

GENE EDITING SYSTEMS AND METHODS FOR TREATING CARDIOVASCULAR DISEASE

FIELD OF DISCLOSURE

[0001] The present disclosure generally relates to gene editing systems and methods for
5 treating cardiovascular disease (CVD). Also disclosed are polynucleotides, vectors, cells,
kits, and compositions comprising components of the gene editing systems, and methods
related to treatment of CVD.

CROSS REFERENCE TO RELATED APPLICATION

[0002] This application claims the priority to and benefits of International Application No.
10 PCT/CN2023/141841, filed December 26, 2023, which is incorporated herein by reference in
its entirety.

SEQUENCE LISTING

[0003] This application contains a Sequence Listing electronically submitted as an XML
file entitled "sequence listing.xml" having a size of 1,356,492 bytes and created on December
15 25, 2024. The information contained in the Sequence Listing is incorporated by reference
herein.

BACKGROUND

[0004] Cardiovascular disease (CVD) remains a prominent cause of morbidity and
mortality globally, with dyslipidemia emerging as a pivotal determinant influencing the risk
20 of atherosclerosis. Elevated plasma levels of low-density lipoprotein cholesterol (LDL-C) are
a well-established risk factor for CVD. The intricate relationship between dyslipidemia and
atherosclerosis plays a notable role in the progression of clinical CVD events such as
coronary artery disease, peripheral artery disease, and stroke and their associated long-term
sequelae. Therefore, current clinical guidelines stress the importance of lipid lowering, with a
25 large emphasis on lowering Low-Density Lipoprotein cholesterol (LDL-C) levels.

[0005] The United States FDA has approved some PCSK9 inhibitors or siRNAs for the
treatment of Atherosclerotic cardiovascular disease (ASCVD), such as Alirocumab or
Inclisiran. However, the necessity for additional LDL-lowering therapeutics (LLT) is
growing due to concerns about off-target events and poor patient compliance associated with
30 conventional treatments. Conventional therapeutics exhibit limitations, especially in patients
with genetically defined extreme levels of LDL-C, where maximum dosed LLT may prove
insufficient to lower LDL-C to target levels. This challenge is further compounded by

prescribers who may be unaware of or reluctant to comply with guidelines. The emergence of novel gene-based therapeutics holds promise for minimizing off-target events and significantly reducing injection frequency, offering a potential breakthrough in addressing these limitations.

5 [0006] Recent advancements have established a link between Lp(a) levels and CVD, prompting the development of medications not solely targeting plasma LDL-C levels. Ongoing or recently completed clinical trials, such as Pelacarsen and Olpasiran, employ antisense oligonucleotide (ASO) or siRNA approaches against the *LPA* gene. These endeavors reflect a shift toward a more nuanced approach to medication, recognizing the
10 importance of targeting specific factors beyond traditional LDL-C levels in mitigating cardiovascular risk.

[0007] In addition to the aforementioned treatment mechanisms, the pathways of Ang II generation and intracellular renin-angiotensin-aldosterone system (RAAS) signaling are considered crucial for cardiovascular and renal disease treatment. Uncontrolled hypertension
15 serves as a significant contributor to cardiovascular risk, necessitating exploration into strategies to regulate blood pressure. The angiotensinogen gene (*AGT*) is a popular factor in this regard, as it is the source of all downstream angiotensin metabolites—a potent regulator of blood pressure. Recent clinical and preclinical data suggest that liver-selective *AGT* reduction presents a superior therapeutic profile in both blood pressure lowering and CVD
20 treatment, offering a targeted and effective approach.

[0008] This dual approach, addressing both lipid levels and blood pressure regulation, tackles multiple facets of the CVD risk. However, there remains the need for the development of novel therapeutic strategies with potential applications in clinical practice for treating CVD.

25 SUMMARY

[0009] In one aspect, the present disclosure provides gene editing systems, polynucleotides, vectors, cells, compositions, kits, and methods to disrupt the expression of genes selected from *PCSK9*, *ANGPTL3*, *ASGR1*, *LPA*, *AGT* and *APOC3*, which contribute to lower Low-Density Lipoprotein cholesterol (LDL-C) levels, lower the level of triglyceride-rich remnant particles and/or lipoprotein(a) (Lp(a)), or regulate blood pressure, so that
30 cardiovascular disease can be prevented or treated.

[0010] In some embodiments, the disruption of the *PCSK9* gene regulates LDL metabolism. In some embodiments, the disruption of the *PCSK9* gene reduces the level of LDL-C. In some embodiments, the disruption of the *PCSK9* gene treats
35 hypercholesterolemia. In some embodiments, the disruption of the *PCSK9* gene treats cardiovascular diseases.

[0011] In some embodiments, the disruption of the *ANGPTL3* gene regulates LDL metabolism. In some embodiments, the disruption of the *ANGPTL3* gene reduces the level of LDL-C. In some embodiments, the disruption of the *ANGPTL3* gene treats hypercholesterolemia. In some embodiments, the disruption of the *ANGPTL3* gene treats cardiovascular diseases.

[0012] In some embodiments, the disruption of the *ASGR1* gene regulates LDL metabolism. In some embodiments, the disruption of the *ASGR1* gene reduces the level of LDL-C. In some embodiments, the disruption of the *ASGR1* gene treats hypercholesterolemia. In some embodiments, the disruption of the *ASGR1* gene treats cardiovascular diseases.

[0013] In some embodiments, the disruption of the *LPA* gene regulates triglyceride-rich remnant particles metabolism. In some embodiments, the disruption of the *LPA* gene regulates lipoprotein(a) (Lp(a)) metabolism. In some embodiments, the disruption of the *LPA* gene reduces the level of triglyceride-rich remnant particles. In some embodiments, the disruption of the *LPA* gene reduces the level of lipoprotein(a) (Lp(a)). In some embodiments, the disruption of the *LPA* gene treats cardiovascular diseases.

[0014] In some embodiments, the disruption of the *AGT* gene regulates expression of angiotensinogen. In some embodiments, the disruption of the *AGT* gene reduces the level of angiotensinogen. In some embodiments, the disruption of the *AGT* gene regulates blood pressure. In some embodiments, the disruption of the *AGT* gene treats hypertension. In some embodiments, the disruption of the *AGT* gene treats cardiovascular diseases.

[0015] In some embodiments, the disruption of the *APOC3* gene regulates triglyceride-rich remnant particles metabolism. In some embodiments, the disruption of the *APOC3* gene reduces the level of triglyceride-rich remnant particles. In some embodiments, the disruption of the *APOC3* gene regulates LDL metabolism. In some embodiments, the disruption of the *APOC3* gene reduces the level of LDL-C. In some embodiments, the disruption of the *APOC3* gene treats the familial chylomicronemia syndrome and hypertriglyceridemia and reduces the risk of ischemic cardiovascular disease. In some embodiments, the disruption of the *APOC3* gene treats cardiovascular diseases.

[0016] In some embodiments, the present disclosure provides a gene editing system for disrupting *PCSK9* gene.

[0017] In some embodiments, the present disclosure provides a gene editing system for disrupting *ANGPTL3* gene.

[0018] In some embodiments, the present disclosure provides a gene editing system for disrupting *ASGR1* gene.

[0019] In some embodiments, the present disclosure provides a gene editing system for disrupting *LPA* gene.

[0020] In some embodiments, the present disclosure provides a gene editing system for disrupting *AGT* gene.

5 [0021] In some embodiments, the present disclosure provides a gene editing system for disrupting *APOC3* gene.

[0022] In one aspect, the present disclosure a gene editing system comprising a base editor and at least one guide RNA that is capable of binding to one or more gene selected from: *PCSK9* gene, *ANGPTL3* gene, *ASGR1* gene, *LPA* gene, *AGT* gene and *APOC3* gene.

10 [0023] In some embodiments, the present disclosure a gene editing system comprising a base editor and at least one guide RNA that is capable of binding to *PCSK9* gene.

[0024] In some embodiments, the present disclosure a gene editing system comprising a base editor and at least one guide RNA that is capable of binding to *ANGPTL3* gene.

15 [0025] In some embodiments, the present disclosure a gene editing system comprising a base editor and at least one guide RNA that is capable of binding to *ASGR1* gene.

[0026] In some embodiments, the present disclosure a gene editing system comprising a base editor and at least one guide RNA that is capable of binding to *LPA* gene.

[0027] In some embodiments, the present disclosure a gene editing system comprising a base editor and at least one guide RNA that is capable of binding to *AGT* gene.

20 [0028] In some embodiments, the present disclosure a gene editing system comprising a base editor and at least one guide RNA that is capable of binding to *APOC3* gene.

[0029] In some embodiments, a highly specific base editor, transformer base editor (tBE), is used to induce efficient and precise gene editing at genomic sites for disrupting the *PCSK9* gene. A tBE is used with a combination of main guide RNA (mgRNA) and helper guide
25 RNA (hgRNA), wherein the mgRNA and hgRNA are capable of binding to the *PCSK9* gene.

[0030] In some embodiments, a highly specific base editor, transformer base editor (tBE), is used to induce efficient and precise gene editing at genomic sites for disrupting the *ANGPTL3* gene. A tBE is used with a combination of main guide RNA (mgRNA) and helper guide RNA (hgRNA), wherein the mgRNA and hgRNA are capable of binding to the
30 *ANGPTL3* gene.

[0031] In some embodiments, a highly specific base editor, transformer base editor (tBE), is used to induce efficient and precise gene editing at genomic sites for disrupting the *ASGR1*

gene. A tBE is used with a combination of main guide RNA (mgRNA) and helper guide RNA (hgRNA), wherein the mgRNA and hgRNA are capable of binding to the *ASGR1* gene.

[0032] In some embodiments, a highly specific base editor, transformer base editor (tBE), is used to induce efficient and precise gene editing at genomic sites for disrupting the *LPA* gene. A tBE is used with a combination of main guide RNA (mgRNA) and helper guide RNA (hgRNA), wherein the mgRNA and hgRNA are capable of binding to the *LPA* gene.

[0033] In some embodiments, a highly specific base editor, transformer base editor (tBE), is used to induce efficient and precise gene editing at genomic sites for disrupting the *AGT* gene. A tBE is used with a combination of main guide RNA (mgRNA) and helper guide RNA (hgRNA), wherein the mgRNA and hgRNA are capable of binding to the *AGT* gene.

[0034] In some embodiments, a highly specific base editor, transformer base editor (tBE), is used to induce efficient and precise gene editing at genomic sites for disrupting the *APOC3* gene. A tBE is used with a combination of main guide RNA (mgRNA) and helper guide RNA (hgRNA), wherein the mgRNA and hgRNA are capable of binding to the *APOC3* gene.

[0035] In some embodiments, the present disclosure provides a gene editing system comprising a main guide RNA (mgRNA) and a helper guide RNA (hgRNA), or at least one DNA polynucleotide encoding the mgRNA and/or the hgRNA, wherein the mgRNA comprises an mgRNA spacer and the hgRNA comprises an hgRNA spacer, wherein the nucleic acid sequences of the mgRNA spacer and the hgRNA spacer comprises the respective sequences as set forth in Table 7A-7F. In some embodiments, the mgRNA and hgRNA comprises the respective sequences as set forth in Table 8A-8C.

[0036] In some embodiments, the mgRNA spacer and/or the hgRNA spacer are capable of binding to the *PCSK9* gene. In some embodiments, the nucleic acid sequence of the mgRNA spacer comprises a sequence selected from SEQ ID NOs: 213-236, 317-328, and 1128.

[0037] In some embodiments, the hgRNA spacer is capable of binding to a site on the target gene that is close to a binding site of the mgRNA spacer. In some embodiments, the hgRNA is capable of binding to a site on the target gene that is within 200 bp upstream or downstream region from the binding site of the mgRNA spacer, preferably within 100 bp upstream or downstream region from the binding site of the mgRNA spacer, more preferably within 91 bp to 34 bp upstream or downstream region from the binding site of the mgRNA spacer, most preferably within 91 bp to 34 bp upstream region from the binding site of the mgRNA spacer.

[0038] In some embodiments, the mgRNA spacer and/or the hgRNA spacer are capable of binding to the *ANGPTL3* gene. In some embodiments, the nucleic acid sequence of the mgRNA spacer comprises a sequence selected from SEQ ID NOs: 403-429 and 550-552.

[0039] In some embodiments, the mgRNA spacer and/or the hgRNA spacer are capable of binding to the *ASGR1* gene. In some embodiments, the nucleic acid sequence of the mgRNA spacer comprises a sequence selected from SEQ ID NOs: 563-584 and 677-684.

5 [0040] In some embodiments, the mgRNA spacer and/or the hgRNA spacer are capable of binding to the *LPA* gene. In some embodiments, the nucleic acid sequence of the mgRNA spacer comprises a sequence selected from SEQ ID NOs: 717-750.

[0041] In some embodiments, the mgRNA spacer and/or the hgRNA spacer are capable of binding to the *AGT* gene. In some embodiments, the nucleic acid sequence of the mgRNA spacer comprises a sequence selected from SEQ ID NOs: 925-961.

10 [0042] In some embodiments, the mgRNA spacer and/or the hgRNA spacer are capable of binding to the *APOC3* gene. In some embodiments, the nucleic acid sequence of the mgRNA spacer comprises a sequence selected from SEQ ID NOs: 1249-1251.

[0043] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 213, and the hgRNA spacer comprises a sequence selected from SEQ ID NOs:
15 237-239, and 277-279.

[0044] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 214, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 240 and 280.

[0045] In some embodiments, the mgRNA spacer comprises a sequence represented by
20 SEQ ID NO: 215, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 241-242, and 281-282.

[0046] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 216, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 243-245, and 283-285.

25 [0047] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 217, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 246-247, and 286-287.

[0048] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 218, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 248-
30 250, and 288-290.

[0049] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 219, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 251-253, and 291-293.

[0050] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 220, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 254 and 294.

5 [0051] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 221, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 255-256, and 295-296.

[0052] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 222, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 257 and 297.

10 [0053] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 223, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 258-259, and 298-299.

[0054] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 224, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 260
15 and 300.

[0055] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 225, the hgRNA spacer comprises a sequence selected from SEQ ID NO: 261 and 301.

[0056] In some embodiments, the mgRNA spacer comprises a sequence represented by
20 SEQ ID NO: 226, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 262 and 302.

[0057] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 227, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 263 and 303.

25 [0058] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 228, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 264 and 304.

[0059] In some embodiments, the mgRNA spacer comprises a sequence represented by
30 SEQ ID NO: 229, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 265 and 305.

[0060] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 230, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 266 and 306.

[0061] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 231, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 267 and 307.

5 [0062] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 232, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 268 and 308.

[0063] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 233, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 269 and 309.

10 [0064] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 234, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 270 and 310.

[0065] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 235, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 271-
15 274 and 311-314.

[0066] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 236, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 275-276 and 315-316.

[0067] In some embodiments, the mgRNA spacer comprises a sequence represented by
20 SEQ ID NO: 317, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 329-331 and 366-368.

[0068] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 318, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 332-333 and 369-370.

25 [0069] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 319, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 334-335 and 371-372.

[0070] In some embodiments, the mgRNA spacer comprises a sequence represented by
30 SEQ ID NO: 320, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 336-337 and 373-374.

[0071] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 321, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 338-340 and 375-377.

[0072] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 322, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 341-344 and 378-381.

5 [0073] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 323, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 345-349 and 382-386.

[0074] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 324, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 350-354 and 387-391.

10 [0075] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 325, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 355-356 and 392-393.

[0076] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 326, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 357-15 359 and 394-396.

[0077] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 327, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 360-363 and 397-400.

[0078] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 328, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 364-20 365 and 401-402.

[0079] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 1128, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1129 and 1130.

25 [0080] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 403, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 430-432 and 490-492.

[0081] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 404, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 433-30 434 and 493-494.

[0082] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 405, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 435-436 and 495-496.

[0083] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 406, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 437 and 497.

5 [0084] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 407, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 438-440 and 498-500.

[0085] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 408, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 441-443 and 501-503.

10 [0086] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 409, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 444-446 and 504-506.

[0087] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 410, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 447-15 449 and 507-509.

[0088] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 411, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 450-452 and 510-512.

[0089] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 412, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 45320 and 513.

[0090] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 413, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 454-456 and 514-516.

25 [0091] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 414, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 457-458 and 517-518.

[0092] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 415, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 459-30 461 and 519-521.

[0093] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 416, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 462-463 and 522-523.

[0094] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 417, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 464-465 and 524-525.

5 [0095] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 418, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 466-468 and 526-528.

[0096] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 419, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 469-470 and 529-530.

10 [0097] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 420, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 471-472 and 531-532.

[0098] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 421, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 473
15 and 533.

[0099] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 422, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 474-475 and 534-535.

[00100] In some embodiments, the mgRNA spacer comprises a sequence represented by
20 SEQ ID NO: 423, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 476-477 and 536-537.

[00101] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 424, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 478
and 538.

25 [00102] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 425, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 479-481 and 539-541.

[00103] In some embodiments, the mgRNA spacer comprises a sequence represented by
30 SEQ ID NO: 426, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 482-484 and 542-544.

[00104] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 427, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 485
and 545.

[00105] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 428, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 486-487 and 546-547.

5 [00106] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 429, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 488-489 and 548-549.

[00107] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 550, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 553 and 558.

10 [00108] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 551, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 554-555 and 559-560.

[00109] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 552, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 556-15 557 and 561-562.

[00110] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 563, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 585 and 631.

20 [00111] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 564, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 586 and 632.

[00112] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 565, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 587-588 and 633-634.

25 [00113] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 566, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 589-590 and 635-636.

[00114] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 567, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 591-30 593 and 637-639.

[00115] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 568, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 594-596 and 640-642.

[00116] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 569, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 597-598 and 643-644.

5 [00117] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 570, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 599-601 and 645-647.

[00118] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 571, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 602-604 and 648-650.

10 [00119] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 572, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 605-606 and 651-652.

[00120] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 573, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 607-15 608 and 653-654.

[00121] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 574, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 609-610 and 655-656.

20 [00122] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 575, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 611-612 and 657-658.

[00123] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 576, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 613-614 and 659-660.

25 [00124] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 577, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 615-616 and 661-662.

30 [00125] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 578, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 617-619 and 663-665.

[00126] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 579, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 620-622 and 666-668.

[00127] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 580, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 623-625 and 669-671.

5 [00128] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 581, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 626 and 672.

[00129] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 582, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 627 and 673.

10 [00130] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 583, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 628 and 674.

[00131] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 584, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 629-630 and 675-676.

[00132] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 677, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 685-687 and 701-703.

20 [00133] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 678, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 688-689 and 704-705.

[00134] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 679, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 690-691 and 706-707.

25 [00135] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 680, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 692-693 and 708-709.

30 [00136] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 681, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 694 and 710.

[00137] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 682, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 695-696 and 711-712.

[00138] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 683, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 697-698 and 713-714.

5 [00139] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 684, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 699-700 and 715-716.

[00140] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 717, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 751-755 and 838-842.

10 [00141] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 718, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 756-760 and 843-847.

[00142] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 719, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 761-15 765 and 848-852.

[00143] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 720, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 766-769 and 853-856.

[00144] In some embodiments, the mgRNA spacer comprises a sequence represented by 20 SEQ ID NO: 721, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 770-773 and 857-860.

[00145] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 722, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 774-775 and 861-862.

25 [00146] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 723, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 776-778 and 863-865.

[00147] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 724, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 779 30 and 866.

[00148] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 725, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 780-782 and 867-869.

[00149] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 726, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 783-785 and 870-872.

5 [00150] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 727, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 786-788 and 873-875.

[00151] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 728, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 789 and 876.

10 [00152] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 729, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 790-792 and 877-879.

[00153] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 730, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 793
15 and 880.

[00154] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 731, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 794-795 and 881-882.

[00155] In some embodiments, the mgRNA spacer comprises a sequence represented by
20 SEQ ID NO: 732, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 796-798 and 883-885.

[00156] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 733, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 799 and 886.

25 [00157] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 734, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 800-802 and 887-889.

[00158] In some embodiments, the mgRNA spacer comprises a sequence represented by
30 SEQ ID NO: 735, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 803-804 and 890-891.

[00159] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 736, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 805-806 and 892-893.

[00160] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 737, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 807 and 894.

5 [00161] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 738, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 808 and 895.

[00162] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 739, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 809-810 and 896-897.

10 [00163] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 740, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 811-813 and 898-900.

[00164] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 741, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 814-15 815 and 901-902.

[00165] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 742, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 816-818 and 903-905.

[00166] In some embodiments, the mgRNA spacer comprises a sequence represented by 20 SEQ ID NO: 743, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 819-820 and 906-907.

[00167] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 744, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 821-823 and 908-910.

25 [00168] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 745, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 824-825 and 911-912.

[00169] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 746, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 826-30 828 and 913-915.

[00170] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 747, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 829-831 and 916-918.

[00171] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 748, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 832-833 and 919-920.

5 [00172] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 749, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 834 and 921.

[00173] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 750, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 835-837 and 922-924.

10 [00174] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 925, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 962-964 and 1034-1036.

[00175] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 926, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 965-15 966 and 1037-1038.

[00176] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 927, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 967-968 and 1039-1040.

[00177] In some embodiments, the mgRNA spacer comprises a sequence represented by 20 SEQ ID NO: 928, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 969-970 and 1041-1042.

[00178] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 929, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 971-972 and 1043-1044.

25 [00179] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 930, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 973-974 and 1045-1046.

[00180] In some embodiments, the mgRNA spacer comprises a sequence represented by 30 SEQ ID NO: 931, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 975-977 and 1047-1049.

[00181] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 932, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 978-980 and 1050-1052.

[00182] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 933, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 981 and 1053.

5 [00183] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 934, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 982-984 and 1054-1056.

[00184] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 935, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 985-987 and 1057-1059.

10 [00185] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 936, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 988-989 and 1060-1061.

[00186] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 937, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 990-15 991 and 1062-1063.

[00187] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 938, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 992-993 and 1064-1065.

[00188] In some embodiments, the mgRNA spacer comprises a sequence represented by 20 SEQ ID NO: 939, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 994-995 and 1066-1067.

[00189] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 940, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 996-997 and 1068-1069.

25 [00190] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 941, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 998-999 and 1070-1071.

[00191] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 942, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 30 1000-1001 and 1072-1073.

[00192] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 943, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1002-1003 and 1074-1075.

[00193] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 944, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1004-1005 and 1076-1077.

5 [00194] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 945, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1006-1007 and 1078-1079.

[00195] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 946, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1008-1009 and 1080-1081.

10 [00196] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 947, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1010-1011 and 1082-1083.

[00197] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 948, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1012
15 and 1084.

[00198] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 949, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1013 and 1085.

[00199] In some embodiments, the mgRNA spacer comprises a sequence represented by
20 SEQ ID NO: 950, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1014-1015 and 1086-1087.

[00200] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 951, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1016-1017 and 1088-1089.

25 [00201] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 952, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1018-1019 and 1090-1091.

[00202] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 953, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1020
30 and 1092.

[00203] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 954, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1021-1022 and 1093-1094.

[00204] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 955, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1023 and 1095.

5 [00205] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 956, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1024 and 1096.

[00206] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 957, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1025-1026 and 1097-1098.

10 [00207] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 958, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1027-1028 and 1099-1100.

[00208] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 959, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 15 1029-1030 and 1101-1102.

[00209] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 960, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1031 and 1103.

20 [00210] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 961, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1032-1033 and 1104-1105.

[00211] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 1249, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1252-1254 and 1259-1261.

25 [00212] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 1250, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1255-1256 and 1262-1263.

[00213] In some embodiments, the mgRNA spacer comprises a sequence represented by SEQ ID NO: 1251, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 30 1257-1258 and 1264-1265.

[00214] In some embodiments, the mgRNA which is capable of binding to a target sequence located in *PCSK9* gene, comprises a sequence selected from SEQ ID NOs: 1109, 1110, 1119, 1121, 1125, and 1127.

[00215] In some embodiments, the hgRNA which is capable of binding to *PCSK9* gene comprises a sequence selected from SEQ ID NOs: 1108, 1118, 1120, 1122-1124, and 1126.

[00216] In some embodiments, the mgRNA comprises a sequence represented by SEQ ID NO: 1109, the hgRNA comprises a sequence selected from SEQ ID NOs: 1108, 1118, 1120,
5 1122 and 1123.

[00217] In some embodiments, the mgRNA comprises a sequence represented by SEQ ID NO: 1110, the hgRNA comprises a sequence selected from SEQ ID NOs: 1108, 1118, 1120, 1122 and 1123.

[00218] In some embodiments, the mgRNA comprises a sequence represented by SEQ ID
10 NO: 1119, the hgRNA comprises a sequence selected from SEQ ID NOs: 1108, 1118, 1120, 1122 and 1123.

[00219] In some embodiments, the mgRNA comprises a sequence represented by SEQ ID NO: 1121, the hgRNA comprises a sequence selected from SEQ ID NOs: 1108, 1118, 1120, 1122 and 1123.

[00220] In some embodiments, the mgRNA comprises a sequence represented by SEQ ID
15 NO: 1125, the hgRNA comprises a sequence represented by SEQ ID NOs: 1124.

