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"Customizable DNA targeting technologies have important applications in biological research and gene therapy…"

The Joung laboratory is developing strategies to reprogram the genome and epigenome of living cells to better understand biology and treat disease. We have developed and optimized molecular tools for customized genome editing that enable scientists to alter the DNA sequence of a living cell—from fruit flies to humans—with great precision. These technologies are based on proteins engineered to recognize and cleave specific genomic sequences. We also use these targeting methodologies to enable activation, repression, or alteration of histone modifications of specific genes. These tools have many potential research uses and may one day lead to more efficient gene therapy capable of correcting disease-related mutations in human cells.

Genome Editing Using Targeted Nucleases

Genome editing technology was recently named runner-up for "Breakthrough of the Year" for 2012 and 2013 by Science magazine and "Method of the Year" for 2011 by Nature Methods. We have previously described two rapid, robust, and publicly available methods for engineering ZFNs known as OPEN (Oligomerized Pool Engineering; Maeder et al., Mol Cell 2008) and CoDA (Context-Dependent Assembly; Sander et al., Nat Methods 2011). In addition, we have also developed and optimized methods for engineering TALENs including an automated, high-throughput method known as FLASH (Fast Ligation-based Automated Solid-phase High-throughput) assembly (Reyon et al., Nat Biotechnol. 2012). We have also recently described reagents that enable the rapid construction of CRISPR RNA-guided nucleases (RGNs) (Hwang et al., Nat Biotechnol. 2013).

Much of our recent work has focused on CRISPR RGNs. We and our collaborators were the first to demonstrate that RGNs can function in vivo (Hwang & Fu et al., Nat Biotechnol. 2013) and the first to show that they can induce significant off-target mutations in human cells (Fu et al., Nat Biotechnol. 2013). We have developed two platforms that improve RGN specificities: one based on the use of truncated guide RNAs (Fu & Sander et al., Nat Biotechnol. 2014) and the other in which we engineered dimerization-dependent CRISPR RNA-guided nucleases (Tsai et al., Nat Biotechnol. 2014).

Epigenome Editing Using Targeted Transcription Factors

We have recently demonstrated that the TALE and CRISPR platforms can also be utilized to create artificial transcription factors that can robustly alter expression of endogenous human genes (Maeder et al., Nat Methods 2013a; Maeder et al., Nat Methods 2013b). In addition, we have collaborated with Brad Bernstein's group to develop fusions of the histone demethylase LSD1 with TALE domains that can induce targeted histone alterations at endogenous human enhancers (Mendenhall et al., Nat Biotechnol. 2013). Finally, we have also developed fusions of engineered TALE domains with the catalytic domain of the TET1 enzyme, enabling the targeted demethylation of CpGs in human cells (Maeder et al., Nat Biotechnol. 2013).

Selected Publications

Tsai SQ, Wyvekens N, Khayter C, Foden JA, Thapar V, Reyon D, Goodwin MJ, Aryee MJ, Joung JK. Dimeric CRISPR RNA-guided FokI nucleases for high specific genome editing. Nat Biotechnol., 2014 Jun;32(6): 569-7.

Sander JD, Joung JK. CRISPR-Cas systems for editing, regulating and targeting genomes. Nat Biotechnol. 2014 Apr;32(4):347-55. Review.

Fu Y, Sander JD, Reyon D, Cascio V, Joung JK. Improving CRISPR-Cas nuclease specificity using truncated guide RNAs. Nat Biotechnol., 2014 Mar;32(3):279-84.

Maeder ML, Angstman JF, Richardson ME, Linder SJ, Cascio VM, Tsai SQ, Ho QH, Sander JD, Reyon D, Bernstein BE, Costello JF, Wilkinson MF, Joung JK. Targeted DNA Demethylation and Endogenous Gene Activation Using Programmable TALE-TET1 Fusions. Nat Biotechnol., 2013 Dec; 31(12):1137-42.

Fu Y, Foden JA, Khayter C, Maeder ML, Reyon D, Joung JK*, Sander JD*. High-frequency off-target mutagenesis induced by CRISPR-Cas nucleases in human cells. Nat Biotechnol. 2013 Jun 23. *Co-corresponding authors

Hwang WY, Fu Y, Reyon D, Maeder ML, Tsai SQ, Sander JD, Peterson RT, Yeh JR, Joung JK. Efficient genome editing in zebrafish using a CRISPR-Cas system. Nat Biotechnol. 2013 Mar;31(3):227-9.