

# SÉMINAIRE DE L'AXE

## Découverte et validation de cibles thérapeutiques

### **A sex-specific evolutionary interaction between ADCY9 and CETP**



**Julie Hussin, Ph. D, Professeure adjointe**  
Faculté de Médecine – Université de Montréal  
Institut de Cardiologie de Montréal

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Genetic variability impacts drug response, which complicates drug discovery and efficacy assessment in clinical trials. Previously, the rs1967309 variant in the adenylyl cyclase type 9 (ADCY9) gene was found to be associated with clinical responses to the cholesteryl ester transfer protein (CETP) modulator dalcetrapib, but the molecular mechanism behind this association remains unknown. Using an approach that combines population genomics, transcriptomics and phenotype screening thanks to multiple databases, our group has identified a novel sex-specific gene-gene interaction between ADCY9 and CETP detected in the Peruvian population from the 1000 Genomes project, which replicates in the independent LIMAA cohort of over 3,400 Peruvians. Analyses of RNA-seq data from two cohorts (CaG, GTEx) further revealed sex-specific epistatic effects on CETP expression levels in multiple tissues and we see significant interaction effects with sex on cardiovascular phenotypes in the UK Biobank, in line with the sex-specific genotype combinations found in Peruvians at these loci. The relationship uncovered indicates that the biological link between dalcetrapib's pharmacogene ADCY9 and the drug target CETP is modulated by sex. Few such interactions have been identified making this a novel finding that, we hope, will motivate more research and methods to look for such effects.