[00221] In some embodiments, the mgRNA comprises a sequence represented by SEQ ID NO: 1127, the hgRNA comprises a sequence represented by SEQ ID NOs: 1126.

[00222] In some embodiments, the mgRNA which is capable of binding to a target
20 sequence located in *ANGPTL3* gene, comprises a sequence selected from SEQ ID NOs: 1132, 1134, and 1136.

[00223] In some embodiments, the hgRNA which is capable of binding to *ANGPTL3* gene comprises a sequence selected from SEQ ID NOs: 1131, 1133, and 1135.

[00224] In some embodiments, the mgRNA comprises a sequence represented by SEQ ID
25 NO: 1132, the hgRNA comprises a sequence represented by SEQ ID NO: 1131.

[00225] In some embodiments, the mgRNA comprises a sequence represented by SEQ ID NO: 1134, the hgRNA comprises a sequence represented by SEQ ID NO: 1133.

[00226] In some embodiments, the mgRNA comprises a sequence represented by SEQ ID NO: 1136, the hgRNA comprises a sequence represented by SEQ ID NOs: 1135.

[00227] In some embodiments, the mgRNA which is capable of binding to a target
30 sequence located in *APOC3* gene, comprises a sequence selected from SEQ ID NOs: 1266, 1268, 1270, 1272, 1274, and 1276.

[00228] In some embodiments, the hgRNA which is capable of binding to *APOC3* gene comprises a sequence selected from SEQ ID NOs: 1267, 1269, 1271, 1273, 1275 and 1277.

[00229] In some embodiments, the mgRNA comprises a sequence represented by SEQ ID NO: 1266, the hgRNA comprises a sequence represented by SEQ ID NO: 1267.

5 [00230] In some embodiments, the mgRNA comprises a sequence represented by SEQ ID NO: 1268, the hgRNA comprises a sequence represented by SEQ ID NO: 1269.

[00231] In some embodiments, the mgRNA comprises a sequence represented by SEQ ID NO: 1270, the hgRNA comprises a sequence represented by SEQ ID NOs: 1271.

10 [00232] In some embodiments, the mgRNA comprises a sequence represented by SEQ ID NO: 1272, the hgRNA comprises a sequence represented by SEQ ID NOs: 1273.

[00233] In some embodiments, the mgRNA comprises a sequence represented by SEQ ID NO: 1274, the hgRNA comprises a sequence represented by SEQ ID NOs: 1275.

[00234] In some embodiments, the mgRNA comprises a sequence represented by SEQ ID NO: 1276, the hgRNA comprises a sequence represented by SEQ ID NOs: 1277.

15 [00235] In some embodiments, the gene editing system disclosed herein comprises (1) an hgRNA comprising a CRISPR motif, an hgRNA spacer, and a first protein-binding motif, or a DNA polynucleotide encoding the hgRNA, (2) an mgRNA comprising a second CRISPR motif and an mgRNA spacer, or a DNA polynucleotide encoding the mgRNA, (3) a first CRISPR-associated protein (Cas protein), or a polynucleotide encoding the first Cas protein,
20 wherein the first Cas protein binds to the first CRISPR motif, (4) a second Cas protein, or a polynucleotide encoding the second Cas protein, wherein the second Cas protein binds to the second CRISPR motif, and (5) a first fusion protein comprising a nucleobase deaminase or a catalytic domain thereof and a first RNA binding domain, or a polynucleotide encoding the first fusion protein, wherein the nucleobase deaminase or the catalytic domain thereof and the
25 first RNA binding domain are optionally connected by a linker, and wherein the first RNA binding domain binds to the first protein-binding motif, and wherein the first Cas protein and second Cas protein are the same or different.

[00236] In some embodiments, the gene editing system disclosed herein comprises (1) an hgRNA comprising a CRISPR motif, an hgRNA spacer, and a first protein-binding motif, or
30 a DNA polynucleotide encoding the hgRNA, (2) an mgRNA comprising a second CRISPR motif and the mgRNA spacer, or a DNA polynucleotide encoding the mgRNA, (3) a first CRISPR-associated protein (Cas protein), or a polynucleotide encoding the first Cas protein, wherein the first Cas protein binds to the first CRISPR motif, (4) a second Cas protein, or a polynucleotide encoding the second Cas protein, wherein the second Cas protein binds to the
35 second CRISPR motif, (5) a first fusion protein comprising a nucleobase deaminase or a

catalytic domain thereof and a first RNA binding domain, or a polynucleotide encoding the first fusion protein, wherein the nucleobase deaminase or the catalytic domain thereof and the first RNA binding domain are optionally connected by a linker, and wherein the first RNA binding domain binds to the first protein-binding motif, (6) a protease, or a polynucleotide
5 encoding the protease, and (7) a nucleobase deaminase inhibitor domain, wherein the first Cas protein and second Cas protein are the same or different, wherein the nucleobase deaminase inhibitor domain is connected to the nucleobase deaminase or the catalytic domain thereof in the first fusion protein optionally by a linker, and wherein there is a cleavage site for the protease between the nucleobase deaminase inhibitor domain and the nucleobase
10 deaminase or the catalytic domain thereof.

[00237] In some embodiments, the gene editing system disclosed herein comprises (1) an hgRNA comprising a CRISPR motif, an hgRNA spacer, and a first protein-binding motif, or a DNA polynucleotide encoding the hgRNA, (2) an mgRNA comprising a second CRISPR motif and an mgRNA spacer, or a DNA polynucleotide encoding the mgRNA, (3) a first
15 CRISPR-associated protein (Cas protein), or a polynucleotide encoding the first Cas protein, wherein the first Cas protein binds to the first CRISPR motif, (4) a second Cas protein, or a polynucleotide encoding the second Cas protein, wherein the second Cas protein binds to the second CRISPR motif, (5) a first fusion protein comprising a nucleobase deaminase or a catalytic domain thereof and a first RNA binding domain, or a polynucleotide encoding the
20 first fusion protein, wherein the nucleobase deaminase or the catalytic domain thereof and the first RNA binding domain are optionally connected by a linker, and wherein the first RNA binding domain binds to the first protein-binding motif, (6) a protease, or a polynucleotide encoding the protease, (7) a nucleobase deaminase inhibitor domain, and (8) a second fusion protein comprising the protease and a second RNA binding domain, or a polynucleotide
25 encoding the second fusion protein, wherein the first Cas protein and second Cas protein are the same or different, wherein the nucleobase deaminase inhibitor domain is connected to the nucleobase deaminase or the catalytic domain thereof in the first fusion protein optionally by a linker, and wherein there is a cleavage site for the protease between the nucleobase deaminase inhibitor domain and the nucleobase deaminase or the catalytic domain thereof,
30 wherein the protease and the second RNA binding domain are optionally connected by a linker, wherein the mgRNA further comprises a second protein-binding motif, and wherein the second RNA binding domain binds to the second protein-binding motif.

[00238] In some embodiments, the protease is split into a first protease fragment and a second protease fragment, wherein the first or second protease fragment alone is not able to
35 cleave the cleavage site.

[00239] In some embodiments, the gene editing system disclosed herein comprises (1) an hgRNA comprising a CRISPR motif, an hgRNA spacer, and a first protein-binding motif, or

a DNA polynucleotide encoding the hgRNA, (2) an mgRNA comprising a second CRISPR motif and an mgRNA spacer, or a DNA polynucleotide encoding the mgRNA, (3) a first CRISPR-associated protein (Cas protein), or a polynucleotide encoding the first Cas protein, wherein the first Cas protein binds to the first CRISPR motif, (4) a second Cas protein, or a polynucleotide encoding the second Cas protein, wherein the second Cas protein binds to the second CRISPR motif, (5) a first fusion protein comprising a nucleobase deaminase or a catalytic domain thereof and a first RNA binding domain, or a polynucleotide encoding the first fusion protein, wherein the nucleobase deaminase or the catalytic domain thereof and the first RNA binding domain are optionally connected by a linker, and wherein the first RNA binding domain binds to the first protein-binding motif, (6) a protease, or a polynucleotide encoding the protease, (7) a nucleobase deaminase inhibitor domain, (8) a second fusion protein comprising the first protease fragment and a second RNA binding domain, or a polynucleotide encoding the second fusion protein, wherein the first protease fragment and the second RNA binding domain are optionally connected by a linker, and (9) a third fusion protein comprising the second protease fragment and a third RNA binding domain, or a polynucleotide encoding the third fusion protein, wherein the second protease fragment and the third RNA binding domain are optionally connected by a linker, wherein the first Cas protein and second Cas protein are the same or different, wherein the nucleobase deaminase inhibitor domain is connected to the nucleobase deaminase or the catalytic domain thereof in the first fusion protein optionally by a linker, and wherein there is a cleavage site for the protease between the nucleobase deaminase inhibitor domain and the nucleobase deaminase or the catalytic domain thereof, wherein the mgRNA further comprises a second protein-binding motif and a third protein-binding motif, wherein the second RNA binding domain binds to the second protein-binding motif, and wherein the third RNA binding domain binds to the third protein-binding motif.

[00240] In some embodiments, the gene editing system disclosed herein comprises (1) an hgRNA comprising a CRISPR motif, an hgRNA spacer, and a first protein-binding motif, or a DNA polynucleotide encoding the hgRNA, (2) an mgRNA comprising a second CRISPR motif and an mgRNA spacer, or a DNA polynucleotide encoding the mgRNA, (3) a first CRISPR-associated protein (Cas protein), or a polynucleotide encoding the first Cas protein, wherein the first Cas protein binds to the first CRISPR motif, (4) a second Cas protein, or a polynucleotide encoding the second Cas protein, wherein the second Cas protein binds to the second CRISPR motif, (5) a first fusion protein comprising a nucleobase deaminase or a catalytic domain thereof and a first RNA binding domain, or a polynucleotide encoding the first fusion protein, wherein the nucleobase deaminase or the catalytic domain thereof and the first RNA binding domain are optionally connected by a linker, and wherein the first RNA binding domain binds to the first protein-binding motif, (6) a protease, or a polynucleotide encoding the protease, (7) a nucleobase deaminase inhibitor domain, (8) a second fusion

protein comprising the first protease fragment and a second RNA binding domain, or a polynucleotide encoding the second fusion protein, wherein the first protease fragment and the second RNA binding domain are optionally connected by a linker, and (9) a third fusion protein comprising the second protease fragment and a third RNA binding domain, or a polynucleotide encoding the third fusion protein, wherein the second protease fragment and the third RNA binding domain are optionally connected by a linker, wherein the first Cas protein and second Cas protein are the same or different, wherein the nucleobase deaminase inhibitor domain is connected to the nucleobase deaminase or the catalytic domain thereof in the first fusion protein optionally by a linker, and wherein there is a cleavage site for the protease between the nucleobase deaminase inhibitor domain and the nucleobase deaminase or the catalytic domain thereof, wherein the mgRNA further comprises a second protein-binding motif and a third protein-binding motif, wherein the second RNA binding domain binds to the second protein-binding motif, wherein the third RNA binding domain binds to the third protein-binding motif, wherein the second and third RNA binding domains are the same or different, and the second and third protein-binding motifs are the same or different.

[00241] In some embodiments, the gene editing system disclosed herein comprises (1) an hgRNA comprising a CRISPR motif, an hgRNA spacer, and a first protein-binding motif, or a DNA polynucleotide encoding the hgRNA, (2) the mgRNA comprising a second CRISPR motif and an mgRNA spacer, or a DNA polynucleotide encoding the mgRNA, (3) a first CRISPR-associated protein (Cas protein), or a polynucleotide encoding the first Cas protein, wherein the first Cas protein binds to the first CRISPR motif, (4) a second Cas protein, or a polynucleotide encoding the second Cas protein, wherein the second Cas protein binds to the second CRISPR motif, (5) a first fusion protein comprising a nucleobase deaminase or a catalytic domain thereof and a first RNA binding domain, or a polynucleotide encoding the first fusion protein, wherein the nucleobase deaminase or the catalytic domain thereof and the first RNA binding domain are optionally connected by a linker, and wherein the first RNA binding domain binds to the first protein-binding motif, (6) a protease, or a polynucleotide encoding the protease, (7) a nucleobase deaminase inhibitor domain, (8) a second fusion protein comprising the first protease fragment and a second RNA binding domain, or a polynucleotide encoding the second fusion protein, wherein the first Cas protein and second Cas protein are the same or different, wherein the nucleobase deaminase inhibitor domain is connected to the nucleobase deaminase or the catalytic domain thereof in the first fusion protein optionally by a linker, and wherein there is a cleavage site for the protease between the nucleobase deaminase inhibitor domain and the nucleobase deaminase or the catalytic domain thereof, wherein the first protease fragment and the second RNA binding domain are optionally connected by a linker, wherein the mgRNA further comprises a second protein-binding motif, and wherein the second RNA binding domain binds to the second protein-binding motif.

[00242] In some embodiments, the protease is a TEV protease, a TuMV protease, a PPV protease, a PVY protease, a ZIKV protease, or a WNV protease.

[00243] In some embodiments, the protease cleavage site is a self-cleaving peptide, such as the 2A peptides. “2A peptides” are 18-22 amino-acid-long viral oligopeptides that mediate
5 “cleavage” of polypeptides during translation in eukaryotic cells. The designation “2A” refers to a specific region of the viral genome and different viral 2As have generally been named after the virus they were derived from. The first discovered 2A was F2A (foot-and-mouth disease virus), after which E2A (equine rhinitis A virus), P2A (porcine teschovirus-1 2A), and T2A (thosia asigna virus 2A) were also identified. A few non-limiting examples of 2A
10 peptides are provided as GSGATNFSLLKQAGDVEENPGP (SEQ ID NO: 210); GSGEGRGSLLTCGDVEENPGP (SEQ ID NO: 211); and GSGQCTNYALLKLAGDVESNPGP (SEQ ID NO: 212).

[00244] In some embodiments, the protease is a TEV protease. In some embodiments, the TEV protease comprises a sequence as set forth in SEQ ID NO: 195.

[00245] In some embodiments, the first and/or the second TEV protease fragment is not
15 able to cleave the TEV cleavage site on its own. However, in the presence of the remaining portion of the TEV protease, this fragment will be able to effectuate the cleavage. The TEV fragment may be the TEV N-terminal domain (e.g., SEQ ID NO: 196) or the TEV C-terminal domain (e.g., SEQ ID NO: 197). In some embodiments, the first TEV protease fragment
20 comprises a sequence of SEQ ID NO: 196. In some embodiments, the first TEV protease fragment comprises a sequence of SEQ ID NO: 197.

[00246] In some embodiments, the nucleobase deaminase inhibitor is an inhibitory domain of a nucleobase deaminase.

[00247] A “nucleobase deaminase inhibitor” or an “inhibitory domain” refers to a protein
25 or a protein domain that inhibits the deaminase activity of a nucleobase deaminase.

[00248] In some embodiments, the nucleobase deaminase inhibitor is an inhibitory domain of a nucleobase deaminase. In some embodiments, the nucleobase deaminase inhibitor is an inhibitory domain of a human cytidine deaminase or mouse cytidine deaminase. In some
embodiments, the nucleobase deaminase inhibitor is a mouse A3 cytidine deaminase domain
30 2 (mA3-CDA2) or human A3B cytidine deaminase domain 1 (hA3B-CDA1).

[00249] In some embodiments, the inhibitory domain of a cytidine deaminase comprises an amino acid sequence selected from SEQ ID NO: 1145-1234, preferably, the inhibitory domain of a cytidine deaminase comprises an amino acid sequence selected from SEQ ID NO: 1145 and 1146.

[00250] Table 1 shows proteins/domains that have significant sequence homology to mA3-CDA2 core sequence and/or hA3B-CDA1. All of these proteins and domains, as well as their variants and equivalents, are contemplated to have nucleobase deaminase inhibition activities.

[00251] Table 1

Name	Sequence	SEQ ID NO:
mouse APOBEC3 cytidine deaminase domain 2 (mA3-CDA2)	MSSSTLSNICLTKGLPETRFWVEGRMDPLSEEEF YSQFYNQVRVKHLCYYHRMKPYLCYQLEQFNGQA PLKGCLLSEKGKQHAELFLDKIRSMELSQVTITC YLTWSPCPNCAWQLAAFKRDRPDILHIYTSRLYF HWKRPFQKGLCSLWQSGILVDVMDLPQFTDCWT NFDVNPKRPFWPWKGLEIISRRTQRRLRRIKESWGL QDLVNDFGNLQLGPPMS	SEQ ID NO: 1145
human APOBEC3B cytidine deaminase domain 1 (hA3B-CDA1)	MNPQIRNPMERMYRDTFYDNFENEPILYGRSYTW LCYEVKIKRGRSNLLWDTGVFRGQVYFKPQYHA EMCFLSWFCGNQLPAYKCFQITWVSWTPCPDCV AKLAEFLSEHPNVTLTISAARLYYYWERDYRRAL CRLSQAGARVKIMDYEEFAYCWENFVYNEGQ	SEQ ID NO: 1146
Mouse APOBEC3 cytidine deaminase domain 2 core (AA282-AA355)	SEKGKQHAELFLDKIRSMELSQVTITCYLTWSPC PNCWQLAAFKRDRPDILHIYTSRLYFHWKRPF QKGLC	SEQ ID NO: 1147
Mus spicilegus A3 (AA248-AA321)	SEKGKQHAELFLDKIRSMELSQVTITCYLTWSPC PNCWQLAAFKRDRPDILPHIYTSRLYFHWKRPF QKGLC	SEQ ID NO: 1148
Cricetulus longicaudatus A3 (AA249-AA322)	SEKGKQHAELFLDKIRSMELSQVTITCYLTWSPC PNCWRLAAFKRDRPDILHIYTSRLYFHWKRPF QKGLC	SEQ ID NO: 1149
Mus terricolor A3 (AA248-AA321)	SEKGKQHAELFLNKIRSMELSQVTITCYLTWSPC PNCWQLAAFKKDRPDILHIYTSRLYFHWKRPF QKGLC	SEQ ID NO: 1150
Mus caroli A3 (AA260-AA333)	SKKGKQHAELFLDKIRSMELSQVTITCYLTWSPC PNCWQLAAFKRDHPDLILHIYTSRLYFHWKRPF QKGLC	SEQ ID NO: 1151

Mus pahari A3 (AA263-AA336)	SKKGKQHAEILFLEKIRSMELSQMRITCYLTWSPC PNCWQLAAFQKDRPDLILHIYTSRLYFHWRRIFQ KGLC	SEQ ID NO: 1152
Mus shortridgei A3 (AA233- AA306)	SKKGKQHAEILFLEKIRSMELSQMRITCYLTWSPC PNCWQLAAFQKDRPDLILHIYTSRLYFHWRRIFQ KGLC	SEQ ID NO: 1153
Mus setulosus A3 (AA29-AA302)	SKKGKQHAEILFLDKIRSMELSQVRITCYLTWSPC PNCWQLETFFKDRPDLILHIYTSRLYFHWKRAF QEGLC	SEQ ID NO: 1154
Grammomys surdaster A3 (AA270-AA344)	SKKGKPHAEILFLDKMWSMEELSQVRITCYLTWS PCPNCARQLAAFKKDHPGLILRIYTSRLYFYWRR KFQKGLC	SEQ ID NO: 1155
Rattus norvegicus A3 (AA256- AA328)	KKGEQHVEILFLEKMRSMEELSQVRITCYLTWSPCP NCARQLAAFKKDHPDLILRIYTSRLYFYWRKKFQ KGLC	SEQ ID NO: 1156
Mastomys coucha A3 (AA258- AA331)	SKKGRQHAEILFLEKVRSMQLSQVRITCYLTWSPC PNCWQLAAFKMDHPDLILRIYASRLYFHWRRRAF QKGLC	SEQ ID NO: 1157
Cricetulus griseus A3B (AA235- AA307)	NKKGKHAEILFIDEMRSLELGQVQITCYLTWSPCP NCAQELAAFKSDHPDLVLRITYSRLYFHWRRKYQ EGLC	SEQ ID NO: 1158
Peromyscus leucopus A3 (AA266-AA338)	NKKGKHAEILFIDEMRSLELGQARITCYLTWSPCP NCAQKLAAFKKDHPDLVLRVYTSRLYFHWRRKY QEGLC	SEQ ID NO: 1159
Mesocricetus auratus A3 (AA268-AA340)	NKKDKHAEILFIDKMRSLELCQVRITCYLTWSPCP NCAQELAAFKKDHPDLVLRITYSRLYFHWRRKY QEGLC	SEQ ID NO: 1160
Microtus ochrogaster A3B (AA266-AA338)	NKKGKHAEILFIDEMRSLKLSQERITCYLTWSPCP NCAQELAAFKRDHPGLVLRITYSRLYFHWRRKY QEGLC	SEQ ID NO: 1161
Nannospalax galili A3 (AA231-AA302)	NKRAKHAEILLIDMMRSMELGQVQITCYITWSPC PTCAQELAAFKQDHPDLVLRITYSRLYFHWKRKF QKGL	SEQ ID NO: 1162
Meriones unguiculatus A3 (AA233-AA305)	NKKGRHAEICLIDEMRSLGLGKAQITCYLTWSPC RKCAQELATFKKDHPDLVLRVYASRLYFHWSRK YQQGLC	SEQ ID NO: 1163
Dipodomys ordii A3 (AA256- AA330)	NKKGHHAEIRFIERIRSMGLDPSQDYQITCYLTWS PCLDCAFKLAKLKKDFPRLTLRIFTSRLYFHWIRK FQKGL	SEQ ID NO: 1164

Jaculus jaculus A3 (AA303- AA374)	NKKGKHAEARFVDKMRSMLDHALITCYLTWSP CLDCSQKLAALKRDHPGLTLRIFTSRLYFHWVKK FQEGL	SEQ ID NO: 1165
Chinchilla lanigera A3H (AA86-AA161)	SPQKGHHAESRFIKRISSMDLDRSRSYQITCFLTWS PCPSCAQELASFKRAHPHLRFQIFVSRLYFHWKRS YQAGL	SEQ ID NO: 1166
Heterocephalus glaber A3 (AA277-AA350)	KKGYHAESRFIKRICSMDLGQDQSYQVTCFLTWS PCPHCAQELVSFKRAHPHLRLQIFTARLFFHWKRS YQEGL	SEQ ID NO: 1167
Octodon degus A3 (AA256- AA329)	KKGQHAEIRFIERIHSMALDQARSYQITCFLTWSP CPFCAQELASFKSTHPRVHLQIFVSRLYFHWKRSY QEGL	SEQ ID NO: 1168
Urocitellus parryii A3 (AA256-AA330)	NKKGHHAEIRFIKKIRSLDLQSQNYEVTCTWSP PCPDCAQELVALTRSHPHVRLRLFTSRLYFHWFW SFQEGL	SEQ ID NO: 1169
Aotus nancymae A3H (AA75- AA146)	NRHAEICFIDEIESMGLDKTQCYEVTCTWSPCP SCAQKLAFTKAQVHLNLRIFASRLYYHWRSSYQ KGL	SEQ ID NO: 1170
Cebus capucinus imitator A3H (AA55-AA126)	NRHAEICFIDEIESMGLDKTQCYEVTCTWSPCP SCAQKLVAFAKAQDHLNLRIFASRLYYHWRRRY KEGL	SEQ ID NO: 1171
Saimiri boliviensis boliviensis A3H (AA56-AA125)	HVEICFIDKIASMELDKTQCYDVTCYLTWSPCPSC AQKLAAFAKAQDHLNLRIFASRLYYHWRRSYQK GL	SEQ ID NO: 1172
Homo sapiens A3H (AA49- AA123)	NKKKCHAEICFINEIKSMGLDETQCYQVTCYLTW SPCSSCAWELVDFIKAHDHLNLGIFASRLYYHWC KPQQKGL	SEQ ID NO: 1173
Homo sapiens ARP10 (AA48- AA123)	ENKKKCHAEICFINEIKSMGLDETQCYQVTCYLT WSPCSSCAWELVDFIKAHDHLNLGIFASRLYYHW CKPQQKGL	SEQ ID NO: 1174
Pan paniscus A3H (AA49- AA123)	NKKKCHAEICFINEIKSMGLDETQCYQVTCYLTW SPCSSCAWKLVDIFIQAHDHLNLRIFASRLYYHWC KPQQEGL	SEQ ID NO: 1175
Symphalangus syndactylus A3H (AA49-AA123)	NKKKRHAEIRFINKIKSMGLDETQCYQVTCYLTW SPCPSCAWELVDFIKAHDHLNLGIFASRLYYHWC RHQQEGL	SEQ ID NO: 1176

