**Supplementary File 3**

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| **WRN domain targeting sgRNAs (N- to C-terminal order)** | |
| **Targeted domain** | **sgRNA sequence** |
| **Exonuclease** | AGTCTATCCGCTGTAGCAAT |
| GACCTGGAGCCTTAACAGTC |
| AACCAGACTGTTAAGGCTCC |
| AGTCTGGTTAAACACCTCTT |
| GGCCACCATTATACAATAGA |
| **Helicase** | GCTCACTGTATTTCTGAGTG |
| AGGCTCACTGTATTTCTGAG |
| CTCACTGTATTTCTGAGTGG |
| ATGATTTTAGGGATTCATTC |
| TTTCTGACTGTGCTGATCCA |
| CATTCATTACGGTGCTCCTA |
| TTACGGTGCTCCTAAGGACA |
| TGCTAAAACTCATGCCCGCA |
| GCCCGCATGGTATGTTCCAC |
| AAGTTCTTGTCACGTCCTCT |
| CATTACGTATCTCAGTAAGA |
| AGTTCCCATAATTCCCAAGG |
| AAAGCCTCCTTGGGAATTAT |
| ACAAGTACAAAAAGCCTCCT |
| ATCTTCATTCTAGCAGATGT |
| **RQC** | GTCTTGCCGATCAATATCGC |
| ACTGTGCCTGCGATATTGAT |
| GACATCTTAGGCGAAAAATT |
| AGGCACAGTTTATTTGGCAC |
| TATCGCAGGCACAGTTTATT |
| **HRDC** | CTACGGTTGAAAACGTAAAA |
| TTTACGTTTTCAACCGTAGT |
| GTTTGTTGCCAGAATAGCTG |
| TCTGGCAACAAACAAGATAC |
| TTTGTTGCCAGAATAGCTGG |
| **HTH** | CCCCTTGATTTGGAGCGAGC |
| TTATCCCAAGCGGTGAAAGC |
| GGCAGCCAGCTTTCACCGCT |
| GGCCTGCTCGCTCCAAATCA |
| CTGCTCGCTCCAAATCAAGG |
| **Control sgRNAs** | **sgRNA sequence** |
| Neg#1 | GGCAGTCGTTCGGTTGATAT |
| Neg#2 | GATACACGAAGCATCACTAG |
| RPA3 | GATGAATTGAGCTAGCATGC |
| PCNA | GGACTCGTCCCACGTCTCTT |
| POLR2A | GTACAATGCAGACTTTGACG |