



Martin Jinek

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Martin Jinek is Associate Professor in the Department of Biochemistry at the University of Zurich. His research focuses on two main topics – (i) CRISPR-Cas systems and their genome editing applications and (ii) mechanistic studies of RNA processing and modification pathways in eukaryotic gene expression.

Originally from the Czech Republic, Martin Jinek studied Natural Sciences at the University of Cambridge (UK). In 2006, he received his PhD from the European Molecular Biology Laboratory (EMBL) in Heidelberg (Germany). He then moved to the University of California in Berkeley (USA) for postdoctoral research with Prof.

Jennifer Doudna, where his pioneering work led to the discovery of the biochemical function of the RNA-guided endonuclease Cas9 and was pivotal for establishing the CRISPR-Cas9 genome editing technology.

Since starting his research group at the University of Zurich in 2013, Martin Jinek has studied the molecular mechanisms of CRISPR-Cas genome editor nucleases in atomic detail, providing fundamental insights into their molecular mechanism and contributing to their engineering to drive further development of genome editing technologies.

In recognition of his work, Martin Jinek has received several awards, including an ERC Starting Grant (2013), the EMBL John Kendrew Young Scientist Award (2014) and the Friedrich Miescher Award of the Swiss Society for Molecular and Cellular Biosciences (2015). He is an EMBO Young Investigator, Valle Scholar of the Bert N and L Kuggie Valle Foundation, and in 2017 became an International Research Scholar of the Howard Hughes Medical Institute.

Abstract: Structural and Mechanistic Insights into CRISPR-Cas Genome Editors

In bacteria, the CRISPR-Cas system functions as an adaptive system to provide resistance against molecular invaders such as viruses and other mobile genetic elements. RNA-guided effector nucleases associated with CRISPR-Cas systems have been repurposed as powerful tools for precision genome editing in eukaryotic cells and organisms. Our current work focuses on studying the molecular mechanisms of Cas9 and other CRISPR-associated nucleases using a combination of structural, biochemical and biophysical approaches. To this end, we initially determined the three-dimensional structures of Cas9 in complex to a guide RNA and target DNA, revealing the atomic interactions underpinning the recognition of a short motif in the substrate DNA (the protospacer adjacent motif, PAM), which is necessary to facilitate strand separation in the DNA and guide RNA hybridization. These studies have established a structural framework for engineering novel Cas9 variants with altered PAM specificities. More recently, we have focused on Cas12a (Cpf1), another RNA-guided nuclease enzyme that has emerged as a complementary genome editing tool to Cas9. The crystal structure of Cas12a bound to a guide RNA shows that, like Cas9, Cas12a structurally preorganizes the seed sequence of the guide RNA to facilitate target DNA recognition. In turn, structures of Cas12a bound to a guide RNA and a double-stranded DNA target capture nuclease in a pre-cleavage state, revealing the mechanism of R-loop formation. Together with supporting biochemical experiments, the structures show that Cas12a contains a single nuclease active site that sequentially cleaves both strands of the target DNA in a defined sequential order. Collectively, our studies provide a mechanistic foundation for understanding the molecular function of CRISPR-based genome editor nucleases and for the ongoing development of CRISPR-Cas genetic engineering for biotechnological and therapeutic applications.