Macaca mulatta A3H (AA49- AA123)	NKKKDHAIEIRFINKIKSMGLDETQCYQVTCYLTW SPCPSCAGELVDFIKAHRHLNLRIFASRLYYHWRP NYQEGL	SEQ ID NO: 1177
Theropithecus gelada A3H (AA54-AA128)	NKKKEHAEIRFINKIKSMGLDETQCYQVTCYLTW SPCPSCAGKLVDIFIKAHHHLNLRIFASRLYYHWRP NYQEGL	SEQ ID NO: 1178
Mandrillus leucophaeus A3H (AA49-AA123)	NKKKHAEIHFINKIKSMGLDETQCYQVTCYLTW SPCPSCARELVDFIKAHRHLNLRIFASRLYYHWRP HYQEGL	SEQ ID NO: 1179
Bos grunniens A3 (AA74-AA148)	NKKQRHAEIRFIDKINSLDLNPSQSYKIICYITWSP CPNCANELVNFITRNNHLKLEIFASRLYFHWIKPF KMGL	SEQ ID NO: 1180
Bubalus bubalis A3 (AA74- AA148)	NKKQRHAEIRFIDKINSLDLNPSQSYKIICYITWSP CPNCASELVDFITRNDHLDLQIFASRLYFHWIKPF KRGL	SEQ ID NO: 1181
Odocoileus virginianus texanus A3H (AA209-AA283)	NKKQRHAEIRFIDKINSLNLDNRQSYKIICYITWSP CPRCASELVDFITGNDHLNLQIFASRLYFHWKPPF QRGL	SEQ ID NO: 1182
Sus scrofa A3 (AA51-AA125)	NKKKRHAEIRFIDKINSLNLDQNCYRIICYVTWS PCHNCAKELVDFISNRHLSLQLFASRLYFHWVR CYQRGL	SEQ ID NO: 1183
Ceratotherium simum simum A3B (AA232- AA306)	NKKKRHAEIRFIDKIKSLGLDRVQSYEITCYITWSP CPTCALELVAFTRDYPRLSLQIFASRLYFHWRRRS IQGL	SEQ ID NO: 1184
Equus caballus A3H (AA79- AA153)	NKKKRHAEIRFIDKINSLGLDQDQSYEITCYVTWS PCATCACKLIKFRKFPNLSLRIFVSRLYYHWFRQ NQQGL	SEQ ID NO: 1185
Enhydra lutris kenyoni A3B (AA243-AA316)	KKKRHAEIRFIDSIRALQLDQSQRFETCYLTWSPC PTCAKELAMFVQDHPHISLRLFASRLYFHWRWKY QEGL	SEQ ID NO: 1186
Leptonychotes weddellii A3H (AA50-AA123)	KKKRHAEIRFIDNIKALRLDTSQRFEITCYVTWSPC PTCAKELVAFVRDHRHISLRLFASRLYFHWLREN KKGL	SEQ ID NO: 1187
Ursus arctos horribilis A3F (AA552-AA626)	NKKKRHAEIRFIDKIRSLQRDSSQTFEITCYVTWSP CFTCAEELVAFVRDHPHVRRLRLFASRLYFHWLRK YQEGL	SEQ ID NO: 1188

Panthera leo bleyenberghi A3H (AA50- AA124)	NKKKRHAEICFIDKIKSLTRDTSQRFEIICYITWSPC PFCAEELVAFVKDNPHLSLRIFASRLYVHWRWKY QQGL	SEQ ID NO: 1189
Panthera tigris sumatrae A3H (AA50-AA124)	NKKKRHAEICFIDKIKSLTRDTSQRFEIICYITWSPC PFCAEELVAFVKDNPHLSLRIFASRLYVHWRWKY QQGL	SEQ ID NO: 1190
Tupaia belangeri A3 (AA46- AA120)	NKKHRHAEVRFIKIRSMSLDLDQKHQLTCYLTW SPCPSCAQELVTFMAESRHLNLQVFVSRLYFHWQ RDFQQGL	SEQ ID NO: 1191
Gorilla A3B (AA29-AA138)	GRSYNWLCYEVKIKRGRSNLLWNTGVFRGQMYS QPEHHAEMCFLSWFCGNQLPAYKCFQITWVFSW TPCPDCVAKLAEFLAEYPNVTLTISTARLYYYWE RDYRRALCRL	SEQ ID NO: 1192
Pan paniscus A3B (AA29- AA138)	GRSYTWLCYEVKIRRGHSNLLWDTGVFRGQMYS QPEHHAEMYFLSWFCGNQLPAYKCFQITWVFSW TPCPDCVAKLAEFLAEHPNVTLTISAARLYYYWE RDYRRALCRL	SEQ ID NO: 1193
Pan troglodytes A3B (AA29- AA138)	GRSYTWLCYEVKIRRGHSNLLWDTGVFRGQMYS QPEHHAEMCFLSWFCGNQLSAYKCFQITWVFSW TPCPDCVAKLAKFLAEHPNVTLTISAARLYYYWE RDYRRALCRL	SEQ ID NO: 1194
Gorilla A3F (AA30-AA137)	RNTVWLCYEVKTKGPSRPPLDAKIFRGQVYFEPQ YHAEMCFLSWFCGNQLPAYKCFQITWVFSWTPCP DCVAKLAEFLAEHPNVTLTISAARLYYYWE	SEQ ID NO: 1195
Pan troglodytes A3F (AA30- AA137)	RNTVWLCYEVKTKGPSRPRLDTKIFRGQVYFEPQ YHAEMCFLSWFCGNQLPAYKCFQITWVFSWTPCP DCVAKLAEFLAEHPNVTLTISAARLYYYWERDYR RALCRL	SEQ ID NO: 1196
Human sapiens A3F (AA30- AA137)	RNTVWLCYEVKTKGPSRPRLDAKIFRGQVYSQPE HHAEMCFLSWFCGNQLPAYKCFQITWVFSWTPCP DCVAKLAEFLAEHPNVTLTISAARLYYYWERDYR RALCRL	SEQ ID NO: 1197
Macaca leonine A3F (AA30- AA137)	RNTVWLCYEVKTRGPSMPTWGTAKIFRGQVCFEPQ YHAEMCFLSRFCGNQLPAYKRQITWVFSWTPCP DCVAKVAEFLAEHPNVTLTISAARLYYYWETDYR RALCRL	SEQ ID NO: 1198

Macaca nemestrina A3F (AA30-AA137)	RNTVWLCYEVKTRGPSMPTWGTKIFRGQVCFEPQ YHAEMCFLSRFCGNQLPAYKRFQITWVFSWTPCP DCVAKVAEFLAEHPNVTLTISAARLYYYWETDYR RALCRL	SEQ ID NO: 1199
Rhinopithecus roxellana A3F (AA30-AA137)	RNTVWLCYEVKTRGPSMPTWGAKIFRGQVYFEP QYHAEMCFLSWFCGNQLPAYKRFQITWVFSWTP CPDCVAKVAEFLAEHPNVTLTISAARLYYYWETD YRRALCRL	SEQ ID NO: 1200
Mandrillus leucophaeus A3F (AA30-AA130)	RNTVWLCYKVKTRGPSMPTWGTKIFRGQVYFQP QYHAEMCFLSWFCGNQLPAYKRFQITWVFSWTP CPDCVVKVAEFLAEHPNVTLTISAARLYYYWETD Y	SEQ ID NO: 1201
Macaca mulatta A3F (AA30-AA137)	RNTVWLCYEVKTRGPSMPTWDTKIFRGQVYSKP EHHAEMCFLSRFCGNQLPAYKRFQITWVFSWTPC PDCVAKVAEFLAEHPNVTLTISAARLYYYWETDY RRALCRL	SEQ ID NO: 1202
Theropithecus gelada A3F (AA30-AA137)	RNTVWLCYEVKTRGPSMPTWGTKIFRGQVYFQP QYHAEMCFLSRFCGNQLPAYKRFQITWVFSWNPC PDCVAKVIEFLAEHPNVTLTISAARLYYYWGRDW RRALRRL	SEQ ID NO: 1203
Cercocebus atys A3B (AA29-AA138)	GRSYTWLCYEVKIRKDPSKLPWYTG VFRGQVYS KPEHHAEMCFLSRFCGNQLPAYKRFQITWVFSWN PCPDCVAKVIEFLAEHPNVTLTISAARLYYYWSRD WQRALCRL	SEQ ID NO: 1204
Macaca fascicularis A3B (AA29-AA138)	GRSYTWLCYEVKIRKDPSKLPWDTGVFRGQVYS KPEHHAEMCFLSRFCGNQLPAYKRFQITWVFSWN PCPDCVAKVIEFLAEHPNVTLTISTARLYYYWGR DWQRALCRL	SEQ ID NO: 1205
Macaca mulatta A3B (AA29-AA138)	GRSYTWLCYEVKIRKDPSKLPWDTGVFRGQVYS KPEHHAEMCFLSRFCGNQLPAYKRFQITWVFSWN PCPDCVAKVIEFLAEHPNVTLTISTARLYYYWGR DWQRALCRL	SEQ ID NO: 1206
Macaca leonina A3B (AA29-AA138)	GRSYTWLCYEVKIRKDPSKLPWDTGVFRGQVYS KPEHHAEMCFLSRFCGNQLPAYKRFQITWVFSWN PCPDCVVKVIEFLAEHPNVTLTISTARLYYYWGR DWQRALCRL	SEQ ID NO: 1207
Mandrillus leucophaeus A3B (AA29-AA138)	GRSYTWLCYEVKIRKDPSKLPWYTG VFRGQVYS KPEHHAEMCFLSRFCGNQLPAYKRFQITWVFSWN	SEQ ID NO: 1208

	PCPDCVAKVIEFLAEHPNVTLTIFTARLYYYWGR DWQRALCRL	
Macaca nemestrina A3B (AA29-AA138)	GRSYTWLCYEVKIRKDPSKLPWDTGVFRGQVYS KPEHHAEMCFLSRFCGNQLPAYKRFQITWVFSWN PCPDCVAKVTEFLAEHPNVTLTISTARLYYYWGR DWQRALCRL	SEQ ID NO: 1209
Rhinopithecus bieti A3F (AA29- AA138)	GRSYTWLCYEVKIRKDPSKLPWDTGVFRGQVYSE PEHHAEMYFLSWFCGNQLPAYKRFQITWVFSWTP CPDCVAKVAEFLTEHPNVTLTISAARLYYYRGRD WRRALCRL	SEQ ID NO: 1210
Rhinopithecus roxellana A3B (AA29-AA138)	GRSYTWLCYEVKIRKDPSKLPWDTGVFRGQVYSE PEHHAEMYFLSWFCGNQLPAYKRFQITWVFSWTP CPDCVAKVAEFLTEHPNVTLTISAARLYYYRGRD WRRALCRL	SEQ ID NO: 1211
Chlorocebus sabaeus A3B (AA29-AA138)	GRSYTWLCYEVKIRKDPSKLPWDTGVFRGQMYS KPEHHAEMCFLSWFCGNQLPAHKRFQITWVFSW TPCPDCVAKVAEFLAEYPNVTLTISAARLYYYWE TDYRRALCRL	SEQ ID NO: 1212
Nomascus leucogenys A3B (AA30-AA138)	RSYTWLCYEVKIRKDPSKLPWDTGVFRGQMYSFQ PEYHAEMCFLSWFCGNQLPAYKRFQITWVFSWTP CPDCVAKVAVFLAEHPNVTLTISAARLYYYWEK DWQRALCRL	SEQ ID NO: 1213
Cercocebus atys A3F (AA29- AA138)	GRSYTWLCYEVKIKKYP SKLLWDTGVFQGQVYF QPQYHAEMCFLSRFCGNQLPAYKRFQITWVFSW NPCPDCVAKVTEFLAEHPNVTLTISAARLYYYWE KDXRRALRRL	SEQ ID NO: 1214
Papio anubis A3F (AA29-AA138)	GRSYTWLCYEVKIKEDPSKLLWDTGVFQGQVYF QPQYHAEMCFLSRFCGNQLPAYKRFQITWVFSW NPCPDCVAKVTEFLAEHPNVTLTISAARLYYYWG RDWRRALRRL	SEQ ID NO: 1215
Chlorocebus aethiops A3D (AA29-AA150)	GRRYTWLCYEVKIKKDPSKLPWDTGVFPGQVRP KFQSNRRYEVYFQPQYHAEMYFLSWFCGNQLPA YKHFQITWVFSWNPCPDCVAKVTEFLAEHRNVTL TISAARLYYYWGKDWRRALCRL	SEQ ID NO: 1216
Chlorocebus sabaeus A3D (AA29-AA134)	GRRYTWLCYEVKIKKDPSKLPWDTGVFPGQPQY HAEMYFLSWFCGNQLPAYKHFQITWVFSWNPCP DCVAKVTEFLAEHRNVTLTISAARLYYYWGKDW RRALCRL	SEQ ID NO: 1217

Chlorocebus sabaeus A3F (AA29-AA150)	GRRYTWLCYEVKIKKDP SKLPWDTGVFPGQVRP KFQSNRRQKVYFQPQYHAEMYFLSWFCGNQLPA YKHFQITWVFSWNP CPDCVAKVTEFLAEHRNVTL TISAARLYYYWGKDWRRALCRL	SEQ ID NO: 1218
Erythrocebus patas A3D (AA29-AA150)	GRRYTWLCYEVKIKKDP SKLPWDTGVFQGQVRP KFQSNRRYEVYFQPQYHAEMCFLSWFCGNQLPA YKHFQITWVFSWNP CPDCVAKVTEFLAEHPNVTL TISAARLYYYWGKDWRRALCRL	SEQ ID NO: 1219
Macaca fascicularis A3D (AA29-AA159)	GRSYTWLCYEVKIRKDP SKLPWDTGVFRGQVRP KLQSNRRYELSNWECRKR VYFQPQYHAEMYFLS WFCGNQLPANKRFQITWFASWNP CPDCVAKVTE FLAEHPNVTLTISVARLYYYRGKDWRRALRRL	SEQ ID NO: 1220
Macaca fascicularis A3F (AA29-AA138)	GRSYTWLCYEVKIRKDP SKLPWDTGVFRGQVYF QPQYHAEMYFLSWFCGNQLPANKRFQITWFASW NP CPDCVAKVTEFLAEHPNVTLTISVARLYYYRG KDWRRALRRL	SEQ ID NO: 1221
Macaca nemestrina A3D (AA29-AA138)	GRSYTWLCYEVKIRKDP SKLPWDTGVFRDQVYF QPQYHAEMCFLSWFCGNQLPANKRFQITWVFSW NP CPDCVT KVTEFLAEHPNVTLTISVARLYYYRG KDWRRALRRL	SEQ ID NO: 1222
Macaca leonina A3D (AA29- AA138)	GRSYTWLCYEVKIRKDP SKLPWYTGVFRGQVYF QPQYHAEMCFLSWFCGNQLPANKRFQITWVFSW NP CPDCVAKVTEFLAEHPNVTLTISVARLYYYRG KDWRRALRRL	SEQ ID NO: 1223
Macaca mulatta A3D (AA29- AA138)	GRSYTWLCYEVKIRKDP SKLPWDTGVFRGQVYF QPQYHAEMCFLSWFCGNQLPAYKR FQITWVFSW NP CPDCVAKVTEFLAEHPNVTLTISVARLYYYRG KDWRRALCRL	SEQ ID NO: 1224
Gorilla A3D (AA29-AA150)	GRSYTWLCYEVKIRRGSSNLLWNTGVFRGPVPPK LQSNHRQEVYFQFENHAEMCFLSWFCGNRLPAN RRFQITWVFSWNPCLPCVVKVTKFLAEHPNVTLT ISAARLYYYRDREWRRVLRL	SEQ ID NO: 1225
Pan paniscus A3D (AA29- AA150)	GRSYTWLCYEVKIKRGCSNLIWDTGVFRGPVLPK LQSNHRQEVYFQFENHAEMCFFSWFCGNRLPAN RRFQITWVFSWNPCLPCVVKVTKFLAEHPNVTLT ISAARLYYYQDREWRRVLRL	SEQ ID NO: 1226
Pan troglodytes A3D (AA29- AA150)	GRSYTWLCYEVKIKRGCSNLIWDTGVFRGPVLPK LQSNHRQEVYFQFENHAEMCFFSWFCGNRLPAN	SEQ ID NO: 1227

	RRFQITWVFSWNPCLPCVVKVTKFLAEHPNVTLT SAARLYYYQDREWRRVLRL	
Homo sapiens A3D (AA29- AA150)	GRSYTWLCYEVKIKRGRSNLLWDTGVFRGPVLPK RQSNHRQEVYFRFENHAEMCFLSWFCGNRLPAN RRFQITWVFSWNPCLPCVVKVTKFLAEHPNVTLT SAARLYYYRDRDWRWVLLRL	SEQ ID NO: 1228
Nomascus leucogenys A3D (AA29-AA150)	GRSYTWLCYEVKIRKDPKLPWDKGVFRGQVLP KFQSNHRQEVYFQLENHAEMCFLSWFCGNQLPA NRRFQITWVFSWNPCLPCVAKVTEFLAEHPNVTL TISAARLYYYRGRDWRRALRL	SEQ ID NO: 1229
Saimiri boliviensis A3C (AA29-AA138)	GKKYTWLCYEVKIKKDTSKLPWNTGVFRGQVNF NPEHHAEMYFLSWFRGKLLPACKRSQITWVFSW NPCLYCVAKVAEFLAEHPNVTLTVSTARLYCYW KKDWRRALRKL	SEQ ID NO: 1230
Saimiri boliviensis A3F (AA29-AA138)	GKKYTWLCYEVKIKKDTSKLPWNTGVFRGQVNF NPEHHAEMYFLSWFRGKLLPACKRSQITWVFSW NPCLYCVAKVAEFLAEHPNVTLTVSTARLYCYW KKDWRRALRKL	SEQ ID NO: 1231
Piliocolobus tephrosceles A3F (AA36-AA145)	GRRYTWLCYEVKIMKDHSLKPWYTG VFRGQVYF EPQNHAEMLSWFCGNQLPAYECCQITWVFSW TPCPDCVAKVTEFLAEHPNVTLTISAARLYYYRG RDWRRALRL	SEQ ID NO: 1232
Colobus angolensis pallatus A3F (AA29-AA138)	GRRYTWLCYEVKISKDPKLPWDTGIFRGQVYFE PQYHAEMLSWYCGNQLPAYKCFQITWVFSWT PCPDCVGKVAEFLAEHPNVTLTISAARLYYYWET DYRRALCRL	SEQ ID NO: 1233
Pongo abelii A3F (AA30-AA150)	RNYTWLCYEVKIRKDPKLAWDTG VFRGQVLPK LQSNHRREVYFEPQYHAEMLSWFCGNQLSAY ERFQITWVFSWTPCPDCVAMLAEFLAEHPNVTLT VSAARLYYYWERDYRGALRL	SEQ ID NO: 1234

[00252] In some embodiments, the nucleotide deaminase of the first fusion protein is a cytidine deaminase or an adenosine deaminase.

- [00253] In some embodiments, the nucleotide deaminase of the first fusion protein is a cytidine deaminase selected from the group consisting of APOBEC3A (A3A), APOBEC3B (A3B), APOBEC3C (A3C), APOBEC3D (A3D), APOBEC3F (A3F), APOBEC3G (A3G), APOBEC3H (A3H), APOBEC1 (A1), APOBEC3 (A3), APOBEC2 (A2), APOBEC4 (A4), and AICDA (AID).

[00254] In some embodiments, the nucleotide deaminase of the first fusion protein is a cytidine deaminase comprising an amino acid sequence of any one of SEQ ID NOs: 159-194 and 1143-1144.

Table 2 Exemplary sequences of cytidine deaminase

Name	Sequence	SEQ ID NO:
Felis catus APOBEC3H	MNPLQEVIQFCRQFGNQHRVPKPYRRTKTYLCYQLKLP EGTLIHKDCLRNKKKRHAEMCFIDKIKALTRDTSQRF EIICYITWSPCPFCAEELVAFVKDNPHLSLRIFASRLYV HWRWKYQQGLRHLHASGIPVAVMSLPEFEDCWRNF VDHQDRSFQWPWNLDQYSKSIKRRLGKILTPLNDLRN DFRNLKLE	SEQ ID NO: 159
Human APOBEC3A	MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEV ERLDNGTSVKMDQHRGFLHNQAKNLLCGFYGRHAEL RFLDLVPSLQLDPAQIYRVTFISWSPCFSWGCAGEV RAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAG AQVSIMTYDEFKHCWDTFVDHQGCPFPWDGLDEHS QALSGRLRAILQNQGN	SEQ ID NO: 160
Cricetulus longicaudatus A3	MGPFCCLGCSHRKCYSPIRNLISQETFKFHFKNLGYAKG RKDTFLCYEVTRKDCDSPVSLHHGVFKNKGNIHAEVC FLYWFHDKVLKVLSPREEFKITWYMSWSPCFECAEQI VRFLATHHYLSLDIFSSRLYNVQDPETQQNLCRLVQE GAQVAAMDLYEFKKCWKKFVTMVAGDSGLGKRLLT NFRYQDSKLQEILRRMDPLSEEEFYQFYNQRVKHL YYHRMKPYLCYQLEQFNGQAPLKGCLLSEKQKQHA ILFLDKIRSMELSQVTITCYLTWSPCPNCAWRLAAFKR DRPDLILHIYTSRLYFHWKRPQKGLCSLWQSGILVDV MDLPQFTDCWTNFTVNPKRPFWPWKGLEIISRRTQRR LRIKESWGLQDLVNDFGNLQLGPPMS	SEQ ID NO: 161
Rattus norvegicus APOBEC3	MGPFCCLGCSHRKCYSPIRNLISQETFKFHFKNLRYAID RKDTFLCYEVTRKDCDSPVSLHHGVFKNKDNIHAEIC FLYWFHDKVLKVLSPREEFKITWYMSWSPCFECAEQ VLRFLATHHNLSDIFSSRLYNIRDPENQQNLCRLVQE GAQVAAMDLYEFKKCWKKFVDNNGRRFRPWKKLLT NFRYQDSKLQEILRPCYIPVPSSSSSTLSNICLTGKLPET RFCVERRRVHLLSEEEFYQFYNQRVKHLCCYHGVKP YLCYQLEQFNGQAPLKGCLLSEKQKQHAELFLDKIRS MELSQVIITCYLTWSPCPNCAWQLAAFKRDRPDLILHI YTSRLYFHWKRPQKGLCSLWQSGILVDVMDLPQFT DCWTNFTVNPKRPFWPWKGLEIISRRTQRRLHRIKESW GLQDLVNDFGNLQLGPPMS	SEQ ID NO: 162

Pongo pygmaeus APOBEC3H	MALLTAKTFSLQFNNKRRIKRPYYPRKALLCYQLTPQ NGSTPTRGYFKNKKKCHAEIRFINEIKSMGLDETQCY QVTCYLTWSPCSPCVRELVAFIKAHDHLNLRIFASRLY CHWCRRQQEGLRLLCGSQVPVEVMGSREFADCWENF VDHEKPLSFNPSEMLEELDKNSRAIKRRLERIKQSWSV DVLENGLRSLQLGPVSSSLRSNSR	SEQ ID NO: 163
Felis catus APOBEC3Ca	MEPWRPSRNPMDRIDPNTFRFHPNLLYASGRKLCY LCFQVETEDYFSCDDSDRGVFRNKVHPWARCHAEQC FLSWFRDQYPYRDEYYNVTWFLSWSPCPTCAEEVVE FLEEYRNLTLSIFTSRLYYFWDPNYQEGLCCKLWDAGV QLDIMSCDDFKHCWDNFVDHKGMRFQRRNLLKDYYD FLAAELQEILR	SEQ ID NO: 164
Human APOBEC3H	MALLTAETFRLQFNNKRRLRRPYPRKALLCYQLTPQ NGSTPTRGYFENKKKCHAEICFINEIKSMGLDETQCYQ VTCYLTWSPCSSCAWELVDFIKAHDHLNLGIFASRLY YHWCKPQQKGLRLLCGSQVPVEVMGFPEFADCWENF VDHEKPLSFNPYKMLEELDKNSRAIKRRLERIKIPGVR AQGRYMDILCDAEV	SEQ ID NO: 165
Macaca mulatta APOBEC3G	MVEPMDPRTFVSNFNNRPILSGLNTVWLCCEVKTDP SGPPLDAKIFQGKVYSKAKYHPEMRFLRWFKWRQL HHDQEYKVTWYVSWSPCTRCANSVATFLAKDPKVTL TIFVARLYYFWKPDYQQALRILCQKRGGPHATMKIM NYNEFQDCWNKFVDGRGKPFKPRNNLPKHYTLLQAT LGELLRHLMDPGTFTSNFNNKPWVSGQHETYLCYKV ERLHNDTWVPLNQHRGFLRNQAPNIHGFQKGRHAEL CFLDLIPFWKLDGQQYRVTCFTSWSPCFSCAQEMAKF ISNNEHVSLCIFAARIYDDQGRYQEGLRALHRDGAKIA MMNYSEFEYCWDTFVDRQGRPFQPWDGLDEHSQAL SGRLRAI	SEQ ID NO: 166
Pan troglodytes APOBEC3G	MKPHFRNPVERMYQDTFSDNFYNRPILSHRNTVWLC YEVKTKGSPRPPLDAKIFRGQVYSKLKYHPEMRFFHW FSKWRKLHRDQEYEVWYISWSPCTKCTRDTVATFLA EDPKVTLTIFVARLYYFWDPDYQEALRSLCQKRDGPR ATMKIMNYDEFQHCWSKFVYSQRELFEPWNNLPKYY ILLHIMLGEILRHSMDPPTFTSNFNNELWVRGRHETYL CYEVERLHNDTWVLLNQRRGFLCNQAPHKHGFLEGR HAELCFLDVIPFWKLDLHQDYRVTCFTSWSPCFSCAQ EMAKFISNNKHVSLCIFAARIYDDQGRCQEGRLTLAK AGAKISIMTYSEFKHCWDTFVDHQGCPFPWDGLEE HSQALSGRLRAILQNQGN	SEQ ID NO: 167
Chlorocebus aethiops APOBEC3G	MNPQIRNMVEQMEPDIFVYYFNNRPILSGRNTVWLCY EVKTKDPSGPPLDANIFQGKLYPEAKDHPEMKFLHWF RKWRQLHRDQEYEVWYVSWSPCTRCANSVATFLA	SEQ ID NO: 168

