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Title of project: Regulation of mitochondrial energy expenditure in obesity

ABSTRACT
Obesity is the fifth leading risk factor for death worldwide and is associated with a range of comorbidities such as cardiovascular diseases, cancer and diabetes. Recently approved anti-obesity drugs can deliver modest weight loss through reduced food intake. However, when even a small weight loss is achieved, the human body will respond by decreasing EE, which is likely a major factor in the difficulty of sustaining weight loss in the long term.
The regulation of EE is poorly understood, but an estimated ~30% of whole-body EE is consumed by thermogenic reactions in mitochondria of peripheral tissues. Basal mitochondrial EE is chiefly mediated by inner membrane proteins that increase EE by uncoupling substrate oxidation from ATP production. However, the dynamic regulation of mitochondrial EE upon changes in energy status has not been characterized. In addition, it is not known to what extent mitochondrial metabolism is involved in the reduction in whole-body EE after weight loss.
This project will investigate how the mitochondrial phosphorylation signature is regulated with changes in EE in muscle biopsies from human donors with/without obesity and type 2 diabetes as well as in a pre-clinical minipig model, which shows an extraordinary downregulation of EE upon energy restriction.
Thus, the project aims to uncover novel regulatory mechanisms controlling EE, which will likely be of great importance in fighting the growing global obesity epidemic.