

RNA Innovation Seminars

Monday, March 15, 2021 4:00 PM
[Zoom Registration](#)

Programmable transcriptional memory by CRISPR-based epigenome editing

James Nuñez, PhD

HMI Hanna Gray Fellow
University of California, San Francisco



Abstract

General approaches for heritably altering gene expression would enable many discovery and therapeutic efforts. I will present CRISPRoff— a programmable epigenetic memory writer consisting of a single dead Cas9 fusion protein that establishes DNA methylation and repressive histone modifications to turn off transcription. Transient CRISPRoff expression initiates highly specific DNA methylation and gene repression that is maintained through cell division and differentiation of stem cells to neurons. Pairing CRISPRoff with genome-wide screens and analysis of chromatin marks enabled us to explore the rules for heritable silencing. We identify sgRNAs capable of silencing the large majority of genes including those lacking canonical CpG islands (CGIs) and reveal a wide targeting window extending beyond annotated CGIs. Our finding that targeted DNA methylation outside of CGIs leads to memorized gene silencing expands the canonical model of methylation-based silencing and broadly enables diverse applications including genome-wide screens, multiplexed cell engineering, enhancer silencing, and mechanistic exploration of epigenetic inheritance.