	EDPKVTLTIFVARLYYFWKPDYQQALRILCQERGGPH ATMKIMNYNEFQHCWNEFVDGQGKPFKPRKNLPKH YTLLHATLGELLRHVMDPGTFTSNFNKPNWVSGQRE TYLCYKVERSHNDTWVLLNQHRGFLRNQAPDRHGFP KGRHAELCFLDLIPFWKLDDQQYRVTCFTSWSPCFSC AQKMAKFISNNKHVSLCIFAARIYDDQGRCQEGLRTL HRDGAKIAVMNYSEFEYCWDTFVDRQGRPFQPWDGL DEHSQALSGRLRAI	
Human APOBEC3F	MKPHFRNTVERMYRDTFSYNFYNRPILSRNNTVWLC YEVKTKGSPRPRLDAKIFRGQVYSQPEHHAEMCFLSW FCGNQLPAYKCFQITWVFSWTPCPDCVAKLAEFLAEH PNVTLTISAARLYYYWERDYRRALCRLSQAGARVKI MDDEEFAYCWENFVYSEGQPFMPWYKFDDNYAFLH RTLKEILRNPMMEAMYPHIFYFHFKNLRKAYGRNESWL CFTMEVVKHHSPVSWKRGVFRNQVDPETHCHAERCF LSWFCDDILSPNTNYEVTWYTSWSPCPECAGEVAEFL ARHSNVNLTIFTARLYYFWDTDYQEGLRSLSQEGASV EIMGYKDFKYCWENFVYNDDEPFKPKWKGLKYNFLFL DSKLQEILE	SEQ ID NO: 169
Human APOBEC3G	MKPHFRNTVERMYRDTFSYNFYNRPILSRNNTVWLC YEVKTKGSPRPPLDAKIFRGQVYSELKYHPEMRFFHW FSKWRKLHRDQEYEVWYISWSPCTKCTRDMATFLA EDPKVTLTIFVARLYYFWDPDYQEALRSLCQKRDGPR ATMKIMNYDEFQHCWSKFVYSQRELFEPWNNLPKYY ILLHIMLGEILRHSMDPPTFTFNFNNEPWVRGRHETYL CYEVERMHNDTWVLLNQRRGFLCNQAPHKHGFLEG RHAELCFLDVIPFWKLDLDQDYRVTCFTSWSPCFSCA QEMAKFISKNHVSLCIFTARIYDDQGRCQEGLRTLA EAGAKISIMTYSEFKHCWDTFVDHQGCPFPQWDGLD EHSQDLSGRLRAILQNQEN	SEQ ID NO: 170
Human APOBEC3C	MNPQIRNPMKAMYPGTFYFQFKNLWEANDRNETWL CFTVEGIKRRSVVSWKTGVFRNQVDSETHCHAERCFL SWFCDDILSPNTKYQVTWYTSWSPCPDCAGEVAEFLA RHSNVNLTIFTARLYYFYQYPCYQEGLRSLSQEGVAVEI MDYEDFKYCWENFVYNDNEPFKPKWKGLKTNFRLLK RRLRESLQ	SEQ ID NO: 171
Human APOBEC3B	MNPQIRNPMERMYRDTFYDNFENEPILYGRSYTWLC YEVKIKRGRSNLLWDTGVFRGQVYFKPQYHAEMCFL SWFCGNQLPAYKCFQITWVFSWTPCPDCVAKLAEFLS EHPNVTLTISAARLYYYWERDYRRALCRLSQAGARV TIMDYEEFAYCWENFVYNEGQQFMPWYKFDENYAF HRTLKEILRYLMDPDTFTFNFNNDPLVLRRTQTYLCY EVERLDNGTWVLMQHMGLFCNEAKNLLCGFYGRH	SEQ ID NO: 172

	AELRFLDLVPSLQLDPAQIYRVTFISWSPCFSWGCA GEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLR DAGAQVSIMTYDEFEYCWDTFVYRQGCPFPQWDGLE EHSQALSGRRLRAILQNQGN	
Macaca mulatta APOBEC3H	MALLTAKTFSLQFNNKRRVKNPYYPRKALLCYQLTP QNGSTPTRGHLKNKKKDHAERFINKIKSMGLDETQC YQVTCYLTWSPCPCAGELVDFIKAHRHLNLRIFASRL YYHWRPNYQEGLLLLCGSQVPVEVMGLPEFTDCWEN FVDHKEPPSFNPSEKLEELDKNSQAIKRRLERIKSRSV DVLENGLRSLQLGPVTPSSSIRNSR	SEQ ID NO: 173
Human APOBEC3D	MNPQIRNPMERMYRDTFYDNFENEPILYGRSYTWLC YEVKIKRGRSNLLWDTGVFRGPVLPKRQSNHRQEVY FRFENHAEMCFLSWFCGNRLPANRRFQITWVSWNPC LPCVVVKVTKFLAEHPNVTLTISAARLYYYRDRDWRW VLLRLHKAGARVKIMDYEDFAYCWENFVCNEGQPF MPWYKFDDNYASLHRTLKEILRNPMEAMYPHIFYHFH KNLLKACGRNESWLCFTMEVTKHHSVFRKRGVFRN QVDPETHCHAERCFLSWFCDDILSPNTNYEVTWYTS WSPCPECAGEVAEFLARHSNVNLTIFTARLCYFWDTD YQEGLCSLSQEGASVKIMGYKDFVSCWKNFVYSDD PFKPWKGLQTNFRLLRRLREILQ	SEQ ID NO: 174
Mus musculus APOBEC3	MQPQRLGPRAGMGPFCCLGCSHRKCYSPIRNLISQETFK FHFKNLGYAKGRKDTFLCYEVTRKDCDSPVSLHHGV FKNKDNIAEICFLYWFDKVLKVLSPREEFKITWYM SWSPCFECAEQIVRFLATHHNLSLDIFSSRLYNVQDPE TQQNLCRLVQEGAQVAAMDLYEFKKCWKKFVDNNGG RRFRPWKRLLTNFRYQDSKLQEILRPCYISVPSSSSSTL SNICLTGKLPETRFWVEGRRMDPLSEEEFYQFYNQR VKHLCYYHRMKPYLCYQLEQFNGQAPLKGCLLSEKG KQHAEILFDKIRSMELSQVTITCYLTWSPCPNCAWQL AAFKRDRPDILHIYTSRLYFHWKRPFQKGLCSLWQS GILVDVMDLPQFTDCWTNFVNPKRPFWPWKGLEIISR RTQRRRLRIKESWGLQDLVNDFGNLQLGPPMS	SEQ ID NO: 175
Rattus norvegicus APOBEC1	MSSETGPVAVDPTLRRRIEPHEFEVFFDPRELKRETC LYEINWGGRHSIWRHTSQNTNKHVEVNFIEKFTTERY FCPNTRCSITWFLSWSPCGECSRAITEFLSRYPHVTLFI YIARLYHHADPRNRQGLRDLISSGVTIQIMTEQESGYC WRNFVNYSPTSNEAHWPYPHLLWVRLYVLELYCIILGL PPCLNILRRKQPQLTFFTIALQSCHYQRLPPHILWATGL K	SEQ ID NO: 176
Human APOBEC1	MTSEKGPSTGDPTRLRRRIEPWEFDVFYDPRELKREACL LYEIKWGMRSRKIWRSSGKNTTNHVEVNFIEKFTSERD FHPSMSCSITWFLSWSPCWECQAIREFLSRHPGVTLV	SEQ ID NO: 177

	IYVARLFWHMDQQNRQGLRDLVNSGVTIQIMRASEY YHCWRNFVNYPGDEAHWPQYPPLWMMLYALELHC IILSLPPCLKISRRWQNHLETFRLHLQNCHYQTIPPHILL ATGLIHPSVAWR	
Oryctolagus cuniculus APOBEC1	MASEKGPSNKDYTLRRRIEPWEFEVFFDPQELRKEAC LLYEIKWGASSKTWRSSGKNTTNHVEVNFLEKLTSEG RLGPSTCCSITWFLSWSPCWECSMAIREFLSQHPGVTL IIFVARLFQHMDRRNRQGLKDLVTSGVTVRVMSVSEY CYCWENFVNYPGKAAQWPRYPPRWMLMYALELYC IILGLPPCLKISRRHQKQLTFFSLTPQYCHYKMIPPYILL ATGLLQPSVPWR	SEQ ID NO: 178
Mus musculus APOBEC1	MSSETGPVAVDPTLRRRIEPHEFEVFFDPRELKRETC LYEINWGGRHVSWRHTSQNTSNHVEVNFLEKFTTER YFRPNTRCSITWFLSWSPCGECSRAITEFLSRHPYVTLF IYIARLYHHTDQRNRQGLRDLISSGVTIQIMTEQEYCY CWRNFVNYPSPNEAYWPRYPHLWVKLYVLELYCIIL GLPPCLKILRRKQPQLTFFTITLQTCHYQRIPPHLLWAT GLK	SEQ ID NO: 179
Mesocricetus auratus APOBEC1	MSSETGPVVVDPTLRRRIEPHEFD AFFDQGELRKETCL LYEIRWGGRHNIWRHTGQNTSRHVEINFIEKFTSER YF YPSTRCSIVWFLSWSPCGECSKAITEFLSGHPNVT LFIY AARLYHHTDQRNRQGLRDLISRGVTIRIMTEQEYCYC WRNFVNYPSPNEVYWPYPNLWMRLYALELYCIHLG LPPCLKIKRRHQYPLTFFRLNLQSCHYQRIPPHILWAT GFI	SEQ ID NO: 180
Monodelphis domestica APOBEC1	MNSKTGPSVG DATLRRRIKPWEFVAFFNPQELRKETC LLYEIKWGNQNIWRHSNQNTSQHAEINFMEKFTAERH FNSSVRCSITWFLSWSPCWECSKAIRKFLDHYPNVT LA IFISRLYWHMDQQHRQGLKELVHSGVTIQIMSYSEYH YCWRNFVDYPQGEEDYWPYPYLWIMLYVLELHCII LGLPPCLKISGSHSNQLALFSLDLQDCHYQKIPYNVLV ATGLVQPFVTWR	SEQ ID NO: 181
Pongo pygmaeus APOBEC1	MTSEKGPSTGDPTLRRRIESWEFDVFYDPRELKRETC LYEIKWGMSRKIWRSSGKNTTNHVEVNFIIKKFTSERR FHSSISCSITWFLSWSPCWECSQAIREFLSQHPGVTLVI YVARLFWHMDQRNRQGLRDLVNSGVTIQIMRASEYY HCWRNFVNYPGDEAHWPQYPPLWMMLYALELHCII LSLPPCLKISRRWQNHLEAFFRLHLQNCHYQTIPPHILL ATGLIHPSVTWR	SEQ ID NO: 182
Bos taurus APOBEC2	MAQKEEAAAAAEPASQNGEEVENLEDPEKLKELIELP PFEIVTGERLPAHYFKFQFRNVEYSSGRNKTFLCYVVE AQSKGGQVQASRGYLEDEHATNHAEEAFFNSIMPTFD	SEQ ID NO: 183

	PALRYMVTWYVSSSPCAACADRIVKTLNKTKNLRLLI LVGRLFMWEEPEIQAALRKLKEAGCRLRIMKPQDFEY IWQNFVEQEEGESKAFEPWEDIQENFLYYEEKLADILK	
Mus musculus APOBEC2	MAQKEEAAEAAAPASQNGDDLENLEDPEKLKELIDLP PFEIVTGVRLPVNFFKFQFRNVEYSSGRNKTFLCYVVE VQSKGGQAQATQGYLEDEHAGAHAEAAFFNTILPAF DPALKYNVTWYVSSSPCAACADRILKTLSTKNLRLL ILVSRLFMWEEPEVQAALKKLKEAGCKLRIMKPQDFE YIWQNFVEQEEGESKAFEPWEDIQENFLYYEEKLADIL K	SEQ ID NO: 184
Human APOBEC2	MAQKEEAAVATEAASQNGEDLENLDDPEKLKELIELP PFEIVTGERLPANFFKFQFRNVEYSSGRNKTFLCYVVE AQKGKGQVQASRGYLEDEHAAAHAEEAFFNTILPAF DPALRYNVTWYVSSSPCAACADRIKTLSTKNLRLLI LVGRLFMWEEPEIQAALKKLKEAGCKLRIMKPQDFEY VWQNFVEQEEGESKAFQPWEDIQENFLYYEEKLADIL K	SEQ ID NO: 185
Pongo pygmaeus APOBEC2	MAQKEEAAAATEAASQNGEDLENLDDPEKLKELIELP PFEIVTGERLPANFFKFQFRNVEYSSGRNKTFLCYVVE AQKGKGQVQASRGYLEDEHAAAHAEEAFFNTILPAF DPALRYNVTWYVSSSPCAACADRIKTLSTKNLRLLI LVGRLFMWEELEIQDALKKLKEAGCKLRIMKPQDFE YVWQNFVEQEEGESKAFQPWEDIQENFLYYEEKLADI LK	SEQ ID NO: 186
Human APOBEC4	MEPIYEEYLANHGTIVKPYWLSFSLDCSNCPYHIRTG EEARVSLTEFCQIFGFPYGTTFPQTKHLTFYELKTSSGS LVQKGHASSCTGNYIHPESMLFEMNGYLDSAIYNND IRHIILYSNNSPCNEANHCCISKMYNFLTITPGITLSIYF SQLYHTEMDFPASAWNREALRSLASLWPRVVLSPISG GIWHSVLSHSFISGVSGSHVFQPILTGRALADRHNA YEI NAITGVKPYFTDVLLQTKRNPNTKAQEALSYPLNNA FPGQFFQMPSGQLQPNLPPDLRAPVVFVLVPLRDLPP MHMGQNPKNPRNIVRHLNMPQMSFQETKDLGRLPTG RSVEIVEITEQFASSKEADEKKGKKGKK	SEQ ID NO: 187
Rattus norvegicus APOBEC4	MEPLYEEYLTHSGTIVKPYWLSVSLNCTNCPYHIRT GEEARVPYTEFHQTFGFPWSTYPQTKHLTFYELRSSG NLIQKGLASNCTGSHTHPESMLFERDGYLDSLIFHDSN IRHIILYSNNSPCDEANHCCISKMYNFLMNYPEVTLSV FFSQLYHTENQFPTSAWNREALRGLASLWPQVTL SAI SGGIWQSILETFVSGISEGLTAVRPFTAGRTLTD RYNA YEINCITEVKPYFTDALHSWQKENQDQKVWAASENQ PLHNTTPAQWQPDMSQDCRTPAVFMLVPYRDLPP IHV NPSPQKPRTVVRHLNTLQLSASKVKALRKSPSGRPVK	SEQ ID NO: 188

	KEEARKGSTRSQEANETNKSXWKKQTLFIKSNICHLL EREQKKIGILSSWSV	
Mus musculus APOBEC4	MEPLYEEILTQGGTIVKPYWLSLSLGCTNCPYHIRTG EEARVPYTEFHQTFGFPWSTYPQTKHLTFYELRSSSKN LIQKGLASNCTGSHNHPEAMLFEKNGYLDAVIFHNSN IRHIILYSNNSPCNEAKHCCISKMYNFLMNYPEVTLVS FFSPLYHTEKQFPTSAWNRKALQSLASLWPQVTLSPIC GGLWHAILEKFVSNISGSTVPQPFIAGRILADRYNTYEI NSIIAAKPYFTDGLLSRQKENQNREAWAAFEKHPLGS AAPAQRPTRGQDPRTPAVLMLVSNRDLPIHVGSTP QKPRTVVRLNMLQLSSFVKVDVKKPPSGRPVEEVE VMKESARSQKANKKNRSQWKKQTLVIKPRICRLER	SEQ ID NO: 189
Macaca fascicularis APOBEC4	MEPTYEEYLANHGTIVKPYWLSFSLDCSNCPYHIRT GEEARVSLTEFCQIFGFPYGTTPQTKHLTFYELKTSS GSLVQKGHASSCTGNYIHPESMLFEMNGYLDSAIYNN DSIRHIILYCNSPCNEANHCISKVYNFLITYPGITLSI YFSQLYHTEMDFPASAWNREALRSLASLWPRVVLSP SGGIWHSVLHSFVSGVSGSHVFQPILTGRALTDRYNA YEINAITGVKPFSTDVLLHTKRNPNNTKAQMALESYPL NNAFPGQSFQMTSGIPDLRAPVVFVLLPLRDLPPMH MGQDPNKPRNIIRHLNMPQMSFQETKDLERLPTRRSV ETVEITERFASSKQAEKTKKKKGKK	SEQ ID NO: 190
Human AICDA	MDSLLMNRKFLYQFKNVRWAKGRRETYLCYVVKR RDSATSFSLDFGYLRNKGCHVELLFLRYISDWDLDP GRCYRVTWFTSWSPCYDCARHVADFLRGPNLSLRIF TARLYFCEDRKAPEGLRRLHRAGVQIAIMTFKDYFY CWNTFVENHERTFKAWEGLHENSVRLSRQLRRILLPL YEVDDLRFDAFRTLGL	SEQ ID NO: 191
Mus musculus AICDA	MDSLLMKQKFLYHFKNVRWAKGRHETYLCYVVKR RDSATSCSLDFGHLRNKSGCHVELLFLRYISDWDLDP GRCYRVTWFTSWSPCYDCARHVAEFLRWPNLSLRIF TARLYFCEDRKAPEGLRRLHRAGVQIGIMTFKDYFY CWNTFVENRERTFKAWEGLHENSVRLTRQLRRILLPL YEVDDLRFDAFRMLGF	SEQ ID NO: 192
Canis lupus familiaris (Dog) AICDA	MDSLLMKQRKFLYHFKNVRWAKGRHETYLCYVVKR RDSATSFSLDFGHLRNKSGCHVELLFLRYISDWDLDP GRCYRVTWFTSWSPCYDCARHVADFLRGYPNLSLRIF AARLYFCEDRKAPEGLRRLHRAGVQIAIMTFKDYFY CWNTFVENREKTFKAWEGLHENSVRLSRQLRRILLPL YEVDDLRFDAFRTLGL	SEQ ID NO: 193

Bos taurus (Bovine) AICDA	MDSLLKKQRQFLYQFKNVRWAKGRHETLYCYVVKR RDSPTSFSLDFGHLRNKAGCHVELLFLRYISDWDLDP GRCYRVTWFTSWSPCYDCARHVADFLRGYPNLSLRIF TARLYFCDKERKAEPEGLRRLHRAGVQIAIMTFKDYF YCWNTFVENHERTFKAWEGLHENSVRLSRQLRRILLP LYEVDDLRLDAFRTLGL	SEQ ID NO: 194
mouse APOBEC3 cytidine deaminase domain 1 (mA3-CDA1)	MGPFCLGCshrkcYSPiRNLISETFKFHfKNLGYAKG RKDTFLCYEVTRKDCDSPVSLHHGVfKNKDNIHAEIC FLYWFHDKVLKVLSPREEFKITWYMSWSPCFECAEQI VRFLATHHNLSLDIFSSRLYNVQDPETQQNLCRLVQE GAQVAAMDLYEFKKCWKKFVDNGGRRFRPWKRLLT NFRYQDSKLQEILRPCYISVPSS	SEQ ID NO: 1143
human APOBEC3B cytidine deaminase domain 2 (hA3B- CDA2)	MQFMPWYKFDENYAFLHRTLKEILRYLMDPDTFTFN FNNDPLVLRRRQTYLCYEVRDLNGTWVLMQDHMG FLCNEAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIY RVTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAA RIYDYDPLYKEALQMLRDAGAQVSIMTYDEFEYCWD TFVYRQGCPFPWDGLEEHSQALSGRLRAILQNQGN	SEQ ID NO: 1144

[00255] In some embodiments, the nucleotide deaminase of the first fusion protein is a human cytidine deaminase, a monkey cytidine deaminase, or mouse cytidine deaminase.

[00256] In some embodiments, the catalytic domain of the nucleotide deaminase of the first fusion protein is a mouse A3 cytidine deaminase domain 1 (mA3-CDA1) or a human A3B cytidine deaminase domain 2 (hA3B-CDA2).

[00257] In some embodiments, the nucleotide deaminase of the first fusion protein is an adenosine deaminase selected from tRNA-specific adenosine deaminase (TadA), adenosine deaminase tRNA specific 1 (ADAT1), adenosine deaminase tRNA specific 2 (ADAT2), adenosine deaminase tRNA specific 3 (ADAT3), adenosine deaminase RNA specific B1 (ADARB1), adenosine deaminase RNA specific B2 (ADARB2), adenosine monophosphate deaminase 1 (AMPD1), adenosine monophosphate deaminase 2 (AMPD2), adenosine monophosphate deaminase 3 (AMPD3), adenosine deaminase (ADA), adenosine deaminase 2 (ADA2), adenosine deaminase like (ADAL), adenosine deaminase domain containing 1 (ADAD1), adenosine deaminase domain containing 2 (ADAD2), and adenosine deaminase RNA specific (ADAR).

[00258] In some embodiments, the adenosine deaminase comprises an amino acid sequence selected from SEQ ID NO: 66-158.

