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EXPANDING THE GENOME EDITING TOOLBOX BY UNLOCKING RNA GUIDED NUCLEASES USING MASSIVE METAGENOMIC DATA

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CRISPR technologies initiated a new era for the advancement of genome editing. The new paradigm brought by the CRISPR technology is the concept of RNA guided nucleases as a mean to ease programmability of genome editing. Yet, various hurdles are limiting the desirable broader use of the genome editing applications. Challenges are imposed by various properties of CRISPR tools including poor compatibility with delivery systems, target sequence constraints and unpredictable efficiency and precision throughout the genome. We recently focused on the development of the technologies by scouting for undiscovered systems existing in nature. To this aim we used a massive metagenomic database to identify new CRISPR systems and RNA guided nucleases with more favorable features for genome editing purposes including low molecular size. Since most novel systems derived from prokaryotes are non-functional in eukaryotic cells, we generated a directed evolution platform using eukaryotic cells, EPICA, allowing the generation of Cas variants with enhanced activity. Our discovery-enhancement pipeline will set the stage to unlock a large variety of nuclease tools matching the complexity of genome editing applications in eukaryotes.