

APPENDIX H.1

Report from Mouse Model Initiative

Mouse Models of Disease

Mouse/Rat Quantitative Organellar Proteomics Initiative

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Through quantitative organellar proteomics, we produce complete molecular maps of the major organelles of both adipose and hepatic tissue and model cell lines from lean and obese rats and mice and most recently with mouse models of diabetes with Dr. R. Kaufman. This includes the mitochondria, the secretory pathway (the ER and the Golgi apparatus), the endocytic pathway, lipid droplets, peroxisomes, autophagosomes and the nucleus.

Proteins and protein complexes of interest are then analyzed for functionality using high end cell biology techniques including correlative microscopy, EM-tomography, knockdown experiments, live cell imaging and high content and high throughput screening. This is followed by an in-depth study in humans where the identified proteins of interest are correlated at the human level drawing on cohorts from existing and past genomics studies in both Canada and Italy to identify and map genetic backgrounds for obesity. Through high-content screening and high throughput screening, we also identify genes and low molecular compounds, respectively that serve as regulatory in energy expenditure with a focus on eliciting facultative thermogenesis, a unique feature of brown adipose tissue whereby energy is converted into heat. A Canada-Italy constellation consists of 13 group participants distributed evenly between the two countries (7 in Canada, 6 in Italy) is in place.

The proteomics (and other genomics technologies) will from the start feed into the outstanding and internationally leading cell biology community of Italy. The cell biology of the secretory pathway through Negri Sud and Milan is also complemented by infrastructure for high throughput screening as well as high end microscopy platforms for high content screening (Negri Sud). Experts on obesity and diabetes are included on both sides of the Atlantic.

Key collaborators ensure access to and support for genomics, transgenic mice strains and high-end bioinformatics. By bringing together the genomics and cell biology of Canada and Italy, respectively, we generate a high impact constellation that neither country can muster alone. The scientific merits of the combined groups alone exceed, by far, the most current and past research constellations with an average citation index of 4849 per team and an average Hirsch-index of 35. GE³LS are included through Dr. Knoppers, Montreal, a highly distinguished specialist in legal and ethical issues pertaining to genomic studies in humans.

Interactions are continuing to take place among Italy, Canada and now the U.S. For the U.S., Randy Kaufman and several other investigators have been brought in to integrate 'mouse models of diabetes project' with that of our Italian colleagues studying organelles in adipose and hepatic tissue. The extension to diabetes is with mouse models of diabetes focusing on stress as an inducer of beta cell death leading to diabetes. These models in turn are extended for comparison with the same organelles isolated from beta cells from human donors, via Dr. Peter Metrakos, Head of Quebec Transplant, providing over 100 donors for pancreatic islets and beta cells for organelle isolation and characterization. Since these donors are rigorously characterized then a match between the human samples and samples from the mouse models will be generated.

As for the collaboration with our Italian colleagues, grant applications are underway for submission.