Table 3 Exemplary sequences of adenosine deaminase

Name	Sequence	SEQ ID NO:
Agrobacterium fabrum TadA	MAERTHFMELALVEARSAGERDEVPIGAVLVLDGRVI ARSGNRTRELNDVTAHAEIAVIRMACEALGQERLPGA DLYVTLEPCTMCAAISFARIRRLYYGAQDPKGGAVE SGVRFFSQPTCHHAPDVYSGLAESESAELRQFFREKR LDD	SEQ ID NO: 66
Arabidopsis thaliana TadA	MFNTYTNSLQWPIRSRNQQDYCSLLPERSESYKLSKA YTSSRCYCVSSRSSCCCCSTPSSSSFVKPKVLINPGFV LYGVRQSTLIQWPSFQRRLLVGGGRLMGCEVYSSCD GIRRKNSFKLRCLEESDECCGGRSCSDDVEAMISFLS EELIDEERKWNLVSRVKEKKKVGNVKVSVEGSNSY GNGRVSQRVKKPEGFGRKEIKEDVKLNERYDCEHC GRRKKSSELESERRGSKLVTGEYIGKSYRGDEEREVR PRRRKSSSCSSYYSLASSGEFESDTEDEEDVEIYREN VRSEKKVVDQSAKRLKSRKEASQMHSRKKRDESST GVDSRYQKQIFEEGENSNQAVTLNQRRRKFSQTENR VSESTGNYEEDMEIHEVHVNDAAETSSQNQKLFNERED YRVHSIRNDSGNENIESSQHQLKERLETRYSSEDRVSE MRRRTKYSSSQEEGINVLQNFPEVTNNQQPLVEERISK QAGTRRTTEHISESSEIHDIDIRNTYVSQREDQIRNQEV HAGLVSGLQSERKQQDYHIEHNPLQTTQSDRTSVSVS HTSDAVRYTEIQRKSEKRLIGQGSTTAVQSDSKVEKN GAQKEDSRLDHANSKKDGGTTGLGLQSYQSKLSEEASS SQSSLMASRTKLQLVLDLVSEEMQGGSETTLIPPSSQLVS RRSGQSYRTGGVSIQEISHGTSESgyTTAFEHPRAGAS VNSQSAGELMGFTSHEDAMGSAHRLEQASEKYVGEF VKKAKHGVINPETEEQRAESNQLKRRDSRRSSGGSGA KGPSDEMWVTDSAQGTTPHPGATEGNAAVGNAIFKRN GRSLWNVIADIARLRWGSRAGSPDSSAKPAGRSSPNE SVSSATWFSGREHDGSSDDNTKGDKVLPQEAPSLHQV EVGQTSPRSQSEYPGTTKLKQRSERHEGVVSSPSSTILE GGSVSNRMSSTSGNQIVGVDEEEGGNFEFRLPETALTE VPMKLPSRNLIRSPPIKESSESSLTEASSDQNFTVGEGR RYPRMDAGQNPLLPGRNLRSPAVMEPPVPRPRMVS GSSSLREQVEQQPLSAKSQEETGSVSADSALIQRKLQ RNKQVVRDSFEEWEEAYKVEAERRTVDEIFMREALV EAKKAADTWEVPVGAVLVHDGKIIARGYNLVEELRD STAHAEOMICIREGSKALRSWRLADTTLYVTLEPCPMC AGAILQARVNTLVWGAPNKLLGADGSWIRLFPGGEG NGSEASEKPPPPVHPFHPKMTIRRGVLESECAQTMQQ FFQLRRKKKDKNSDPPTPTDHHHHHLPKLLNKMHVQV LPFFCL	SEQ ID NO: 67

Aquifex aeolicus TadA	MGKEYFLKVALREAKRAFEKGEVPVGAIIVKEGEIISK AHNSVEELKDPTAHAEMLAIKEACRRLNTKYLEGCEL YVTLEPCIMCSYALVLSRIEKVIFSALDKKHGGVVSF NILDEPTLNHRVKWEYYPLEEASELLSEFFKKLRNNII	SEQ ID NO: 68
Streptococcus pyogenes serotype M3 TadA	MPYSLEEQTTFMQUEALKEAEKSLQKAEIPIGCVIVKD GEIIGRGHNAAREESNQAIMHAEMMAINEANAHEGNW RLDITTLFVTIEPCVMCSGAIGLARIPHVYIGASNQKF GGADSLYQILTDERLNHRVQVERGLLAADCANIMQTF FRQGRERKKIAKHLIKEQSDPFD	SEQ ID NO: 69
Bacillus subtilis TadA	MTQDELYMKEAIKEAKKAEKGEVPVIGAVLVINGEIIA RAHNLRETEQRSIAHAEMLVIDEACKALGTWRLEGAT LYVTLEPCPMCAGAVVLSRVEKVVFGAFDPKGGCSG TLMNLLQEERFNHQAEEVSGVLEEECGGMLS AFFREL RKKKKAARKNLSE	SEQ ID NO: 70
Haemophilus influenzae TadA	MDAAKVRSEFDEKMMRYALELADKAEALGEIPVGA VLVDDARNIIGEGWNLSIVQSDPTAHAEIILRNAGAKN IQNYRLLNSTLYVTLEPCTMCAGAILHSRIKRLVFGAS DYKTGAIGSRFHFFDDYKMNHTLEVTSGVLAEECSQK LSTFFQKRREEKKIEKALLKSLSDK	SEQ ID NO: 71
Buchnera aphidicola TadA	MKYEKDKNWMKIALKYAAYAKEKGEIPIGAILVFKE RIIGIGWNSSISKNDPTAHAEIILRGAGKKIKNYRLLN TTLTYVTLPQIMCCGAIISRIKRLVFGANCNSSDHRFS LKNLFCDPQKDYKLDIKKNVMQRECSILINFFQKKR KNKIHIKKI	SEQ ID NO: 72
Escherichia coli TadA	MSEVEFSHEYWMRHALTLAKRAWDEREVPVGAVLV HNNRVIGEGWNRPIGRHDPTAHAEIMALRQGGLVMQ NYRLIDATLYVTLEPCVMCAGAMIHSRIGRVVFGARD AKTGAAGSLMDVLHHPGMNHRVEITEGILADECAAL LSDFFRMRRQEIKAKKKAQSSTD	SEQ ID NO: 73
Streptococcus pyogenes serotype M1 TadA	MPYSLEEQTTFMQUEALKEAEKSLQKAEIPIGCVIVKD GEIIGRGHNAAREESNQAIMHAEMMAINEANAHEGNW RLDITTLFVTIEPCVMCSGAIGLARIPHVYIGASNQKF GGVDSLYQILTDERLNHRVQVERGLLAADCANIMQTF FRQGRERKKIAKHLIKEQSDPFD	SEQ ID NO: 74
Rickettsia bellii TadA	MREALKQAEIAFSKNEVPVGAVIVDRENQKIISKSYNN TEEKNNALYHAEIIAINEACRIISSKNLSDYDIYVTLEP CAMCAAAIAHSRLKRLFYGASDSKHGAVESNLRYFN SKACFHRPEIYSGIFAEDSALLMKGFFKKIRD	SEQ ID NO: 75
Rickettsia felis TadA	MEQALKQAGIAFDKNEVPVGAVIVDRLNQKIIVSSH NTEKNNALYHAEIIAINEACNLISSKNLNDYDIYVTL EPCAMCAAAIAHSRLKRLFYGASDSKHGAVESNLRYF NSSVCFYRPEIYSGILAEDSRLLMKEFFKRIR	SEQ ID NO: 76

Salmonella typhimurium TadA	MSDVELDHEYWMRHALTLAKRAWDEREVPVGAVLV HNHRVIGEGWNRPIGRHDPTAHAEIMALRQGGLVLQ NYRLDITLYVTLEPCVMCAGAMVHSRIGRVVFGAR DAKTGAAGSLIDVLHHPGMNHRVEIIEGVLRDECATL LSDFFRMRRQEIKALKKKADRAEGAGPAV	SEQ ID NO: 77
Escherichia coli O6 TadA	MSEVEFSHEYWMRHAMTLAKRAWDEREVPVGAVLV HNNRVIGEGWNRPIGRHDPTAHAEIMALRQGGLVMQ NYRLIDATLYVTLEPCVMCAGAMIHSRIGRVVFGARD AKTGAAGSLMDVLHHPGMNHRVEITEGILADECAAL LSDFFRMRRQEIKAAQKKAQSSTD	SEQ ID NO: 78
Buchnera aphidicola subsp. Baizongia pistaciae (strain Bp) TadA	MKSNRDSYWMKIALKYAYYAEENGEVPIGAILVFQE KIIGTGWNSVISQNDSTAHAEIIALREAGRNIKNYRLV NTTLYVTLQPCMMCCGAIINSRIKRLVFGASYKDLKK NPFLKKIFINLEKNKLKIKKHIMRNECAKILSNFFKNKR F	SEQ ID NO: 79
Streptococcus pyogenes serotype M18 TadA	MPYSLEEQTYFMQEALKEAEKSLQKAEIPIGCVIVKD GEIIGRGHNAREESNQAIMHAEMMAINEANAHEGNW RLDITLFTVETIEPCVMCSGAIGLARIPHVIYGASNQKF GGADSLYQILTDERLNHRVQVERGLLAADCANIMQTF FRQGRERKKNS	SEQ ID NO: 80
Rickettsia prowazekii TadA	MEQALKQARLAFDKNEVPVGVVIVCRLNQKIIVSSH NIEEKNPLCHAEIIAINTACNLISSKNLNDYDIYVTLE PCAMCASAISHSRLKRLFYGASDSKHGAVESNLRYFN SNSCFYRPEIYSGILSEHSRFLMQEFFQRIRSAID	SEQ ID NO: 81
Rickettsia typhi TadA	MEQALKQARLAFDKNEVPVGVVIVYRLNQKIIVSSH NIEEKNALCHAEIIAINEACNLISSKNLNDYDIYVTLE PCAMCASAISHSRLKRLFYGASDSKQGAVESNLRYFN SSACFHRPEIYSGILSEHSRFLMKEFFQKMRSTID	SEQ ID NO: 82
Buchnera aphidicola subsp. Schizaphis graminum (strain Sg) TadA	MHDSDKYFMKCAIFLAKISEMIGEVPGAVLVFNNTII GKGLNSSILNHDPTAHAEIKALRNGAKFLKNYRLHT TLYVTLEPCIMCYGAIHSRISRLVFGAKYKNLQKYIC CKNHFFINKNFRKISITQEVLESECSNLLSSFFKRKRKI ATKYFNNII	SEQ ID NO: 83
Rickettsia conorii TadA	MEQALKQAKIAFDKNEVPVGVVVDRLHQKIIASTH NNTTEKNNALYHAEIIAINEACNLISSKNLNDYDIYVT LEPCAMCAAAIAHSRLKRLFYGASDSKHGVVESNLRY FNSSACFHRPEIYSGILAEDSGLLMKEFFKRIRTVISSH RMT	SEQ ID NO: 84

Staphylococcus aureus TadA	MTNDIYFMTLAIEEAKKAAQLGEVPIGAIITKDDEVIA RAHNLRETLQQPTAHAEHIAIERAAKVLGSRLEGCT LYVTLEPCVMCAGTIVMSRIPRVVYGADDPKGGCSGS LMNLLQQSNFNHRAIVDKGVLKEACSTLLTFFKNLR ANKKSTN	SEQ ID NO: 85
Arabidopsis thaliana ADAT1	MEEDWGKTVSEKVISAYMSLPKKGKPGGREVTVLSA FLVSSPSQDPKVIALGTGTKCVSGSLLSPRGDIVNDSH AEVVARRALIRFFYSEIQRMQLTSGKSNEAKRQRIDSE TSSILESADSSCPGEVKYKLKSGCLLHLYISQLPCGYAS TSSPLYALKKIPSTQVDDSLVQASDICSSRHSDVPEIG SNSNKGNGSQVADMVQRKPGRGETTSLVSCSDKIAR WNVLGVQGALLYQVLQPVYISTITVGQSLHSPDNFSL ADHLRRSLYERILPLSDELLTSFRLNKPLFFVAPVPPSE FQHSETAQATLTCGYSLCWNYSGLHEVILGTTGRKQG TSAKGALYPSTQSSICKQRLLELFLKETHGHKRESSKS KKSRELKKNKATEYYLMSKIFKGKYPFNNWLRKPLN CEDFLIN	SEQ ID NO: 86
Schizosaccharomyces pombe ADAT1	MEEFTLDRNSNVGNLIALAVLNKFDELARHGKPIIRA NGVREWTTLAGVVIQKKMENEFICVCLATGVKCTPA GIIKNEQLGSVLHDCHAEILALRCFNRLLEHCILIKES KKDTWLLEVADNGKFTLNSNLLIHLVYSECPCGDAS MELLASRLENNKPWNLTVDSEKLMRGRADFGLLGIV RTKPGRPDAPVSWWSKCTDKLAAKQYLSILNSQTSLIC EPIYLSVCVLYKKVIVKSAIDRAFGPFGRCAPLAEFGE KDNPPYFHPFTVLETDENFLYSRPLNQAECTATSTNV LIWIGDKMQCTQVIHNGIKAGTKAKDVEKSQTLICRK SMMNLLHQLSQSLTNEKNYYEWKKNLKRCCQKQIL RNILKNWIPNGGNEFQWI	SEQ ID NO: 87
Saccharomyces cerevisiae ADAT1	MVSCQGTRPCIVNLLTMPSEDKLGEEISTRVINEYSKL KSACRPIIRPSGIREWTILAGVAAINRDGGANKIEILSIA TGVKALPDSELQRSEGKILHDCHAEILALRGANTVLL NRIQNYNPSSGDKFIQHNDIEIPARFNLKENWELALYIS RLPCGDASMSFLNDNCKNDDFIKIEDSDEFQYVDRSV KTILRGRLNFNRRNVVRTKPGRYDSNITLSKSCSDKLL MKQRSSVLNCLNYELFEKPVFLKYIVIPNLEDETKHHL EQSFHTRLPLNDNEIKFLNCLKPFYDDKLDEEDVPGL MCSVKLFMDDFSTEEAILNGVRNGFYTKSSKPLRKHC QSQVSRFAQWELFKKIRPEYEGISYLEFKSRQKKRSQ LIAIKNILSPDGWIPTRTDDVK	SEQ ID NO: 88
Macaca fascicularis ADAT1	MWTADEIALLCYEHYGIRLPKKGKPEPNHEWTLLAA VVKIQSPADQDCDTPDKPAQVTKEVVSMTGTGKCIG QSKMRKSGDILNDSHAIEVIARRNFQRYLLHQLQLAAT LKEDSIFVPGTQKGLWKLRRDLFFVFFSSHTPCGDASII	SEQ ID NO: 89

	PMLEFEDQPCCPVIRDWASSSSVEASSNLEAPGNERKC EDLDSPVTKKMRLEPMTAAREVTNGATHHQSFGKQE SGPISPGINSCNLTVEGLAAVTRIAPGSAKVIDVYRTG AKCVPGEAGDSRKPGAAFHQVGLLRVKPGRGDRTRS MSCSDKMARWNVLGCQGALLMHFLEPIYLSAVVIG KCPYSQEAMQRALTGRRQNVSALPKGFGVQELKILQS DLLFEQSRCAVQAKRADSPGRLVPCGA AISWSAVPEQ PLDVTANGFPQGTTKKTIGSLQARSQISKVELLRSFQK LLSRIARDKWPD SLRVQKLD TYQDYKEA ASSYQEAW STLRKQAFGSWIRNPPDYHQFK	
Gallus gallus ADAT1	MWTADEIAELCYEHYRSRLPKQGKPDPSREWTSLAA VVKVESAANEAGSAVLGTLQVAKEVVALGTGTCIG LNKMRKTGDVLNDSHAEVVAKR SFQRYLLHQMRLA TSYQQCSIFIPGTETGKWKLKPNIIFFCSHTPCGDASII PIRETENHLSKSVDGHDIAQSVLCSSSNCDHRGPEDK RKSEKMASSHMIKRMKNADGGFFSTITEDMAVQQVF AKPEGNVNPECCESSEEMQAANKETNAGKLKAVGVY RTGAKFVPGELSDTLIPGIEYHCVGLLRVKPGRGDRTC SMSCSDKLARWNVLGCQGALLMHFLQYPVYLSAVIV GKCPYSQEAMQRAVIERCRHISLLPDGFLTQEVQLLQS DLQFEHSRQAIQEGQTSSKRKLVPCSA AISWSAVPEGP LDVTSDGFRQGTTKKGIGSPQSR SKICKVELFHEFQKL VTSISKENLPD TLRMKTLETYWDYKEAALNYQEAWK ALRSQALLGWIKNAQEYLLFM	SEQ ID NO: 90
Human ADAT1	MWTADEIAQLCYEHYGIRLPKKGKPEPNHEWTLLAA VVKIQSPADKACDTPDKPVQVTKEVVSMGTGTCIG QSKMRKNGDILNDSHAEVIARRSFQRYLLHQLQLAAT LKEDSIFVPGTQKGVWKLRRDLIFVFFSHTPCGDASII PMLEFEDQPCCPVFRNWAHNSSVEASSNLEAPGNERK CEDPDSPVTKKMRLEPGTAAREVTNGAAHHQSFGKQ KSGPISPGIHSCDLTVEGLATVTRIAPGSAKVIDVYRTG AKCVPGEAGDSGKPGAAFHQVGLLRVKPGRGDRTRS MSCSDKMARWNVLGCQGALLMHLLEPIYLSAVVIG KCPYSQEAMQRALIGRCQNVSALPKGFGVQELKILQS DLLFEQSRSAVQAKRADSPGRLVPCGA AISWSAVPEQ PLDVTANGFPQGTTKKTIGSLQARSQISKVELFRSFQK LLSRIARDKWPHSLRVQKLD TYQEYKEA ASSYQEAW STLRKQVFGSWIRNPPDYHQFK	SEQ ID NO: 91
Mus musculus ADAT1	MWTADEIAQLCYAHYNVRLPKQGKPEPNREWTLAA VVKIQASANQACDIPEKEVQVTKEVVSMGTGTCIGQ SKMRESGDILNDSHAEIARRSFQRYLLHQLHLAAVLK EDSIFVPGTQRGLWRLRPDLSFVFFSHTPCGDASIIPM LEFEEQPCCPVIRSWANNSPVQETENLED SKDKRNCE	SEQ ID NO: 92

	DPASPVAKKMRGLGTPARSLSNCAVHHGTQESGPVKP DVSSSDLTKKEEPDAANGIASGSFRVVDVYRTGAKCVP GETGDLREPGAAYHQVGLLRVKPGRGDRTCSMSCSD KMARWNVLGCQGALLMHFLEKPIYLSAVVIGKCPYS QEAMRRALTGRCEETLVLPGRFGVQELEIQQSGLLFE QSRCAVHRKRGDSPGRLVPCGAAISWSAVPQQPLDVT ANGFPQGTTKKEIGSPRARSRISKVELFRSFQKLLSSIA DDEQPD SIRVTKKLDTYQEYKDAASAYQEAWGALRR IQPFASWIRNPPDYHQFK	
Drosophila melanogaster ADAT1	MCDNKKPTVKEIAELCLKKFESLPKTGKPTANQWTL AGIVEFNRNTEACQLVSLGCGTKCIGESKLCPNGLILN DSHAEVLARRGFLRFLYQELKQDRIFHWNSTLSTYDM DEHVEFHFLSTQTPCGDACILEEEQPAARAKRQRLDE DSEMVYTGAKLISDLSDDPMLQTPGALRTKPGRGERT LSMSCSDKIARWNVIGVQGALLDVLISKPIYFSSLNFC CDDAQLESLEIAIFKRFD CRTFKHTRFQPPRQINIDP GIRFEFSQRSDWQPSPNGLIWSQVPEELRPYEISVNGK RQGVTKKKMKTSQAALAI SKYKLF LTFL ELVKFNPKL SEMFDQQLSDPERIAYASCKDLARDYQFAWREIKEKY FLQWTKK PHELLDFNPMSNK	SEQ ID NO: 93
Xenopus tropicalis ADAT1	MQAKGLWSADEIAALS YGHYTTQLPKQGLPDPSREW TLMAAVIQIESVEDTKVIKKVVAMGTGTCIGQAKLR KTGDVLQDSHAEIIAKRSFQRYLLHQLSLAVSDTKDC LFIPGTEKGKWMRLRPEISFVFFTSHTPCGDASIIPVISHE DELGHPLPSEVTEKDHSSNNVCESVNTTYKRKVRSEE DIGFISKKMKH SIDEILTRPENYEEENRHDFPSTCQKAL DVHRTGAKCVAGELQDSYSPGVNYHTVGVLRIKPGR GDRTMSMSCSDKMARWNVLGCQGALLMHFLQQPIY LSAVVVGKCPFSQDAMERALYNRCHKVLSLPCAFRL NRVQIIQSDLEFQHGRHALTKKDATRKL VPCGA AVS WSAVPHHPLDVTANGYRQGTTRKAIGSPQCRSRICKA EIFNTFREL VQRLSEKQRSESLSSQGLKTYWDYKAAAI TYQEAWNCLRQQAFTSWIQT PRDFLMFS	SEQ ID NO: 94
Dictyostelium discoideum ADAT1	MSWKLDKQFSDKICNFSHDFFNKKLIKKGKPISGEWT VLATLVLVVENTSSYEIKQVLSLGTGNRCLGKSSLSN QGDVLNDSHAEIICKRSFQKFCYNEILNLLQSKYYNSI LFNIEYHDSNNNNKDNNDNNGSLPTISIKKGHSLHFYVN QTPCGDCSIFPFKKETQPENFIEKEKLEKDGKDKIENH EKKEQKDIKQVDKDKDEENYEDEESKRKLKVKDD NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN NNNINNNNNNQYDDIQR TGAKTVFGEPEDKKLIGVDY HQIGVLRVKPGRGDPTVSMSCSDKIARWNVLGIQGS LSHFIEK E OIFLSSITIGDLFNHSSIYRGLIGRLLPNPTTTT	SEQ ID NO: 95

	TETSSSSSSSSSSNTIPNFKLNSDLEIFSTNIQFQFSKLL LESDQQNNNKSTSSGLAISFCYPNQHEVTIAINGKKMG TNQKNFNAISQRSSICKFNLFKLFHQLVLIKNKNSNEE NEKNNQIVLIDSLFNYYECKHLSKKYYQEYEKLKEFK FKNWLTNSSDLENFVLDN	
Schizosacchar omyces pombe ADAT2	MAGDSVKSAIIGIAGGPFSGKTQLCEQLLERLKSSAPS TFSKLIHLTSFLYPNSVDYALSSYDIEAFKKVLSLISQ GAEKICLPDGSCIKLPVDQNRILIEGYLLLPPELLPY TSKIFVYEDADTRLERCVLQRVKAEGDLTKVLNDFV TLSPAYDSSIHPTRENADIILPQKENIDTALLFVSQHL QDILAEMNKTSSSNTVKYDTQHETYMKLAHEILNLGP YFVIQPRSPGSCVFVYKGEVIGRGFNETNCSLSGIRHA ELIAIEKILEHYPASVFKETTLVTVPECLMCAAALKQ LHIKAVYFGCGNDRFGGCGSVFSINKDQSIDPSYPVYP GLFYSEAVMLMREFYVQENVKAPVPQSKKQRVLKRE VKSLDLSRFK	SEQ ID NO: 96
Saccharomyce s cerevisiae ADAT2	MQHIKHMRTAVRLARYALDHDETPVACIFVHTPTGQ VMAYGMNDTNKSLTGVAHAEFMGIDQIKAMLGSRG VVDVFKDITLYVTVEPCIMCASALKQLDIGKVVFSGC NERFGNGTVLSVNHDCTCLVPKNNSAAGYESIPGIL RKEAIMLLRYFYVRQNERAPKPRSKSDRVLDKNTFPP MEWSKYLNEEAFIETFGDDYRTCFANKVDLSSNSVD WDLIDSHQDNIIQEELEEQCKMFKFNVHKSKV	SEQ ID NO: 97
Xenopus tropicalis ADAT2	MTEEIQNWMHKAQMAQDALNNGEVPVGCLMVYD NQVVGKGRNEVNETKNATRHAEMVAIDQVLDWCEK NSKKS RDVFENIVLYVTVEPCIMCAGALRLKIPLVVY GCRNERFGGCGSVLNVAGDNIPDTGTETFKYIGGYQAE KAVELLKTFYKQENPNAPRSKVRKKE	SEQ ID NO: 98
Bos taurus ADAT2	MEAKAGPTAATDGAYSVSAAETEKWMEQAMQMAK DALDNTEVPVGCLMVYNNEVVGKGRNEVNQTKNAT RHAEMVAIDQALDWCRRRGRSPSEVFEHTVLYVTVE PCIMCAAALRLMRIPLVVGQCNERFGGCGSVLDIAS ADLPSTGKPFQCTPGYRAEEAVEMLKTFYKQENPNAP KSKVRKKECHKS	SEQ ID NO: 99
Danio rerio ADAT2	MQEVGVDPEKNDLQPSDSEVQTWMAKAFDMAVEA LENGEVPVGCLMVYNNEIIGKGRNEVNETKNATRHA EMVALDQVLDWCRLREKDCKEVCEQTVLYVTVEPCI MCAAALRLLRIPFVVGCKNERFGGCGSVLDVSSDHL PHTGTSFKCIAGYRAEEAVEMLKTFYKQENPNAPKPK VRKDSINPDGAAVIQVMRGPPDEETETIAHLS	SEQ ID NO: 100

Arabidopsis thaliana ADAT2	MEEDHCEDSHNYMGFALHQAklALEALEVPVGCvFL EDGKVIASGRNRTNETRNATrHAEMEAIQDLVGQWQ KDGLSPSQVAEKFSKCVLYVTCEPCIMCASALSFLGIK EVYYGCPNDKFGGCGSILSLHLGSEEAQRGKGyKCRG GIMAEeAVSLFKCFYEQGNPNAPKPHRPVVQRERT	SEQ ID NO: 101
Mus musculus ADAT2	MEEKVESTTTTPDGPCVVSvQETEKWMEEAMRMAKE ALENIEVPVGCLMVYNNEVVGKGRNEVNQTKNATRH AEMVAIDQVLDWCHQHGGQSPSTVFEHTVLYVTVEPCI MCAAALRLMKIPLVVYGCQNERFGGCGSVLNIAAD LPNTGRPFQCIPIGYRAEEAVELLKTFYKQENPNAPKSK VRKKDCQKS	SEQ ID NO: 102
Human ADAT2	MEAKAAPKPAASGACSVSAEETEKWMEEAMHMAKE ALENTEVPVGCLMVYNNEVVGKGRNEVNQTKNATR HAEMVAIDQVLDWCRQSGKSPSEVFEHTVLYVTVEP CIMCAAALRLMKIPLVVYGCQNERFGGCGSVLNIAA DLPNTGRPFQCIPIGYRAEEAVEMLKTFYKQENPNAPK SKVRKKECQKS	SEQ ID NO: 103
Arabidopsis thaliana ADAT3	MDSDAWEIIHIPEKPSLSPDHQPTVKVYASLIKPRFAN TIVRHLCKIAPLEDLRHVkrVKKILPDCGETQLTVIL CLAPEHNDQLSDMPPDVQRLVDPYELSPFITQVCKYA AVSKEEWEEQSKIWPTSFHPPTYNIDGIGGFSEEETQSI CKFMRVVIDMAVSGHTPLVNAAVIVDPSVRRIIASETD QVYASSAPRDMTSAETRPFEETGEICLNDTLEKQNGSL SALSCLNPWQWSLQPHDTENCsqWHPLRHASMVAIE SSSARDRNLFNPNSKIFDQDHVPPSNTDSPAKKQKTSS QSPDVQNDsREETVRDPsMERPYLCTGYDIFLLLEPCT MCAMALVHQRIKRIFYAFPNTTAGGLGSVHRLQGEKS LNHHYAVFRVLLPDDALRQMTTV	SEQ ID NO: 104
Mus musculus ADAT3	MEPTSGFAEQPGPVKAEESEEQEPAQWQALPVLSEQQS GAVELILAYAAPVLDKRQTSRLLREVSaVYPLPAQPH LKRVRPSRSAGGAQSSDLLLCLAGPSAGPRSLAELLPR PAVDPRGLGTPFLVPVPARPLTRsQFEEARAHWPTSF HEDKQVTSALAGQLFSTQERAAMQTHMERAVCAAQ RAAAQGLRAVGAVVVDPASDRVLATGHDCSSVASPL LHAVMVCIDLVAQGQGRGSCDLRSHpACsFTQATAT QGARAGSVRKLEDSLPYVCTGYDLYVTREPCVMCA MALVHARIQRVfYGAPSPDGALGTLFRVHARPDNLH RFQVFRGILEDQCRQLDPDP	SEQ ID NO: 105
Danio rerio ADAT3	MEPQAKRKKEMDDYDDTWEVLPVLSDEQSQDPELLP AYAAPILERRETSRLVKELSLIHPLPNLQHIKRVrPCKH KDSPHPLEVIVCLVSDVQCTDPKKVTLShLLHTQCFNS NGLGDPFIVQIPANPPLTRPQFEKASKHWPTSFHEDKL VTFALKGQLFTAHQKTKMREYMCVAVKAAKSGREL	SEQ ID NO: 106

