

## Abstract

Chromatin, formed by DNA wrapped around histone proteins, regulates gene activity through combinatorial chemical modifications of histones residues. These modifications determine whether genomic regions adopt an open configuration permissive to transcription or a compact and repressive state. While DNA sequence is stable, these epigenetic modifications vary between cell types and are heritable, making them key drivers of cellular diversity. However, despite extensive mapping efforts, the mechanisms that place histone modifications at specific genomic loci—and the rules governing their interactions—remain poorly understood.

This project aims to uncover the principles that shape the human repressive epigenetic landscape. We will address two central questions:

- 1) How do DNA sequence features influence the establishment of repressive histone modifications?
- 2) Which components of the epigenetic landscape are intrinsically stable versus amenable to remodelling?

To answer these questions, we propose an integrated synthetic epigenomics strategy combining deep learning, DNA synthesis, genome engineering and epigenome editing. We will train an AI model on ChIP-seq data to identify DNA motifs predictive of repressive histone modifications, focusing on H3K9me3 and H3K27me3. Predicted motifs will be embedded into synthetic DNA fragments and inserted into human RPE1 cells to test their ability to recruit histone marks *in vivo*. Using CRISPR-based epigenetic editors, we will selectively write or erase histone modifications on these synthetic loci to determine how local DNA context affects the acquisition, maintenance, or removal of repressive chromatin features. Functional genomics readouts will then reveal which epigenetic states are dynamically tunable and which represent stable, hard-wired components of cellular identity. This project adopts a strongly interdisciplinary framework integrating machine learning, synthetic biology and functional genomics, thanks to two highly complementary teams. Their combined capabilities will establish causal, sequence-resolved rules for repressive histone marks and precisely demarcate which repressive states are reversible versus stably maintained in human cells.