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Genome editing: from chromatin dynamics to precision therapeutics

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Genome engineering technologies, including CRISPR-Cas9, ZFNs, and TALENs, enable a wide spectrum of fundamental and translational research, ranging from precise dissection of chromatin architecture and dynamics to therapeutic correction of disease-causing mutations. We demonstrate allele-selective transcriptional repression of mutant *HTT* in Huntington's disease using engineered zinc finger repressors fused to Krüppel-associated box (KRAB) domains, achieving >70% reduction of pathogenic protein aggregates in patient-derived neuronal models while preserving wild-type allele expression. In cystic fibrosis, ZFN-mediated correction of the *CFTR* ΔF508 mutation in induced pluripotent stem cells (iPSCs) restored chloride channel function to near-wild-type levels, with electrophysiological confirmation in differentiated airway organoids showing sustained rescue. For cancer immunotherapy, ZFN-based targeted disruption of *PD-1* via homology-directed repair in tumor-infiltrating lymphocytes enhanced cytotoxic T-cell activity and memory formation, driving complete tumor regression in metastatic melanoma PDX models. Similarly, *IL2RG* correction in hematopoietic stem/progenitor cells achieved multilineage engraftment and restored NK-cell cytotoxicity in SCID-X1 xenotransplant systems. Our recent work established clonally verified CRISPR-engineered reporter cell lines through site-specific integration into genomically stable safe harbor loci (*AAVS1*, *ROSA26*). We investigating whether this targeted approach improves signal consistency compared to random integration and enables superior longitudinal monitoring of TGF-β signaling dynamics. Our long-time goal is to bridge chromatin-scale mechanistic insights to clinical translation, using genome editing's dual utility as a versatile discovery platform and transformative therapeutic modality for precision medicine.

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