**The CRISPR-Cas mechanism for adaptive immunity and alternate bacterial functions fuels diverse biotechnologies**

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Supplementary Table 1

**Supplementary Table 1. Expanded CRISPR-Cas biotechnology applications**

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| **Biotechnology Application** | **Cas Protein and CRISPR-Cas type, relevant activities, modifications** | **References** |
| A. Gene editing | 1a. SpyCas9 (type II-A), sequence specific DNA cleavage producing a mixture of staggered and blunt ends1b. Hyper-accurate Cas9 (HypaCas9), four amino acid mutations near the RNA-DNA interface1c. High-fidelity SpyCas9 (SpCas9-HF), mutation of four amino acids that non-specifically contact target DNA 1d. Enhanced specificity SpyCas9 (eSpCas9), three amino acid mutations in a groove that stabilizes the non-target strand of the target DNA1e. Light activated Cas9, split into two fragments and fused to dimerization domains1f. sgRNA regulation to control Cas91g. chemically inducible Cas9, various modifications2. Cas12a (type V-A), sequence specific DNA cleavage producing staggered ends3. CASCADE (type 1-E), sequence specific DNA binding, fused to FokI nuclease 4. CASCADE and Cas3 (type I-A), sequence specific DNA cleavage and degradation of one of the strands of a DNA5. Cmr (type III-B), sequence specific interference of transcriptionally active DNA6. Direct injection of CRISPR-Cas-based drug into the retina to treat hereditary blindness7. Cas10-Csm and Csm6 (type III-A), viral DNA and RNA cleavage that increases viral gene editing efficiency by selecting against unedited phage 8. Anti-CRISPR proteins, CRISPR-Cas inhibition as a selectable marker for editing viral genomes 9. Anti-CRISPR proteins, CRISPR-Cas inhibition quenches gene editing reactions to minimize off-targeting  | 1a. (Jinek et al., 2012; Cho et al., 2013; Jiang et al., 2013; Chu et al., 2015)1b. (Chen et al., 2017)1c. (Kleinstiver et al., 2016)1d. (Slaymaker et al., 2016)1e. (Nihongaki et al., 2015; Yu et al., 2020)1f. (Lee et al., 2016; Liu et al., 2016b; Ferry et al., 2017; Maji et al., 2017; Tang et al., 2017)1g. (Davis et al., 2015; Dow et al., 2015; Zetsche et al., 2015; Liu et al., 2016a; Maji et al., 2017)2. (Hur et al., 2016; Ferenczi et al., 2017; Yan et al., 2017)3. (Cameron et al., 2019)4 & 5. (Li et al., 2015)6. ClinicalTrials.gov Identifier: NCT03872479 7. (Nayeemul Bari and Hatoum-Aslan, 2019)8. (Mayo-Muñoz et al., 2018)9. (Marino et al., 2020) |
| B. Base editing  | 1. SpyCas9 nickase (type II-A), sequence specific DNA binding, fused to both cytidine deaminase and uracil DNA glycosylase inhibitor 2. SpyCas9 (type II-A), sequence specific DNA binding, nuclease inactivated and fused to an engineered adenosine to inosine deaminase capable of targeting DNA 3. nuclease inactivated Cas12a (type V-A), sequence specific DNA binding, fused to cytidine deaminase and uracil DNA glycosylase inhibitor 4. nuclease inactivated Cas13 (type VI-B), sequence specific RNA binding, fused to adenosine deaminase  | 1. (Komor et al., 2016)2. (Gaudelli et al., 2017)3. (Li et al., 2018) 4. (Cox et al., 2017) |
| C. Gene knockdown via ssRNA cleavage | 1. *Staphylococcus aureus* Cas9 (II-A), *Neisseria meningitidis* Cas9 (II-C) ssRNA cleavage2. Cmr (III-B), ssRNA cleavage3. Cas13 (VI-A and D), crRNA maturation and ssRNA cleavage4. nuclease inactivated SpyCas9 (type II-A) fused to RNA endonuclease domain, sequence specific ssRNA binding  | 1. (Rousseau et al., 2018; Strutt et al., 2018)2. (Zebec et al., 2014)3. (Abudayyeh et al., 2017; Konermann et al., 2018)4. (Batra et al., 2017) |