	GMDAVGAVIVDPKTEQIIA VAHDCKRGSHPLHHAVM VCIDL VACGQDGGAYNYEKYPACRFSCSNSVCDGKE TGLPYICTGYDLYVTREPCVMCAMLVHSRISR VFY G ASTADGAFGSRYKIH CQKDLNHRFEVFKGVMVNACE DLC KE	
Schizosacchar omyces pombe ADAT3	MVKTNISKNSPKEATVPELDWPFKLIKSHLETRKLETE NVWIA CFEPKYASKVTQYVKQIRSKQKESLLHCNRLR RIQDENG SLELQIIICPEKSMTANEIGKDFEDLGIVSKMI FLYAVPAFPPLTDEQFHEWNSVWPVSYRKHVQRQDV FTVHELKRIESILEDLINAAGASHKHGEIGCAA IYDPT TDTVLA VSVDERSKLKNPINHCVMNAINLVAKRELSR RQNRTD GSKDRYLCKDLTVVMTHEPCVMC SMGL LH SRIRRLIYCKKQPLTGGIESLYGIHWRAELNHRYLAYS GWNKPVPSIKENIHV	SEQ ID NO: 107
Saccharomyce s cerevisiae ADAT3	MVKKVNNPLKIDYQNGIENRLLQIRNFKDVNTPKLIN VWSIRIDPRDSKKVIELIRNDFQKNDPVSLRHLKRIRK DIETSTLEVVLCSKEYICDEGEINNKLKSIWVGTKKYE LSDDIEVPEFAPSTKELNNAWSVKYWPLIWNGNPNDQ ILNDYKIDMQEVRNELSRASTLSVKMATAGKQFPMVS VFVDPSRKKDKVVAEDGRNCENSLPIDHSVMVGIRAV GERLREGVDEDANSYLCLDYDVYLTHEPCSMCSMAL IHSRVR RVFLTEMQRTGSLKLTSGDGYCMNDNKQL NSTYEA FQWIGEEYPVGQVDRDVCC	SEQ ID NO: 108
Human ADAT3	MEPAPGLVEQPKCLEAGSPEPEPAPWQALPVLSEKQS GDVELV LAYAAPVLDKRQTSRLLKEVSALHPLPAQPH LKRVRPSRDAGSPHALEMLLCLAGPASGPRSLAELLP RPAVDPRGLGQPFLVPVPARPLTRGQFEEARAHWPT SFHEDKQVTSALAGRLFSTQERAAMQSHMERAVWA ARRAAARGLR AVGAVVVD PASDRVLATGHDCSCAD NPLLHVMVCVDLVAR GQGGRGTYDFRPF PACSFAPA AAPQAVRAGAVRKLD ADEDGLPYLCTGYDLYVTREP CAMCAMLVHARILRVFY GAPSPDGALGTRFRIHARP DLNHRFQVFRGVLEE QCRWLDPDT	SEQ ID NO: 109
Rattus norvegicus ADAT3	MEPTSGFAEQPGPEKVESEEQEPAQWQALPVLSEQQS GAVELV LAYAAPVLDKRQTSRLLREVSAVYPLPAQPH LKRVRPSRSAGGAHSSDLLLCLAGPSAGPRSLAELLPR PAVDPRGLGTPFLVPVPARPLTRS QFEEARAHWPTSF HEDKQVTSALAGQLFSAQARAAMQTHMERAVRAAQ RAAAQGLRAVGAVVVD PASDHVLATGHDC CSEASPL LHAVMVCIDLVAQGQGRGSCDLRRHPACSFTQATAT QSARAGSVRKLEDESLPYVCTGYDLYVTREPCVMCA MALVHARIQR VFY GAPSPDGALGTRFRVHARPD LN H RFQVFRGILEDQCRQLDPDP	SEQ ID NO: 110

Rattus norvegicus ADARB1	MDIEDEENMSSSIDVKENRNLDNMPPKDSSTPGPGE GIPLSNGGGGSTSRKRPLEEGSNGHISKYRLKKRRKTP GPVLPKNALMQLNEIKPGLQYMLLSQTGPVHAPLFV MSVEVNGQVFEGSGPTKKKAKLHAAEKALRSFVQFP NASEAHLAMGRTLSTVNTDFTSDQADFPDTLNGFETP DKSEPPFYVGSNGDDSFSSSGDVLSASPVPASLTQPP LPIPPFPFPPSGKNPVMILNELRPGLKYDFLSESGESHA KSFVMSVVVDGQFFEGSGRNKKLAKARAAQSALATV FNLHLDQTPSRQPVLSEGLQLHLPQVLADAVSRLVLG KFSDLTDNFSSPHARRKVLSGVVMTTGTDTVKDAKVIS VSTGTHKINGEYMSDRGLALNDCHAEIISRRSLLRFLY AQLELYLNNKEDQKKSIFQKSERGGFRLKDTVQFHL ISTSPCGDARIFSPHEPVLEGMAPDSHQLTEPADRH PNRKARGQLRTKIESGEGTIPVRSNASIQTWGVLQGERL LTMSCSDKIARWNVVGIQGALLSIFVEPIYFSSIILGSLY HGDHLSRAMYQRISNIEDLPPLYTLNKPILLSGISNAEA RQPGKAPNFSVNWTVGDTAIEVINATTGKDELGRPSR LCKHALYCRWMRVHGKVPPHLLRTKITKPTTYHESK LAAKEYQAAKARLFTAFIKAGLGAWVEKPTEQDQFS FTP	SEQ ID NO: 111
Human ADAR	MNPRQGYSLSGYYTHPFQGYEHRQLRYQQPGPGSSPS SFLKQIEFLKGQLPEAPVIGKQTPSLPPLPGLRPRFPV LLASSTRGRQVDIRGVPRGVHLRSQGLQRGFQHPSPR GRSLPQRGVDCLSHFQELSIYQDQEQRILKFLEELGE GKATTAHDLGKLGTPKKEINRVLYSLAKKGKLQKE AGTPPLWKIAVSTQAWNQHSGVVRPDGHSQGAPNSD PSLEPEDRNSTSVSEDLLEPFIAVSAQAWNQHSGVVRP DSHSQGSPPNDPGLEPEDSNSTSALEDPLEFLDMAEIK EKICDYLFNVSDSSALNLAKNIGLTKARDINAVLIDME RQGDVYRQGTTPPIWHLTDKKRERMQIKRNTNSVPET APAAIPETKRNAEFLTCNIPTSNASNNMVTTEKVEN GQEPVIKLENRQEARPEPARLKPPVHYNGPSKAGYVDF ENGQWATDDIPDDLNSIRAAPGEFRAIMEMPSFYSHG LPRCSPYKKLTECQLKNPISGLLEYAQFASQTCEFNMI EQSGPPHEPRFKFQVVINGREFPPAEAGSKKQVAKQDA AMKAMTILLEEAKAKDSGKSEESSHYSTEKESEKTAE SQTPTPSATSFSGKSPVTTLLECMHKLGNSCFEFRLS KEGPAHEPKFYCVAVGAQTFPSVSAPSKKQVAKQMA AEEAMKALHGEATNSMASDNQPEGMISESLDNLESM MPNKVRKIGELVRYLNTNPVGGLLEYARSHGFAAEF KLVDQSGPPHEPKFVYQAKVGGRWFPVCAHSSKKQ KQEAADAALRVLIGENEAERMGFTEVTPVTGASLRR TMLLSRSPEAQPKTLPLTGSTFHDQIAMLSHRCFNTL	SEQ ID NO: 112

	TNSFQPSLLGRKILAAIIMKKDSEDMGVVVSLGTGNR CVKGDSLKGETVNDCHAEIISRRGFIRFLYSELMKY NSQTAKDSIFEPAKGGKELQIKKTVSFHLYISTAPCGD GALFDKSCSDRAMESTESRHYPVFENPKQGKLRTKVE NGEGTIPVESSDIVPTWDGIRLGERLRMTSCSDKILRW NVLGLQGALLTHFLQPIYLKSVTLGYLFSQGHLTRAIC CRVTRDGSFEDGLRHPFIVNHPKVGRVSIYDSKRQS GKTKETSVNWCLADGYDLEILDGTRGTVDGPRNELS RVSKKNIFLLFKKLCSFRYRRDLLRLSYGEAKKAARD YETAKNYFKKGLKDMGYGNWISKPQEEKNFYLCPV	
Rattus norvegicus ADAR	MSQGFRGPTGVFPHQTQPCLDPSYEHKRWYLQPRGS ESYLSFQLQQIEFLKGRLEAPLIGAQTQSLPPFLPGH WPRFPGPPAQGKQPEIWGFPRSVTLRNQGFHIGPPLPP PHSRGPPWRGAEGLCSHFQELSIQNPEQKVLNRLEEL GEGKATTAYALARELRTPKKDINRILYSLERKGLHR GVGKPLWSLVPLSQACTQPPRAVNSDKEVPRGEPDL DSEDGDPASDLEGPSELDMAEIKEKICDYLFNVSKSS ALNLAKNIGLAKARDVNAVILDLERQGDVYREGATPP IWYLTDKKRERLQMKRSTHSGPAATPAAVSEATQSTS FPTCHPPQSGSSMATSKRVENGQEPVTKYESRHEA RPGPVRLRPHAYHNGPSRAGYVASENGPWATDDIPD NLNSIHTAPGEFRAIMEMPSFYSPTLPRCSPYKKLTEC QLKNPVSGLLEYAQFTSQTCDFNLIEQSGPSHEPRFKF QVVINGREFPPAEAGSKKQDAAVKAMAILLREA KAKDSGQPEELSNCPMEEDPEKPAESQPPSSSATSLS GKSPVTTLLECMHKLGNCEFRLLSKEGPAHDPKFQY CVAVGAQTFPSVSAPSKKQMAAAEEAMKALQEE AANSADDQSGGANTDSLDESAPNKRIRGELVRYLN TNPVGGLLEYARSHGFAAEFKLIDQSGPPHEPKFVYQ AKVGGRWFPAVCAHSKKQKQDAADAALRVLIGESE KAEQLGFAEVTPTGASLRRTMLLSRSPDAHPTLP LTGSTFHDQIAMLSHRCFNALTNSFQPSLLGRKILAAI MKRDPEDMGVVVSLGTGNRCVKGDSLKGETVND CHAEIISRRGFIRFLYSELMKYNHHTAKNSIFELARGG EKLQIKKTVSFHLYISTAPCGDGAHFDKSCSDRAVEST ESRHYPVFENPKQGKLRTKVENEGTIPVESSDIVPTW DGIRLGERLRMTSCSDKILRWNVLGLQGALLTHFLQP VYLKSVTLGYLFSQGHLTRAICCRVTRDGNFEDGLR YPFIVNHPKVGRVSVYDSKRQSGKTKETSVNWCLAD GYDLEILDGTRGTVDGPGKELSRVSKKNIFLQFKKLCS FRARRDLLQSYGEAKKAARDYDLAKNYFKKSLRDM GYGNWISKPQEEKNFYLCVPND	SEQ ID NO: 113

Human ADARB1	MDIEDEENMSSSSTDVKENRNLDNVSPKDGSTPGPGE GSQLSNGGGGGPGRKRPLEEGSNHGSKYRLKKRRKT PGPVLPKNALMQLNEIKPGLQYTLLSQTGPVHAPLFV MSVEVNGQVFEGSGPTKKKAKLHAAEKALRSFVQFP NASEAHLAMGRTL SVNTDFTSDQADFPDTL FNGFETP DKAEPPFYVGSNGDDSFSSSGDLSLSASPVPASLAQPP LPVLPFPFPPSGKNPVMILNELRPGLKYDFLSESGESHA KSFVMSVVVDGQFFEGSGRNKKLAKARAAQSALAAI FNLHLDQTPSRQPIPSEGLQLHLPQVLADAVSRLVLGK FGDLTDNFSSPHARRKVL AGVVM TTTGTDVKDAKVIS VSTGTKCINGEYMSDRGLALNDCHAEIISRRSLLRFLY TQLELYLNNKDDQKRSIFQKSERGGFRLKENVQFHL Y ISTSPCGDARIFSPHEPILEGSRSYTQAGVQWCNHGSL QPRPPGLLSDPSTSTFQGAGTTEPADRHPNRKARGQL RTKIESGEGTIPVRSNASIQTW DGV LQGERLLTMS CSD KIARWNVVGIQGSLLSIFVEPIYFSSIILGSLYHGDHLSR AMYQRISNIEDLPPLYTLNKPLLSGISNAEARQPGKAP NFSVNWTVGDSAIEVINATTGKDELGRASRLCKHALY CRWMRVHKGKVP SHLLRSKITKPNVYHESKLAAKEYQ AAKARLFTAFIKAGLGAWVEKPTEQDQFSLTP	SEQ ID NO: 114
Mus musculus ADARB1	MDIEDEENMSSSSTDIKENRNLDNMPPKDSSTPGPGE IPLSNGGGGGSTSRKRPLEEGSNHGSKYRLKKRRKT VLPKNALMQLNEIKPGLQYMLLSQTGPVHAPLFVMS VEVNGQVFEGSGPTKKKAKLHAAEKALRSFVQFPNA SEAHLAMGRTL SVNTDFTSDQADFPDTL FNGFETPDK SEPPFYVGSNGDDSFSSSGDVLSLSASPVPASLTQPPLPI PPFPFPPSGKNPVMILNELRPGLKYDFLSESGESHA KSF VMSVVVDGQFFEGSGRNKKLAKARAAQSALATVFNL HLDQTPSRQPVLSEGLQLHLPQVLADAVSRLVLGKFS DLTDNFSSPHARRKVL SGVVM TTTGTDVKDAKVISVST GTKCINGEYMSDRGLALNDCHAEIISRRSLLRFLYAQL ELYLNNKEDQKKSIFQKSERGGFRLKDTVQFHL YIST PCGDARIFSPHEPVLEGMT PDSHQLTEPADRHPNRKA RGQLRTKIESGEGTIPVRSNASIQTW DGV LQGERLLT SCSDKIARWNVVGIQGSLLSIFVEPIYFSSIILGSLYHGD HLSRAMYQRISNIEDLPPLYTLNKPLLSGISNAEARQP GKAPNFSVNWTVG DATIEVINATTGKDELGRPSRLCK HALYCRWMRVHKGKVP PHLLRTKITKPTTYHESKLAA REYQAAKARLFTAFIKAGLGAWVEKPTEQDQFSFTP	SEQ ID NO: 115
Mus musculus ADAR	MSQGFRGPTGVFPHQTQSYLDPSHEHSKWRYPPQPQP ESYPRSFQLQQIEFLKGR LPEAPLIGIQTQSLPPFLPGH WPRFPGPPAQDRQLEIWEFPRSVTLRNQGFHIGPPLPP PHSRGTPWRGADGLCSHFRELSISQSPEQKVLNRLEEL	SEQ ID NO: 116

	GEGKATTAHVLAARELRIPKRDINRILYSLEKKGKLHRG RGKPPLWSLVPLSQAWTQPPGVVNPDSQIEFPRGEP GLDSEDGDPASDLEGPSEPLDMAEIKEKICDYLFNVSN SSALNLAKNIGLTKARDVTSVLIDLERQGDVYRQGAT PPIWYLTDDKKRERLQMKRSTHSAPAPTPTAVPEATRSP SFPACHPPPAGASSSVAASKRVENGQEPAIKHESRHEA RPGPMRLRPHAYHNGPSRAGYVASENGQWATDDIPD NLNSIHTAPGEFRAIMEMPSFYSPTLPRCSPYKKLTEC QLKNPVSGLLEYAQFTSQTCDFNLIEQSGPSHEPRFKF QVVINGREFPPAEAGSKKQDAAVKAMAILLREA KAKDSGQPEDLSHCPMEEDSEKPAEAQAPSSSATSLFS GKSPVTTLLECMHKLGNCEFRLLSKEGPAHDPKFQY CVAVGAQTFPPVSAPSKKQMAAAEAMKALQEE AASSADDQSGGANTDSLDESMAPNKIRRIGELVRYLN TNPVGGLLEYARSHGFAAEFKLIDQSGPPHEPKFVYQ AKVGGRWFPAVCAHSKKQKQDAADAALRVLIGESE KAEQLGFAEVPVTGASLRRTMLLSRSPDAHPTLP LSGSTFHDQIAMLSHRCFNALTNSFQPSLLGRKILAAII MKRDPEDMGVVVSLGTGNRCVKGDSLKGETVND CHAEIISRRGFIRFLYSELMKYNHHTAKNSIFELARGG EKLQIKKTVSFHLYISTAPCGDGFALFDKSCSDRAVEST ESRHYPVFENPKQGLRRTKVENEGGTIPVESSDIVPTW DGIRLGERLRTMSCSDKILRWNVLGLQGALLTHFLQP VYLKSVTLGYLFSQGHLETRAICCRVTRDGKAFEDGLR YPFIVNHPKVGRVSVYDSKRQSGKTKETSVNWCMA GYDLEILDGTRGTVDGPGKELSRVSKKNIFLQFKKLC FRARRDLLQSYGEAKKAARDYDLAKNYFKSLRDM GYGNWISKPQEEKNFYLCVPND	
Human ADARB2- AS1	MKQLFPPPGTSLTHALGAWRGRERAQAATSLASSA SQFPTAVEDALMSVLTSCHCAPSTPAATRAQQTGTRGH IHPACPCQQSCV GASRPPGRPQIFLPLTTALSLEYAA DTCSAADFLHNPSSWGKVWYLN EASFDLYSYHYFW	SEQ ID NO: 117
Rattus norvegicus ADARB2	MASVLGSGRGSGGLSSQLKCKSKRRRRRRRSKRKDKV SILSTFLAPFKYLSPGTTNTEDEDNLSTSSAEVKENRN VSNLGRPLPPGDWARGGSTPSVKRKRPLEEGNGGHF CKLQLIWKKLSWSMTPKNALVQLHELKPGQLQYRMVS QTGPVHAPVFVAVEVNGLTFEGTGPTKKKAKMRAA EMALKSFVQFPNAFQAHLAMGSSTSPCTDFTSDQADF PDTLFKEFEPSSRNEDFPGCCPVDTEFLSSAYRRGRLL YHTLDLMGQALPDRSRLAPGALGERNPVVVLNELRS GLRYVCLSETAEKPRVKSFVMAVCVDGRTFEGSGRS KKLAKGQAAQALQALFDIRLPGHIPSRSKSNLLPQDF ADSVSQLVTQKFRELTVGLTSVYARHKTLAGIVMTK	SEQ ID NO: 118

	GLDTKQAQVIVLSSGTKCISGEHISDQGLVVNDCHAEI VARRAFLHFLYTQLELHLSKHQEDPERSIFIRVKEGGY RLRENILFHLVYSTSPCGDARLNSPYEITIDLNSSKHIV RKFRGHLRTKIESGEGTVPVVRGPSAVQTDGILLGEQ LVTMSCTDKIASWNVLGLQGALLCHFIEPVYLHSIIVG SLHHTGHLARVMHRMEGIGQLPASRQNRPLLSGV NAEARQPGKSPHFSANWVVGSDLEIINATTGKRSCG GSSRLCKHVFSARWARLHGRLSTRIPGHGDTPSMYCE AKRGAHTYQSVKQQLFKAFQKAGLGTWVRKPPEQD QFLLSL	
Mus musculus ADARB2	MASVLGSGRGSGGLSSQLKCKSKRRRRRRRSKRKDKV SILSTFLAPFKYLSPGTTNTEDEDNLSTSSAEVKENRN VSNLGRPLPPGDWARGSTPSVKRKRPLEEGNGGHFC KLQLIWKKLSWSVTPKNALVQLHELKPGQLYRMVSQ TGPVHAPVFAVAVEVNGLTFEGTGPTKKKAKMRAAE MALKSFVQFPNAFQAHLAMGSSTSPCTDFTSDQADFP DTLFKEFEPSSKNEDFPGCHPVDTEFLSSAYRRGRLLY HTLDLMGQALPDRSRLAPGALGERNPVVVLNELRSG LRYVCLSETAEKPRVKSFVMAVCVDGRTFEGSGRSK KLAKGQAAQAALQALFDIRLPGHIPSRKSNLLPQDFA DSVSQLVLTQKFRELTVGLTSVYARHKTLAGIVMTKGL DTKQAQVIVLSSGTKCISGEHISDQGLVVNDCHAEIVA RRAFLHFLYSQLELHLSKHQEDPERSIFIRLKEGGYRL RENILFHLVYSTSPCGDARVNSPYEITIDLNSSKHIVRK FRGHLRTKIESGEGTVPVVRGPSAVQTDGILLGEQLIT MSCTDKIASWNVLGLQGALLCHFIEPVYLHSIIVGSLH HTGHLARVMHRMEGIGQLPASRQNRPLLSGVSHA EARQPGKSPHFSANWVVGSDLEIINATTGKRSCGGS SRLCKHVFSAAWARLHGRLSTRIPSHGDTPSMYCEA KQGAHTYQSVKQQLFKAFQKAGLGTWVRKPPEQDQ FLLSL	SEQ ID NO: 119
Human ADARB2	MASVLGSGRGSGGLSSQLKCKSKRRRRRRRSKRKDKV SILSTFLAPFKHLSPGITNTEDDDTLSTSSAEVKENRN GNLAARPPPSGDRARGGAPGAKRKRPLEEGNGGHLC KLQLVWKKLSWSVAPKNALVQLHELRLPGLQYRTVSQ TGPVHAPVFAVAVEVNGLTFEGTGPTKKKAKMRAAE LALRSFVQFPNACQAHLAMGGPGPGTDFTSDQADFP DTLFQEFEPAPRPGLAGGRPGDAALLSAAYGRRRL CRALDLVGPTPATPAAPGERNPVVLLNRLRAGLRYVC LAEPAERRARSFVMAVSVDGRTFEGSGRSKKLARGQ AAQAALQELFDIQMPGHAPGRARRTPMPQEFADSISQ LVTQKFREVTTDLTPMHARHKALAGIVMTKGLDARQ AQVVALSSGTKCISGEHLSQGLVVNDCHAEVVAR	SEQ ID NO: 120

	AFLHFLYTQLELHLSKRREDSERSIFVRLKEGGYRLRE NILFHLVYSTSPCGDARLHSPYEITDLHSSKHLVRKF RGHLRTKIESGEGTVPVRGPSAVQTDGVLGELIT MSCTDKIARWNVLGLQGALLSHFVEPVYLQSIVVGS HHTGHLARVMSHRMEGVGQLPASVRHNRPLLSGVSD AEARQPGKSPPFSMNWVVGSALEIINATTGRRSCGG PSRLCKHVLSARWARLYGRLSTRTPSPGDTPSMYCEA KLGHAITYQSVKQQLFKAFQKAGLGTWVRKPPEQQQF LLTL	
Rattus norvegicus AMPD1	MPLFKLTGQGKQIDDAMRSFAEKVFASEVKDEGGRH EISPFVDVEICPISLREMQAHIFHMENLSMSMDGRRKR RFQGRKTVNLSIPQSETSSTKLSHIEEFISSPTYESVPD FQRVQITGDYASGVTVEDFEVVCKGLYRALCIREKYM QKSFQRFKTPSKYLRNIDGEALVAIESFYVPVTPPPKK GEDPFRREDLPANLGYHLKMKGGVIYIYPDEAAASRD EPKPYPYNLDDFLDDMNFLALIAQGPVKTYTHRRL KFLSSKFQVHQMLNEMDELKELKNNPHRDFYNCRKV DTHIHAAACMNQKHLLRFIKKSYHIDADRVVYSTKEK NLTLKELFAQLNMHPYDLTVDSLVDHAGRQTFQRFD KFNDKYNPVGASELRDLYLKTNDYINGEYFATIIKEV GADLVDAKYQHAEPRLSIYGRSPDEWSKLSSWFGN RIYCPNMTWMIQVPRIYDVFRSKNFLPHFGKMLENIFL PVFEATINPQTHPDLVFLKHITGFDSVDDSKHSGHM FSSKSPKPEEWTMENNPSTYYAYMYANIMVLNCL RKERGMNTFLFRPHCGEAGALHMTAFMIADNISHG LNLKKSPVLQYLFFLAQIPIAMSPLSNNSLFLEYAKNPF LDFLQKGLMISLSTDDPMQFHFTKEPLMEEYAIAAQV FKLSTCDMCEVARNSVLQCGISHEEKAKFLGNNYLEE GPVGNDIRRTNVAQIRMA YRYETWCYELNLIAEGLKS TE	SEQ ID NO: 121
Human AMPD1	MPLFKLPAAEKQIDDAMRNFAEKVFASEVKDEGGRQ EISPFVDVEICPISHHEMQAHIFHLETLSSTEARRKKR FQGRKTVNLSIPLSETSSTKLSHIDEYISSPTYQTVPDF QRVQITGDYASGVTVEDFEIVCKGLYRALCIREKYM KSFQRFKTPSKYLRNIDGEAWVANESFYVPVTPPVK KGEDPFRDNLNLPENLGYHLKMKDGVVYVYPNEAAVS KDEPKPLPYPNLDTFLLDDMNFLALIAQGPVKTYTHR RLKFLSSKFQVHQMLNEMDELKELKNNPHRDFYNCR KVDTHIHAAACMNQKHLLRFIKKSYQIDADRVVYST KEKNLTLKELFAKLKMHYPYDLTVDSLVDHAGRQTFQ RFDKFNDKYNPVGASELRDLYLKTNDYINGEYFATIIK EVGADLVEAKYQHAEPRLSIYGRSPDEWSKLSSWFC NRIHCPNMTWMIQVPRIYDVFRSKNFLPHFGKMLENI	SEQ ID NO: 122

