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Title: Modeling human non-coding mutations reveals new insights into diabetes and pancreas development

Abstract: This seminar will explore the role of non-coding DNA variation on Type 2 diabetes (T2D) and how enhancer mutations lead to a rare form of neonatal diabetes and isolated pancreatic agenesis. The first section of the talk will focus on our investigation of common non-coding genetic variants associated with T2D contribute to disease risk. Through the integration of highly accurate regulatory maps in human pancreatic islets and chromatin 3D datasets we were able to link enhancers containing disease-predisposing SNPs and their endogenous target genes, generating a useful catalogue between T2D-associated variants and pathways. We also identified 3D enhancer hubs that guided the generation of a polygenic risk score to stratify population based on predisposition to develop T2D.

Since regulatory genomics can also be used to dissect mechanisms of Mendelian disorders, the seminar will next cover our efforts to understand how single base pair mutations in an enhancer of *PTF1A* gene leads to isolated pancreatic agenesis. Through modeling of the non-coding defect in a CRISPR-Cas9 engineered mouse model and pluripotent stem cells, we show how the enhancer is specifically active in multipotent pancreatic progenitors and seems to be essential for the specification of insulin-producing beta cells. Our study suggests that diabetes might be caused by an early failure in endocrine differentiation induced by an unsuspected role of *PTF1A* in priming pancreatic progenitors. Hence, this work highlights the importance of modelling non-coding mutations and shed insights into how *Ptf1a* enhancer affects pancreas development and beta cell specification.