| D. Transcriptional repression | 1. nuclease inactivated SpyCas9 (type II-A), sequence specific DNA binding 2. nuclease inactivated SpyCas9 (type II-A) fused to an epitope tag that recruits antibody-fused methyltransferase that methylates the genomic target to repress transcription, sequence specific DNA binding 3. nuclease inactivated Cas12a (type V-A), crRNA maturation and sequence specific DNA binding4. CASCADE (type I-E), DNA binding | 1. (Qi et al., 2013)2. (Huang et al., 2017)3. (Zhang et al., 2017)4. (Rath et al., 2014) |
| E. Gene activation | 1a. nuclease inactivated SpyCas9 (type II-A) fused to a transactivation domain, sequence specific DNA binding 1b. Light activated SpyCas9, nuclease inactivated and fused to a light-inducible heterodimerizing protein2. Cas12a (type V-A), crRNA maturation and sequence specific DNA binding, fused to a transactivation domain3. CASCADE (type I-E), crRNA maturation and sequence specific DNA binding, fused to plant transcriptional activation domain | 1a. (Perez-Pinera et al., 2013)1b. (Polstein and Gersbach, 2015)2. (Breinig et al., 2019)3. (Young et al., 2019) |
| F. Nucleic acid detection | 1. Cas12a (type V-A), collateral ssDNA cleavage activity upon target binding2. Cas13 (type VI-A and B), collateral ssRNA cleavage activity upon target binding3. Csm6 (type III-A), non-specific nuclease | 1-3. (Gootenberg et al., 2018)1. (Chen et al., 2018) |
| G. Antimicrobial | 1. SpyCas9 (type II-A), dsDNA interference2. CASCADE and Cas3 (type I-E), dsDNA interference3. Cas13a (type VI-A), promiscuous ssRNA cleavage4. Anti-CRISPR proteins, CRISPR-Cas inhibition to expand the host range for phage-derived therapeutics | 1. (Citorik et al., 2014)2. (Gomaa et al., 2014)3. (Kiga et al., 2020)4. (Marino et al., 2020) |
| H. Transposition or genome tagging | 1. CASCADE (type I-F), sequence specific DNA binding, fused to transposition protein2. Cas1 and Cas2 (type I-E), sequence-selective DNA integration | 1. (Klompe et al., 2019)2. (Wright et al., 2017) |
| I. Protect plants from both RNA and DNA viruses | 1. Cas13 (type VI-A), crRNA maturation and sequence specific ssRNA cleavage2. SpyCas9 (type II-A), sequence specific DNA interference | 1. (Aman et al., 2018)2. (Ali et al., 2015) |
| J. Decrease bacterial pathogenicity | Anti-CRISPR proteins to inhibit CRISPR-Cas systems involved in bacterial pathogenicity | (Marino et al., 2020) |
| K. Record transcription | Cas1:Cas2 complex (type III-D), natural fusion to reverse transcriptase, reverse transcription and sequence selective DNA integration | (Schmidt et al., 2018) |
| L. Store digital information | Cas1:Cas2 complex (type I-E), sequence selective DNA integration | (Shipman et al., 2017) |
| M. Visualizing nucleic acid localization | 1. nuclease inactivated SpyCas9 (type II-A) fused to GFP, sequence specific binding to target DNA 2. nuclease inactivated Cas13 (type VI-A) fused to GFP, sequence specific ssRNA binding  | 1. (Chen et al., 2013; Nelles et al., 2016)2. (Abudayyeh et al., 2017) |
| N. Mediate chromatin immunoprecipitation for downstream analysis of epiproteome (interacting proteins, histone post translational modifications, RNAs, and neighboring genomic regions) via mass spectrometry and nucleic acid sequencing | nuclease inactivated and affinity tagged SpyCas9 (type II-A), sequence specific DNA binding  | (Waldrip et al., 2014; Fujita and Fujii, 2015) |
| O. Subnuclear proteomic profiling | nuclease inactivated SpyCas9 (type II-A) fused to APEX2 (an engineered soybean ascorbate peroxidase that labels near-by proteins with biotin), sequence specific DNA binding  | (Gao et al., 2019) |
| P. Influence mRNA splicing outcomes without hindering translation to protein (potential treatment for diseases caused by gene mis-splicing) | Cas13d (CasRx, type VI-D), sequence specific DNA binding, nuclease inactivated | (Konermann et al., 2018) |

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