	FMPVFEATINPQADPELSVFLKHITGFDSVDDDESKHSG HMFSSKSPKPQEWTLKKNPSYTYYYAYMYANIMVLN SLRKERGMNTFLFRPHCGEAGALTHLMTAFMIADDIS HGLNLKKSPVLQYLFFLAQIPIAMSPLSNNSLFLEYAK NPFLDFLQKGLMISLSTDDPMQFHFTKEPLMEEYAIAA QVFKLSTCDMCEVARNSVLQCGISHEEKVKFLGDNYL EEGPAGNDIRRTNVAQIRMAYRYETWCYELNLIAEGL KSTE	
Oryctolagus cuniculus AMPD1	MNQKHLLRFIKKSYQVDADRVVYSTK	SEQ ID NO: 123
Gallus gallus AMPD1	MNQKHLLRFIKKSYRVDADRVVYDAK	SEQ ID NO: 124
Mus musculus AMPD1	MPLFKLTGQGKQIDDAMRSFAEKVFASEVKDEGGRH EISPFVDDEICPISLHEMQAHIFHMENLSMDGRRKRRF QGRKTVNLSIPQSETSSTKLSHIEEFISSPTYESVPDFQ RVQITGDYASGVTVEDFEVVCKGLYRALCIREKYM KSFQRFKTPSKYLRNIDGEALVGNESFYVPFTPPPKK GEDPFRTECLPANLGYHLKMKAGVIYIYPDEAAANRD EPKPYPYPNLDDFLDDMNFLALIAQGPVKTYAHRRL KFLSSKFQVHQMLNEMDELKELKNNPHRDFYNCRKV DTHIHAAACMNQKHLLRFIKKSYHIDADRVVYSTKEK SLTLKELFAKLNMHYPDLTVDSLVDHAGRQTFQRF KFNDKYNPVGASELRDLYLKTNDYINGEYFATIIKEV GADLVEAKYQHAEPRLSIYGRSPDEWNKLSSWFVCN RIYCPNMTWMIQVPRIYDVFRSKNFLPHFGKMLENIFL PVFEATINPQAHPDLSVFLKHITGFDSVDDDESKHSGHM FSSKSPKPEEWTMENNPSYTYYYAYMYANITVLNSLR KERGMNTFLFRPHCGEAGALTHLMTAFMIADNISHGL NLKKSPVLQYLFFLAQIPIAMSPLSNNSLFLEYAKNPFL DFLQKGLMISLSTDDPMQFHFTKEPLMEEYAIAAQVF KLSTCDMCEVARNSVLQCGISHEEKAKFLGNNYLEEG PVGNDIRRTNVAQIRMAYRYETWCYELNLIAEGLKAT E	SEQ ID NO: 125
Dictyostelium discoideum AMPD1	MSTPLRGSSPQVSFYESELDQEGGSDASHFTYRNYME DDKINSFTFNMARKDQTQLFQRIILTNESESEIEEYAEV AEQLLDAINLREKYVFHPKIWKADAPVGEKPPYSPFES DESTNCATEHMFKEVNGVYFVYSNETDMKSNKALFS VPHTLASYYKDINNLMMLSSYGPAKTFTFKRLQLLES KFNMTLLNDSLELFQQKTAPHRDFYNVRKVDTHVH HSSSMNQKHLLKFIKRKLKENPNEIVIFRDDKYLTLAE VFKSLNLDVDELSVDTLVDHADNNTFHRFDKFNLY NPCGQSRLREIFLKTDLNLIKGYLAESISKEVFTDLESSK	SEQ ID NO: 126

	YQCAEYRLSIYGRKMSEWDTLASWIVDNDLFSTKVR WLIQVPRLYDVYRETSTTTTFQDFLNNVFHPLFEVTKD PSSHPKLHLFLQQVVGIDCVDDSKFEKKFTEKFPVPG EWSSEHNPPYTYLYLYLYANLYTLNQFREEKGLNILT LRPHSGEAGEVDHMGAAFYLAHGINHGINLRKTPVLQ YLYYLTQIGIAMSPLSNNSLFLTYNRNPFPAFFARGLN VSISTDDPLQFHYTKEPLMEEYSIATQVWRLSVCDICEI ARNSVLQSGFEHNVKSHWLGPDIANS GGNDIKKTNIS DIRVCFRNETLIEELHLILKSLQTLPNFKNLNINFLDK LPSEITTGNDYKLKKAQLKLN GANKLRNSSVGSTPNN GTPSSSGTPSLSSPGAIVHLMKTKPYIPPLSLNIKQEN NNNNNNNNNNNNNNNNNNNTNTNTNSNSTTTNQDDN SKSDK	
Human AMPD3	MPRQFPKLNISEVDEQVRLLAEKVFAKVLREEDSKDA LSLFTVPEDCPIGQKEAKERELQKELAEQKSVETAKR KKSFKMIRSQSLSLQMPQQDWKGPPAASPAMSPPTP VVTGATSLPTPAPYAMPEFQRTISGDYCAGITLEDYE QAAKSLAKALMIREKYARLAYHRFPRTSQYLGHPR DTAPPEEGLPDFHPPPLQEDPYCLDDAPPNLDYLVH MQGGILFVYDNKKMLEHQEPHSLPYPDLETYTVDM HILALITDGPTKTYCHRRNLFLSKFSLHEMLNEMSEF KELKSNPHRDFYNVRKVDTHIAAACMNQKHLLRFI KHTYQTEPDRTVAEKGRKITLRQVFDGLHMDPYDL TVDSL DVHAGRQTFHRFDKFN SKYNPVGASELRDLY LKTENYLGGEYFARMVKEVARELEESKYQYSEPRLSI YGRSPEEWPNLAYWFIQHKVYSPNMRWIIQVPRIYDIF RSKKLLPNFGKMLENIFLPLFKATINPQDHRELHLFLK YVTGFDSVDDESKHSDHMFSDKSPNPDVWTSEQNPP YSYYLYYMYANIMVLNNLRRERGLSTFLFRPHCGEA GSITHLVSAFLTADNISHGLLLKKSPVLQYLYYLAQIPI AMSPLSNNSLFLEYSKNPLREFLHKGLHVSLSTDDPM QFHYTKEALMEEYAIAAQVWKLSTCDLCEIARNSVLQ SGLSHQEKQKFLGQNYKKEGPEGNDIRKTNVAQIRM AFRYETLCNELSFLSDAMKSEEITALTN	SEQ ID NO: 127
Human AMPD2	MRNRGQGLFRLRSRCLHQSLPLGAGRRKGLDVAEP GPSRCRSDSPAVAAVVPAMASYPSGSGKPKAKYPFK KRASLQASTAAPEARGLGAPPLQSARSLPGPAPCLK HFPLDLRTSMDGKCKEIAEELFTRSLAESELRSAPYEF PEESPIEQLEERRQRLERQISQDVKLEPDILLRAKQDFL KTDSDSLQLYKEQGEGQGDRSLRERDVLEREFQRT ISGEEKCGVPFTDLLDAKSVVRALFIREKYMALSLQS FCPTTRRYLQQLAEKPLETRTYEQGPDPVPSADAPVH PPALEQHPYEHCEPSTMPGDLGLGLRMVRGVVHVYT	SEQ ID NO: 128

	RREPDEHCSEVELPYPDLQEFVADVNVLMALIINGPIK SFCYRRLQYLSSKFQMHVLLNEMKELAAQKKVPHRD FYNIRKVDTHIHASSCMNQKHLLRFIKRAMKRHLEEI VHVEQGREQTLREVFESMNLTAYDLSVDTLVDHADR NTFHRFDKFNAYNPIGESVLRIFIKTDNRVSGKYFA HIIKEVMSDLEESKYQNAELRLSIYGRSRDEWDKLAR WAVMHRVHSPNVRWL VQVPRLFDVYRTKGQLANFQ EMLENIFLPLFEATVHPASHPELHLFLEHVDGFDSVDD ESKPENHVFNLESPLPEAWVEEDNPPYAYYLYYTFAN MAMLNHLRRQRGFHTFVLRPHCGEAGPIHHLVSAFM LAENISHGLLLRKAPVLQYLYYLAQIGIAMSPLSNNSL FLSYHRNPLPEYLSRGLMVSLSTDDPLQFHFTKEPLME EYSIATQVWKLSSCDMCELARNSVLMSGFSHKVKSH WLGPNYTKEGPEGNDIRRTNVPDIRVGYRYETLCQEL ALITQAVQSEMLETIPEEAGITMSPGPQ	
Mus musculus AMPD2	MASEARSGLGASPLQSARSPLGNAPCLKHFPDLRTS MDGKCKEIAEELFSRSLAESELRSAPYEFPEESPIEQLE ERRQRLERQISQDVKLEPDILLRAKQDFLKTDSDSLQ LYKEQGEGQGDRGLWERDVVLEREFQRVIIISGEEKCG VPFTDLLDAAKSVVRALFIREKYMALSLQSFCPTTRR YLQQLAEKPLETRTYEQSPDTPVSADAPVHPPALEQH PYEHCEPSAMPDGLGLGLRMVRGVVHVYTRRDPDEH CPEVELPYPDLQEFVADVNVLMALIINGPIKSFCYRRL QYLSSKFQMHVLLNEMKELAAQKKVPHRDFYNIRKV DTHIHASSCMNQKHLLRFIKRAMKRHLEEIVHVEQGR EQLREVFESMNLTAYDLSVDTLVDHADRNTFHRFD KFNAYNPIGESVLRIFIKTDNKISGKYFAHIIKEVMA DLEESKYQNAELRLSIYGRSRDEWDKLARWAVNHKV HSPNVRWL VQVPRLFDVYRTKGQLANFQEMLENIFL LFEATVHPASHPELHLFLEHVDGFDSVDDDESKPENHV FNLESPLPEAWVEEDNPPYAYYLYYTFANMAMLNHL RRQRGFHTFVLRPHCGEAGPIHHLVSAFM LAENISHG LLRKAPVLQYLYYLAQIGIAMSPLSNNSLFLSYHRNP LPEYLSRGLMVSLSTDDPLQFHFTKEPLMEEYSIATQV WKLSSCDMCELARNSVLMSGFSHKVKSHWLGPNYT KEGPEGNDIRRTNVPDIRVGYRYETLCQELALITQAVQ SEMLETIPEEVGIVMSPGP	SEQ ID NO: 129
Rattus norvegicus AMPD2	MASYPGPGKSKAKYPFKKRASLQASAAPEARSGLG ASPLQSARSPLGTAPCLKHFPDLRTSMDGKCKEIAEE LFSRSLAESELRSAPYEFPEESPIEQLEERRQRLERQISQ DVKLEPDILLRAKQDFLKTDSDSLQLYKEQGEGQGD RGLWERDVVLEREFQRVIIISGEEKCGVPFTDLLDAAK SVVRALFIREKYMALSLQSFCPTTRRYLQQLAEKPLET	SEQ ID NO: 130

	RTYEQSPDTPVSADAPVHPPALEQHPYEHCEPSTMPG DLGLGLRMVRGVVHVYTRRDPDEHCPEVELPYPDLQ EFVADVNVLMALIINGPIKSFCYRRLQYLSSKFQMHV LLNEMKELAAQKKVPHRDFYNIRKVDTHIHASSCMN QKHLLRFIKRAMKRHLEEIVHVEQGREQTLREVFESM NLTA YDLSVDTL DVHAD RNTFHRFDKFN AKYNPIGES VLREIFIKTDNKISGKYFAHIIKEVMSDLEESKYQNAEL RLSIYGRSRDEWDKLARWAVNHRVHSPNVRWLQV PRLFDVYRTKGQLANFQEMLENIFLPLFEATVHPASHP ELHLFLEHVDGFDSDVDESKPENHVFNLESPLPEAWV EEDNPPYAYYLYYTFANMAMLNHLRRQRGFHTFVLR PHCGEAGPIHHLVSAFMLAENISHGLLLRKAPVLQYL YYLAQIGIAMSPLSNNSLFLSYHRNPLPEYLSRGLMVS LSTDDPLQFHFTKEPLMEEYSIATQVWKLSSCDMCEL ARNSVLMMSGFSHKVKSHWLGPNTKEGPEGNDIRRT NVPDIRVGYRYETLCQELALITQAVQSEMLETIPEEVG IVMSPGP	
Plasmodium gallinaceum ADA	MTILHEEINFLKKDELNINLKCLDKKERYKIWRRIPKC ELHCHLDLCFSLEFFLKCVRKYNLQPDLTDDDEVVDYY LFKDKGKSLNEFIERSRRVTDIFINYDIIKDIKNAVN KYKEGVILIEFRYSPSYIAYKYNLCIDLHK TIVEGINEA VEKLNHKKIHVGLICIGETGISEESLRKAAEFCVKNKKD FVGFDHAGHERDLKPYKEIYDYVRENGIPLTIHAGED LTLPNLNTIYSAIEVLKAKRIGHGIRVIESEDLINLIKKN DILLEICPISNLLLNNVKSMDTHPIKKLYDSGIKVSNT DDPGMFLTEINDEYEELYNLNFNLEDFMKMNLWAL EKS FVKSEIKDKLKKLYF	SEQ ID NO: 131
Plasmodium knowlesi ADA	MNILQEPIDFLKKDELKNIDLSQMDKKERYKIWKRIK CELHCHLDLCFSADFFLSCVRKYNLQPNLSDEEVLDY YLFAKGGKSLGEFVEKAIRVADIFQDYEMIEDLAKHA VFNKYKEGVVLMEFRYSPTFVAFKHNLDIELIHQAIV KGIKEVVELL DHKIDVTLLCIGDTGHRAADIKASADFC LKHKADFVGFDHGGHEVDL KPYKEIFDYVKEGGMHL TVHAGEDVTLPNLNTLYSAIQVLKVERIGHGIRVSESQ ELIDMVKENNILLEVCPISNVLLKNAKSFDTHPIRKLY DAGVKVSVSSDDPGMFLTNINDDYEKLYTHLHFTLED FMKMNEWALEKSFIGCDIKEKIKKLYF	SEQ ID NO: 132
Plasmodium berghei ADA	MEIPNEEIKFLKKEDIKNINLNGMNKKERYEIWKKIPK VELHCHLDLTFSGKFFLKWVRKYNLQPNMTDDQVLD HYLFTKEGKSLAEFIRKAISVSDIYRDYDILEDLAKWA VIEKYKEGVVLMEFRYSPTFVSSSHGLDIELIHKA FVK GIKNATEMLNNKIYVALICISDTGHSAASIKHSGDFAIK HKHDFVGFDHGGREIDLKDHKD VYHSVRNHGLHLTV	SEQ ID NO: 133

	HAGEDATLPNLNTLYTAINILNVERIGHGIRVSESEELI ELVKKNILLEVCPISNLLNNVKSMIDTHPIRKLFDAG VKVSVNSDDPGMFLTDINDNYEKLYIHLNFTLEEFMT MNNWALEKSFVNDDIKSKLKTMYF	
Plasmodium vivax ADA	MNILQEPIDFLKKEELKNIDLSQMSKKERYKIWKRIPK CELHCHLDLCFSADFFVSCIRKYNLQPNLSDEEVLDY YLFAGGKSLGEFVEKAIVADIFHDYEVIEDLAKHA VFNKYKEGVVLMEFRYSPTFVAFKYNLDIELIHQAIV KGIKEVVVELLDHKIHVALMCIGDTGHEAANIKASADF CLKHKADFVGFDHGGHEVDLKEYKEIFDYVRESGVP LSVHAGEDVTLPNLNTLYSAIQVLKVERIGHGIRVAES QELIDMVKEKNILLEVCNISVLLKNAKSMIDTHPIRQL YDAGVKVSVNSDDPGMFLTNINDDYEELYTHLNFTLE DFMKMNEWALEKSFMDSNIKDKIKNLYF	SEQ ID NO: 134
Plasmodium cynomolgi ADA	MNILQEPIDFLKKDEIKNIDLSQMSKKERYKIWKRIPK CELHCHLDLCFSADFFLSCIRKYNLQPNLSDEEVLDYY LFAKGGKSLGEFVEKAIRVADIFHDYEVIEDLAKHAV FNKYKEGVVLMEFRYSPTFVAFKYKLDIELIHQAIVK GIKEVVVELLDHKIHVALMCIGDTGHEAANIKASADFC LKHRAADFVGFDHGGHEVDLKQYKEIFDYVRESGIPLS VHAGEDVTLPNLNTLYSAIQVLKVERIGHGIRVSESQE LIDMVKEKNILLEVCNISVLLKNAKSMIDTHPIRQLYD AGVKVSVNSDDPGMFLTNINDDYEELYTHLNFTLEDF MKMNEWALEKSFMDSNIKDKVKNLYF	SEQ ID NO: 135
Human ADA	MAQTPAFDKPKVELHVHLDGSIKPETILYYGRRRGIAL PANTAEGLLNVIGMDKPLTLPDFLAKFDYYMPAAGC REAIKRIAYEFVEMKAKEGVVYVEVRYSPLLANSKV EPIPWNQAEGDLTPDEVVALVGQGLQEGERDFGVKA RSILCCMRHQPNWSPKVVELCKKYQQQTVVAIDLAG DETIPGSSLLPGHVQAYQEAVKSGIHRTVHAGEVGSA EVVKEAVDILKTERLGHGYHTLEDQALYNRLRQENM HFEICPWSSYLTGAWKPDTEHAVIRLKNQDQANYSLNT DDPLIFKSTLTDYQMTKRDMGFTEEEFKRLNINAAG SSFLPEDEKRELLDLYKAYGMPPSASAGQNL	SEQ ID NO: 136
Mus musculus ADA	MAQTPAFNPKPKVELHVHLDGAIKPETILYFGKKRGIA LPADTVEELRNIIGMDKPLSLPGFLAKFDYYMPVIAGC REAIKRIAYEFVEMKAKEGVVYVEVRYSPLLANSKV DPMPWNQTEGDTVTPDDVVDLVNQGLQEGEQAFGIKV RSILCCMRHQPSWSLEVLELCKKYNQKTVVAMDLAG DETIEGSSLFPGHVEAYEGAVKNGIHRTVHAGEVGSP EVVREAVDILKTERVGHGYHTIEDEALYNRLLENM HFEVCPWSSYLTGAWDPKTTHAVVRFKNDKANYSLN	SEQ ID NO: 137

	TDDPLIFKSTLTDYQMTKKDMGFTEEEFKRLNINAA KSSFLPEEEKKELLERLYREYQ	
Bos taurus ADA	MAQTPAFNPKVELHVHLDGAIKPETILYYGRKRGIA LPADTPEELQNIIGMDKPLSLPEFLAKFDYYMPAAGC REAVKRIAYEFVEMKAKDGVVYVEVRYSPELLANSK VEPIWPNQAEGDLTPDEVVSLVNQGLQEGERDFGVK VRSILCCMRHQPSWSSEVVELCKKYREQTVVAIDLGA DETIEGSSSLFPGHVKAYAEAVKSGVHRTVHAGEVGSA NVVKEAVDTLKTERTLGHGYHTLEDATLYNRLRQENM HFEVCPWSSYLTGAWKPDTEHPVVRFKNDQVNYSLN TDDPLIFKSTLTDYQMTKNEMGFTEEEFKRLNINAA KSSFLPEDEKKELLDLLYKAYGMPSPASAEQCL	SEQ ID NO: 138
Gallus gallus ADA	MERGVRVFGEPKVELHIHLDGAIRPETILHFGKKRGVP LPGSTVDELMKHVSQYQTPLSLKLFEKFNHYMPAAG DREAVRRIAYELVETKAKEGVVYVEVRYSPELLANC RVEPIWQQAEGDLTPEEVVNLVNQGLQDGERNFRIK ARSILCCMRHMPWSPEVVELCKKYQNNVVAIDLGA GDELLMASSDHKAAEYEAERCGIHRTVHAGEAGPAT MIKEAVYLLKAERIGHGYHVLEDPELYRELLRTRMHF EVCWPWSSYLTGACLPDFRKHPVVQFKKDQANYSINTD DPLIFNSNIDKDYGIVKEYMDFTTEEDFKRVNINAAQSS FLPEKEKQELLNTLYEAYGMVPATS	SEQ ID NO: 139
Danio rerio ADA	MNGKPAFDKPKVELHVHLDGAIRLKTVDVAKRRGI SLPVSMEELKELCTVNEPATLTEFLGKFSHFMHVIAAG DREAIKRIAYEFVETKAKEGVIIYVEARYSPHFLANKG VEPLWDQKPGDITPDDVVDLVNQGFKGEQAFKTK ARSILCCMRHMPNWSMEVVELCKKFHKDGVVAIDLGA GDESMNCESYPGHKKAFFEEAVRSNVHRTVHAGEVGP ASVVREAVEVLKAERIGHGYHTLEDQNLKQLLHQN MHFEMCPVSSRLTGACEPDFTKHPLITFKKDKANYSL NTDDPTIFNSTLNSDYEVVQKYMDFTTEEEFKRLNINA AKSCFLPEKEKEKLLNQLYEAYGMRKSTSF	SEQ ID NO: 140
Xenopus laevis ADA	MESKAFNPKPKVELHVHLDGSIKPETIIHFAKKRQIKLP ADTVEGLLEHVSYPEPLSLTEFLQKFNHYMPAAGDR EAIKRIAYEFVEMKAKEGVIIYVEVRYSPELLANSKVD PIPWGQKEGDITPDEVVDLVNQGLRKGEKTFNIKARSI LCCMRHMPNWSSEVIELCKKYQNDTVVAIDLGADES LNCESYPGHRKAYEEAVKCGIHRTVHAGEVGPPSVV KEAVEVLKAERIGHGYHTTEDPNLYKELLENNMHFE VCPWSSYLTSAHPDFTKHPATQFRKDKANFSLNTDD PLIFGSTLDVDYSIAVQHMGFTEDEFKRVNINAAKSSF LPDNEKKELLYKLYEAYGMILSTGL	SEQ ID NO: 141

Plasmodium falciparum ADA	MNCKNMDTSYEIINYLTKDELDIDLSCMDKKERYKIW KRLPKCELHCHLDVCFVSDFFLNVIRKYNIQPNMSDE EIIDYYLFSKPGKSLDEFVEKALRLTDIYIDYTVVEDLA KHAVFNKYKEGVVLMEFRYSPSFMSFKHNLDKDLIH EAIVKGLNEAVALLEYKIQVGLLCTGDGGLSHERMKE AAEFCIKHKKDFVGYDHAGHEVDLKPFKDIFDNIREE GISLSVHAGEDVSIPNLNSLYTAINLLHVKRIGHGIRVS ESQELIDLVEKDILLEVCPISNVLLNNVKSMDTHPIR MLYDAGVKVSVNSDDPGMFLTNTDNYEELYTHLNF TLADFMKMNLWAVQKSFVDPDIKNKIISKYF	SEQ ID NO: 142
Drosophila melanogaster ADA	MEQFLKGLPKVELHAHLNGSLGIKSLCDLGERLYGTS CKDFLKLCAHFSRFEKDMDACFEKFAFVHELTSTREG LRFATELAIRDAEDNVQYVEMRTTPKANENYSRRDY LQIVIDAIKAASETYPEITVKLLPSINRAEPVDVAEETV SLAVELARAHPNLILGIDLSGNPGKGRFSDFAPILAQA RDKGLKLAIHCAEIENPSEVKEMLHFGMSRCGHGTFL TPEDIGQLKQRNIAIECCLTSNVKSGTVPSLEEHHLKRI MEADAPKVICITDDSGVFDTTLTKEFLIAAETFGLTREQ CIDLTLEAVHHSFASEQEQIQMADRVGNYADILVK	SEQ ID NO: 143
Xenopus tropicalis ADA	MESKAFNPKVELHVHLDGSIKPETIIHFAKKRQIKLP ADTVEGLLEHVSYKEPLSLTEFLSKFNHYMPAIAHDR EAIKRIAYEFVEMKAKEGVVYVEVRYPHFLANSKVEP IPWGQKEGDITPDEVVDLVNQGLRKGEKAFNIKARSIL CCMRHMPSWSTEVVELCKKYQNDTVVAIDLAGEDES NCESYPGHRKAYEEAVKCGIHRTVHAGEVGPSSVVK EAVEVLKAERIGHGYHTTEDPNLYKELLEKNMHFEV CPWSSYLTGACHPDFTKHPATQFRKDKANYSLNTDD PLIFGSTLDVDYSIAAKHMGFTEEEFKRVNINAAKSSF LPESEKKELLYKLYEAYGMILSTGL	SEQ ID NO: 144
Rattus norvegicus ADA	MAQTPAFNPKVELHVHLDGAIKPETILYYGKKRGID LPADTVEGLRNIIGMDKPLSLPDFLAKFDYYMPAIAAGC REAIKRIAYEFVEMKAKEGVVYVEVRYPHLLANSKV DPIPWNQAEGLTPDEVVDLVNQGLQEGEQAFGIKVR SILCCMRHQPSWSPEVLELCKKYHQKTVVAMDLAGD ETIEGSSLFPGHVEAYEGAVKDGIIHRTVHAGEVGS AEVVRVAVDILKTERVGHGYHTIEDEALYNRLLENMHF EVCWSSYLTGAWNPKTTTHAVVRFKDDQANYSLNSD DPLIFKSTVDTDYQMVKKDMGFTEEEFKRLNINA AKSSFLPEDEKKELLERLYKEYQ	SEQ ID NO: 145
Mus musculus ADAD1	MATAGGSRRAPVPGPRLGLPLAAHLPASLGGEAKD SVGGEKTSNNNDWFQSSRVPSFAQMLKKNLPVQPSA QVTTLPTGYSSCSLSNMASKVTQVTGNFPEPLLSKG LSSISNPVLPKKLPKEFIMKYKRGEINPVSAHQFAQ	SEQ ID NO: 146

