

## **Cold Spring Harbor Laboratory Functional Genomics Facility**

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The Cold Spring Harbor Laboratory (CSHL) Functional Genomics Core facility provides investigators (internal and external) with access to advanced RNAi/CRISPR reagents and screening technologies. A major focus of this Core is in assisting investigators with the design, implementation, and data analysis of multiplexed RNAi/CRISPR screens in mammalian cells. The Core provides training and assistance to users at all stages of the screening project. This facility has generated unique shRNA and CRISPR reagents that are not readily available elsewhere based on advancements developed by CSHL scientists. CSHL has developed shRNA/sgRNA design algorithms as well as collections of verified screening libraries representing various gene families and whole genomes (human and mouse). Using these algorithms, the Core designs and constructs custom shRNA/sgRNA libraries. Targeted loss-of-function, genetic screening using CRISPR in human and mouse cells has provided an alternative and complementary functional genomics tool to RNAi. The capabilities of genome editing are particularly evident in positive selection screens, but its performance in negative screening is more variable. CSHL investigators have made significant improvements in the performance of individual sgRNAs targeting the same gene. The current targeting strategy of sgRNAs to 5' exons of candidate genes, which often produces in-frame variants that retain functionality, can obscure strong genetic dependencies. By applying CRISPR mutagenesis to exons encoding functional protein domains, a higher proportion of null mutations are observed and consequently substantial increases in the potency of negative selection phenotypes in genetic screens. Screening in patient-derived organoids of different cancers are currently being developed using this screening approach. It is the goal of this facility to leverage its innovative approaches to RNAi and genome editing to promote a deeper understanding of cancer pathways with the potential for discovery of new therapeutic targets and generation of disease-relevant models for improving human health.