins will be determined in two BC mouse models; MCF7 human BC xenograft in immunodeficient mice, and MT2 murine BC allograft (HER2-positive) in immunocompetent mice.

This study will address significant voids in the field by providing valuable physiological and mechanistic knowledge about metabolic disorders in BC survivors. Such knowledge could form the basis for better treatment in the future for the largest group of cancer survivors.