Project title: Pathogenic mechanisms and therapeutic strategies in Autosomal Dominant adult-onset LeukoDystrophy (ADLD)
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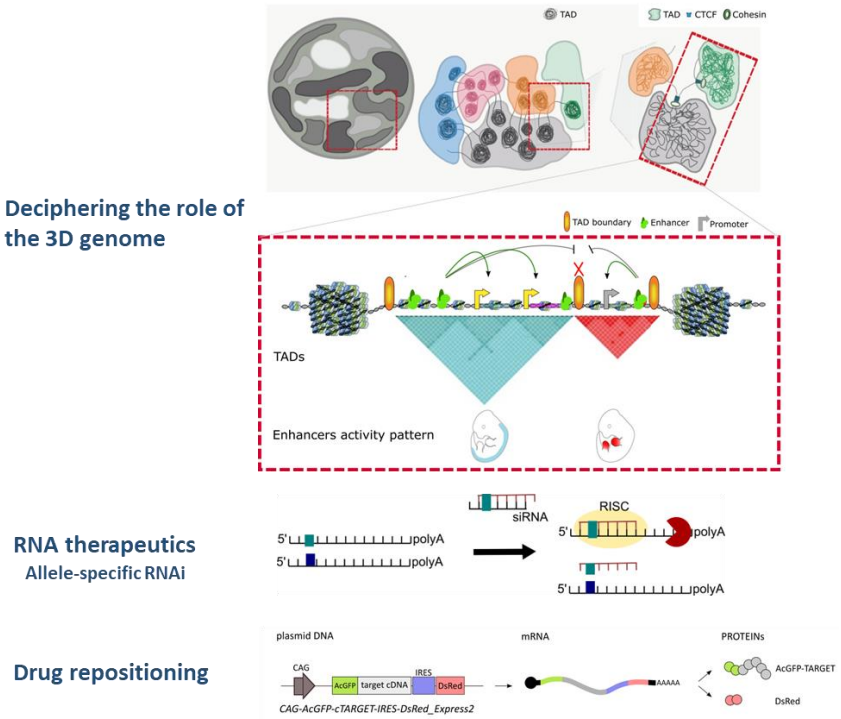
Background: Autosomal Dominant adult-onset LeukoDystrophy (ADLD) is a rare and fatal neurodegenerative disorder that affects myelin the central nervous system. Genetically, it is characterized by coding duplications or noncoding deletions at the *LMNB1* locus resulting in an excessive Lamin B1 production. ADLD onset is in the 4/5th decade of life with autonomic symptoms, which precede cerebellar and pyramidal abnormalities. The trigger in ADLD neuropathology is the accumulation of LMNB1 protein, a component of nuclear lamina, in patients' brains and currently no therapy is available to cure or slow the advance of the disease. Over the last decade, Giorgio's group has reported new evidence about different clinical and neuroradiological manifestations of the disease based on the type and the size of rearrangements at the *LMNB1* locus, ranging from canonical and non-canonical phenotypes to asymptomatic carriers. Our preliminary findings suggest that this clinical variability is due the different effects of rearrangements on the 3D genome architecture but further validations on disease-relevant cellular models are required. Giorgio's group has identified and preliminary validated two different and complementary therapeutic approaches for ADLD: allele-specific silencing of the *LMNB1* gene and a drug able to reduce LMNB1 protein level.

Aims: This project will
ii) redefine ADLD pathology in disease-relevant cellular models (hiPSC-derived astrocytes); ii) decipher the role of 3D position effects in ADLD, contributing to a better understanding of the genotype-phenotype correlation of rearrangements at the *LMNB1* locus; iii) validate on disease-relevant cellular models the two therapeutic strategies already developed.

Techniques: drug-repositioning approaches, generation of astrocytes from hiPSCs, real-time PCR, western blotting, immunohistochemistry, treatment/transfection, or transduction of cells with therapeutic molecules, Hi-C, ATAC-seq, scRNA-sequencing, bulk RNA-sequencing.



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