	MQRVQLDLKETVTTGNVMGPYFAFCAVVDGIQYKTG LGQNKESRSNAAKLALDELLQLDEPEPRVLEPAGPP PIPAEPVVTPEAAAYVSKVQYEGRQVQYAKISQLVKET FGQLISNHSQYLCSSSLAAFIERAGHHEVVAIGTGEY NYSQCIKPNGRVLHDTHAVVTARRSLLRYFYRQLLLF YSKNPAMMEKSIFCTEPASNLLTLKQNINLYLYMNQL PKGSAQIKSQLRLNPHSISAFEANEELSLHVAVEGKIY LTVYCSADGVNRVNSMSSSDKLTRWEVLGVQGALLS HFIQPVYISSILVGDGNCNDTRGLEIAINQRVDDALTSK LPMFYLVNRPHISLVPTAYPLQINLDHKSLSLNWAQAG DNSLEIVDGLNGKITESSPFKSGLSMASRLCKAAMLSR FNLLAKEAKTDDLLEARTYHAAKCMSGPYQEAKALL KAYLQQHGYGSWIVKSPCIEQFSM	
Rattus norvegicus ADAD1	MATAGGSRRAPVPGPRLGLPLAAHLPASLGGEAKD SLGGEKTSGNNDWFQSSRVPSFAQMLKKNLPVQSSA QTVTLPTGYSSSCSLSNMASKVTQVTGNFPEPLLSKG LSSISNPVLPKKIPKEFIMKYRRGEINPVSAHQFAQM QRVQLDLKETVTTGNVMGPYFAFCAVVDGIQYKTGL GQNKESRSNAAKLALDELLQLDEPEPRALEPAGPPPI PAEPIVTPEAAAYISKVQYEGRQVQYAKISQLVKETFSQ LISSHSQYLCSSSLAAFIERGGHHEVVAIGTGEYNYS QCIKPNGRVLHDTHAVVTARRSLLRYFYRQLLLFYSK NPAMMEKSIFCTEPASNLLTLKQNINLYLYMNQLPKG SAQIKSQLRLNPHSISAFEANEELSLHVAVEGKIYLT YCSADGVNRVNSMSSSDKLTRWEVLGVQGALLSHFI QPVYISSILVGDGNCNDTRGLEIAINQRVDDALTSKLP MFYLVNRPHISLVPTAYPLQINLDHKSLSLNWAQAGDN SLEIVDGLSGKITESSPFKSGLSMASRLCKAAMLSR FNLLAKEAKTDDLLEARTYHAAKCLSGPYQEAKALLKA YLQQHGYGSWIVKSPCIEQFSM	SEQ ID NO: 147
Xenopus laevis ADAD1	MASNRNWSQHSSVPSFAQMLKKNLPDPGTSPAVNQT STLSTCCLYNQPCGTARVTRITGNFPEPFLSKMIVPPS LSSLTPRKVTKEFMVKYRRGDLNPISALYQFAQMQR MEIELKETVTTGNVFGAYFAFCAVVDGLEKYTGGMGQ NKKEAKANAAKLALDELLHEDPALIDSENQSLNVIE NPPPLPMNPRGTTETSTISRTRTDKRTFIHEKISSIIKET TNLVSKYPEYENCSSSLAAFVIEKGGQHWEVVAIGTG EFNYGQSLQSDGRVLHDSHAMVVARRSLLRYFYRQL LLLYSGNNGMMDKSIFCTEPATNLLALKPNLNIFLYM NQLPKGAAQTNPQLCLSPHLSAHEANDKLSLHVSVE GKNIPASYYSGEIVHNLYSMSSTDKLTRWEVLGVQGA LLSIFIQPVYINSIIIGNAACSDTRGLEIAVKQRIDDALTS RLPMFYLVNRPYMSIVSSTHLTNNDTANKTSLNWSQ	SEQ ID NO: 148

	GDACVEVVDAAGRTVEGSPFKSGSCLASRLCKAAML CRFNLVVKESKRNAIPSGLSYHEAKRLAGPYQEAKCL LNSYFKQQGFGSWIAKPPIIGEFTM	
Human ADAD1	MASNNHWFQSSQVPSFAQMLKKNLPVQPATKTITPT GWSSSEYGLSKMASKVTQVTGNFPEPLLSKNLSSISNP VLPPKKIPKEFIMKYKRGEINPVSALHQFAQMQRVQL DLKETVTTGNVMGPYFAFCAVVDGIQYKTGLGQNK ESRSNAAKLALDELLQLDEPEPRILETSGPPFPAEPVV LSELAYVSKVHYEGRHIQYAKISQIVKERFNQLISNRS EYLKYSSSLAAFIERAGQHEVVAIGTGEYNYSQDIKP DGRVLHDTHAVVTARRSLLRYFYRQLLLFYSKNPAM MEKSIFCTEPTSNNLLTLKQININCLYMNQLPKGSAQIKS QLRLNPHSISAFEANEELCLHVAVEGKIYLTVYCPKDG VNRISMSSSDKLTRWEVLGVQGALLSHFIQPVYISSIL IGDGNCSDTRGLEIAIKQRVDDALTSKLPMFYLVNRP HISLVPSAYPLQMNLEYKFLSLNWAQGDVSLEIVDGL SGKITESSPFKSGMSMASRLCKAAMLSRFNLLAKEAK KELLEAGTYHAAKCMSASYQEAKCKLKSYLQQHGY GSWIVKSPCIEQFNM	SEQ ID NO: 149
Bos taurus ADAL	MMEAEQPWKTTFYSKLPKVELHAHLNGSISSTIRK LIAKKPDLKIHDQMTMIDKGEKRTLEECLQMFQIIHLL TTTPEDVLMVTKDVIKEFADDGVKYLELRSTPRGEDA TGMTKKTYESILEGIKQSKEENVVIDVRYLISIDRRG GSSAAKEAVKLAEEFFLSAEDTVLGLDLSGDPSAGQA KDFLEPLLEAKKSGKLALHLSEIPNQKTETQVLLNLF PDRIGHGTFLSSSEEGSPDLVDFVRQHQPILCLTSNV KSQTVPAYDQHHFGFWYSVAHPAVICTDDKGVFATR LSQEYQLVAETFHLTQSQVWDLSEYISYIFASDSTKA DLRKKWSHLKPHF	SEQ ID NO: 150
Danio rerio ADAL	MDTEADLFYRQLPKVELHAHLNGSVSFETMEKLIK PHLNIEHSMTAIRRGQRRTLDECQVFKVIHQLVDSEE DILMVAKSVIQEFAADGVKYLELRSTPREVTETGLSK QRYIETVLEAIRQCKQEGVDIDVRFLVAVDRRHGPEV AMQTVKLAEDFLSSDGTVVGLDLSGDPTVGHGKDL LAALQKAKNCGLKLALHLSEVPSQIDETELLLNLPPDR IGHGTFLHPDVGGSDSLVDKVCKQNIPIECLTSNVKG QTVPSYDKHHFKYWYNRGHPCVLCDDKGVFCTDLS QEYQLAASTFGLTKEAVWILSQQAIGYTFAPEPIKQRL EKTWAEKQQILQ	SEQ ID NO: 151
Xenopus laevis ADAL	MAGEGALQFYRDLPKVELHAHLNGSISTATMKKLMA RKPHLDIQHGTMIDKGQKRTLEECFQMFKIIHQITDT AEDILLVTKDVIKEFAADGVKYLELRSTPRDTPAGLTK QAYVETVLEGIKQCKEEGVDIDVRFLLAIDRRGGPTA	SEQ ID NO: 152

	AKETVKLAEDFFCSSNELVLGLDLSGDPTVGHGRDFM EPLNKARQSGGLKLALHLSEIPSQTEETELLGLPPDRIG HGTFLLTSAHIVEIVKKQHIPLELCITSNIKGQTVSSYN EHHFGFWYNLHHPFVLCTDDKGVFATDLSVEYEIAA KTFNLTPHHVWDLASYQAIDYTFASADVKANLKEKWL LLKPDVFRHAL	
Human ADAL	MIEAEEQQPCKTDFYSELPKVELHAHLNGSISSTMK KLIAQKPDLDKIHDQMTVIDKGKKRTLEECFQMFQTIH QLTSSPEDILMVTKDVIKEFADDGVKYLELRSTPRREN ATGMTKKTYVESILEGIKQSKQENLDIDVRYLIAVDRR GGPLVAKETVKLAEEFFLSTEGTVLGLDLSGDPTVGQ AKDFLEPLLEAKKAGLKLALHLSEIPNQKQKQILLDL LPDRIGHGTFLNSGEGGSLDLVDFVRQHRIPLELCITS NVKSQTVPSYDQHHFGFWYSIAHPSVICTDDKGVFAT HLSQEYQLAAETFNLTQSQVWDLSESYNYIFASDSTR SELRKKWNHLKPRVLHI	SEQ ID NO: 153
Caenorhabditis elegans ADAL	MPNNSKHKKKQQRQQAQKKSRAKQIETDKKND LDELDEVSPVIDDDMTEFKNMPKVELHAHLSGSLS PETIKLIMESDETRAEEIMKKYKLEKPENMTGVFDCFP VIHAILRKPEAIRAIRQTIKEFEEDNCVYLELRTSPKET DFMTYEDYLQVCIESFEAAKHEFPRIKTLIVSLDRRM PFETAHILGLIGEAAQRTNVIVGVELSGDPHLDGRRRL LKLFWAARRFHGLGITIHLAEVLQNMADVEDYLNLRP DRIGHGTFLHTDPYTEYLTNKKIPLEICLSSNVYSKTT TNYRNSHFNYWRKRGVPVFICTDDKGVIPGATLTEEY YKAAITFDLSTEELIGINQDALLNSFAYKYNVTDLTET FRKINNNVLD	SEQ ID NO: 154
Mus musculus ADAL	MEAGQQWPGKTDLYLQPKVELHAHLNGSISSTMK KLIKKPHLNVHGHMTMIDKGKKRTLQECFQMFQVI HQLTTSAEDILMVTKDVIKEFADDGVKYLELRSTPRE ENATGMTRKTYVESVLEGIKQCKQENLDIDVRYLMAI DRRGPTIARETVELAKEFFLSTENTVLGLDLSGDPTI GQANDFLEPLLEAKKAGLKLALHLAEIPNREKENQML LSLLPDRIGHGTFLSASEAGALDQVDFVRQHQIPLELC LTSNIKSQTVPSYDQHHFGFWYSIAHPSVICTDDKGVF ATYLSQEYQLAAETFNLTQVQVWDLSESYNYIFACDN TRSELKRKRWTHLKQKVLNCNEVNYF	SEQ ID NO: 155
Human ADAD2	MASASQGADDDGSRRKPRLAASLQISPQPRPWRPLPA QAQSAWGPAPAPATYRAEGGWPQVSVLRDSGPGAG AGVGELGAARAWENLGEQMGKAPRVPPAGLSLPL KDPPASQAVSLLTEYAASLGIFLLFREDQPPGPCFPFSV SAELDGVVCPAGTANSKTEAKQQAALSALCYIRSQLE NPESPQTSSRPPLAPLSVENILTHEQRCAALVSAGFDLL	SEQ ID NO: 156

	LDERSPYWACKGTVAGVILEREIPRARGHVKEIYKLVALGTGSSCCAGWLEFSGQQLHDCHGLVIARRALLRFLFRQLLLATQGGPKGKEQSVLAPQPGPGPPFTLKPRVFLHLYISNTPKGAARDIYLPPTSEGGLPHSPPMRLQAHVLGQLKPVCYVAPSLCDTHVGCLSASDKLARWAVLGLGALLAHLVSPLYSTSLILADSCHDPPTLSRAIHTRPCLDSVLGPCLPPPYVRTALHLFAGPPVAPSEPTPDTTCRGLSLNWSLGDPGIEVVDVATGRVKANAALGPPSRLCKASF LRAFHQAAARAVGKPYLLALKTYEAAKAGPYQEARRQLSLLDQQQLGAWPSKPLVGKFRN	
Mus musculus ADAD2	MASVDEGGRRRPRLAASLQISPGPWKPSGGQEPTAGDAAPRTAEHGVAGAQAHEACKALGGSVLSPGPAGDFPGALHGLSMLPKDPPPAQAVALLTQCMANLGVSLTFLEDQTAGPGSSFSVCADLDGLVCPAGTGSSKLEAKQQAALSALQYIQKQLERPEPLVTPRQPLLTSLSIETILTHEQRCAAVVSAGLDRLLSESPYQACKGTVA AVILEREVQGSIGHSKETYELVALGTGSSSCAGWLEFSGRRLHDCHGLVIARRALLRFFFRQLLLV TQGGPKGQERSVLT PQPGPGPPFALKPGVFLHLYVSNTPKGA AHDIYLPLAS EDSVLHSPA FRLQAHVCGQLKPVSYVAPALRDTHVGCLSASDKLARWAILGLGGLLAHFLPLYATSLVLADPCHDPSTLNRVIHSRPRLDSVLGSLPCPYVRTTLHLFAGPLVAPSDPGPSTCHSLNWSLGDPDIEVVDVATGRVKTDSSVGPPSRLCKAAFLSAFRQVARALEKPQLLSLQTYEAAKAVPYREARQQLSLLDQQQLGAWPSKPLVGKFRH	SEQ ID NO: 157
Macaca fascicularis ADAD2	MASASQGADDGSRRKPRLAASLQISPEPRPWRPLPPQAQGAWE PAPAMDHAEGGQPQVSVLRDSGPGAGAGVGELGAAQAWENLGEQMGRTPRPVPPAGLSLPLKDPASQAVSLLTEYAASLGIILLFREDQQPGPCFPFSVSAELDGVVCPAGTANSKTEAKQQAALSALCYIRSQLESPE SPQTSSRPPPPPLSVDSILTHGQRCAALVSAGFDLLLDERSPYWACKGTVAGVILEREIPGARGHVKEIYKLVALGTGSSCCAGWLEFSGQQLHDCHGLVIARRALLRFLFRQ LLLATQGGAKGKEQSVLAPQPGPGPPFTLKPRVFLHLHLYISNTPKGAARDIYLPPTSEGGLPHSPPMRLQAHVLGQLKPVCYVAPSLCDTHVGCLSASDKLARWAVLGLGGA LLAHLVSPLYSTSLILADSCHDPPTLSRAIHTRPCLDSVLGPCLPPPYVRTALHLFSGPPVAPSEPTPDTCHGLSLNWSLGDPGIEVVDVATGRVKANAALGPPSRLCKASF LRAFHQVARAVGKPYLLALKTYEAAKAGPYQEARRQLSLLDQQQLGAWPSKPLVGKFRN	SEQ ID NO: 158

[00259] In some embodiments, the first fusion protein further comprises an uracil glycosylase inhibitor (UGI).

[00260] The “Uracil Glycosylase Inhibitor” (UGI), which can be prepared from *Bacillus subtilis* bacteriophage PBS1, is a small protein (9.5 kDa) which inhibits *E. coli* uracil-DNA glycosylase (UDG) as well as UDG from other species. Inhibition of UDG occurs by reversible protein binding with a 1 : 1 UDG : UGI stoichiometry. UGI is capable of dissociating UDG-DNA complexes. A non-limiting example of UGI is found in *Bacillus phage AR9* (YP_009283008.1). In some embodiments, the UGI comprises the amino acid sequence of
"TNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVHTAYDESTDENVMLLTS
DAPEYKPWALVIQDSNGENKIKML (SEQ ID NO: 209) or has at least 70%, 75%, 80%, 85%, 90% or 95% sequence identity to SEQ ID NO: 209 and retains the uracil glycosylase inhibition activity.

[00261] In some embodiments, the first fusion protein further comprises at least one nuclear localization sequence (NLS).

[00262] A “nuclear localization signal or sequence” (NLS) is an amino acid sequence that tags a protein for import into the cell nucleus by nuclear transport. Typically, this signal consists of one or more short sequences of positively charged lysines or arginines exposed on the protein surface. Different nuclear localized proteins may share the same NLS. An NLS has the opposite function of a nuclear export signal (NES), which targets proteins out of the nucleus. A non-limiting example of NLS is the internal SV40 nuclear localization sequence (iNLS).

[00263] In some embodiments, a peptide linker is optionally provided between each of the fragments in any of the fusion proteins. In some embodiments, the peptide linker has from 1 to 100 amino acid residues (or 3-20, 4-15, without limitation). In some embodiments, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% of the amino acid residues of peptide linker are amino acid residues selected from the group consisting of alanine, glycine, cysteine, and serine.

[00264] The term “Cas protein” or “clustered regularly interspaced short palindromic repeats (CRISPR)-associated (Cas) protein” refers to RNA-guided DNA endonuclease enzymes associated with the CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) adaptive immunity system in *Streptococcus pyogenes*, as well as other bacteria. In some embodiments, the Cas protein is Cas9, a dead Cas9 (dCas9), or a Cas9 nickase (nCas9) selected from the group consisting of SpCas9, FnCas9, St1Cas9, St3Cas9, NmCas9, SaCas9, AsCpfI, LbCpfI, FnCpfI, VQR Cas9, EQR Cas9, VRER Cas9, Cas9-NG, xCas9, eCas9,

SpCas9-HF1, HypaCas9, HiFiCas9, sniper-Cas9, SpG, SpRY, KKH SaCas9, CjCas9, Cas9-NRRH, Cas9-NRCH, Cas9-NRTH, ScCpf1, PcCpf1, BpCpf1, LiCpf1, PmCpf1, Lb2Cpf1, PbCpf1, PeCpf1, PdCpf1, MbCpf1, EeCpf1, CmtCpf1, BsCpf1, BhCas12b, AkCas12b, BsCas12b, AmCas12b, AaCas12b, RfxCas13d, LwaCas13a, PspCas13b, PguCas13b, and RanCas13b.

[00265] In some embodiments, the Cas protein comprises an amino acid sequence selected from SEQ ID NOs: 1-52.

Table 4A Exemplary Cas proteins

Cas protein types	Cas proteins
Cas9 proteins	Cas9 from <i>Staphylococcus aureus</i> (SaCas9) Cas9 from <i>Neisseria meningitidis</i> (NmeCas9) Cas9 from <i>Streptococcus thermophilus</i> (StCas9) Cas9 from <i>Campylobacter jejuni</i> (CjCas9)
Cas12a (Cpf1) proteins	Cas12a (Cpf1) from <i>Acidaminococcus</i> sp BV3L6 (AsCpf1) Cas12a (Cpf1) from <i>Francisella novicida</i> sp BV3L6 (FnCpf1) Cas12a (Cpf1) from <i>Smithella</i> sp SC K08D17 (SsCpf1) Cas12a (Cpf1) from <i>Porphyromonas crevioricanis</i> (PcCpf1) Cas12a (Cpf1) from <i>Butyrivibrio proteoclasticus</i> (BpCpf1) Cas12a (Cpf1) from <i>Candidatus Methanoplasma termitum</i> (CmtCpf1) Cas12a (Cpf1) from <i>Leptospira inadai</i> (LiCpf1) Cas12a (Cpf1) from <i>Porphyromonas macacae</i> (PmCpf1) Cas12a (Cpf1) from <i>Peregrinibacteria bacterium GW2011 WA2 33 10</i> (Pb3310Cpf1) Cas12a (Cpf1) from <i>Parcubacteria bacterium GW2011 GWC2 44 17</i> (Pb4417Cpf1) Cas12a (Cpf1) from <i>Butyrivibrio</i> sp. NC3005 (BsCpf1) Cas12a (Cpf1) from <i>Eubacterium eligens</i> (EeCpf1)
Cas12b (C2c1) proteins	Cas12b (C2c1) <i>Bacillus hisashii</i> (BhCas12b) Cas12b (C2c1) <i>Bacillus hisashii</i> with a gain-of-function mutation (see, e.g., Strecker et al., Nature Communications 10 (article 212) (2019)) Cas12b (C2c1) <i>Alicyclobacillus kakegawensis</i> (AkCas12b) Cas12b (C2c1) <i>Elusimicrobia bacterium</i> (EbCas12b) Cas12b (C2c1) <i>Laceyella sediminis</i> (Ls) (LsCas12b)
Cas13 proteins	Cas13d from <i>Ruminococcus flavefaciens</i> XPD3002 (RfCas13d) Cas13a from <i>Leptotrichia wadei</i> (LwaCas13a) Cas13b from <i>Prevotella</i> sp. P5-125 (PspCas13b)

	Cas13b from <i>Porphyromonas gulae</i> (PguCas13b) Cas13b from <i>Riemerella anatipestifer</i> (RanCas13b)
Engineered Cas proteins	Nickases (mutation in one nuclease domain) Catalytically inactive mutant (dCas9; mutations in both of the nuclease domains) Enhanced variants with improved specificity (see, e.g., Chen <i>et al.</i> , <i>Nature</i> , 550, 407-410 (2017))

Table 4B Exemplary sequences of Cas proteins

Name	Sequence	SEQ ID NO:
SpCas9	MDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGN TDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRR KNRICYLQEIFSNEMAKVDDSFHRLSEESFLVEEDKKH ERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKAD LRLIYLALAHMIKFRGHFLIEGDLNPDNSDVKLFIQL VQTYNQLFEENPINASGVDAKAILSARLSKSRLENLI AQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAK LQLSKD TYDDDLDNLLAQIGDQYADLFLAAKNLSDAI LLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKAL VRQQLPKEYKEIFFDQSKNGYAGYIDGGASQEEFYKFI KPILEKMDGTEELLVKNREDLLRKQRTFDNGSIPHQI HLGELHAILRRQEDFYFPLKDNREKIEKILTFRIPYYVG PLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQS FIERMTNFDKNLPNEKVLPHSLLYEYFTVYNELTKV KYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQ LKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIK DKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYA HLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSG KTILDFLKSDGFANRNFQMQLIHDDSLTFKEDIQKAQVS GQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVM GRHKPENIVIMARENQTTQKGQKNSRERMKRIEEGI KELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYV DQELDINRLSDYVDHIVPQSFLKDDSIDNKVLTRSDK NRGKSDNVPSEEVVKMKMKNYWRQLLNAKLITQRKFD NLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILD SRMNTKYDENDKLIREVKVITLKS KLVSDFRKDFQFY KVREINNYHHAHDAYLNAVVG TALIKKYPKLESEFV YGDYKVYDVRKMIKSEQEIGKATAKYFFYSNIMNFF KTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVR KVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIAR	SEQ ID NO: 1

	KKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKL KSVKELLGITIMERSSSFENPIDFLEAKGYKEVKKDLII KLPKYSLFELENGRKRMLASAGELQKGNELALPSKYV NFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEII EQISEFSKRVLADANLDKVLSAYNKHRDKPIREQAEN IIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDT LIHQSTGLYETRIDLSQLGGD	
dSpCas9	MDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGN TDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRR KNRICYLQEIFSNEMAKVDDSFHRLSEESFLVEEDKKH ERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKAD LRLIYLALAHMIKFRGHFLIEGDLNPDNSDVKLFIQL VQTYNQLFEENPINASGVDAKAILSARLSKSRLENLI AQLPGEKKNGLFGNLIASLGLTPNFKSNFDLAEDAK LQLSKDTYDDDLNLLAQIGDQYADLFLAAKNLSDAI LLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKAL VRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFI KPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQI HLGELHAILRRQEDFYFPLKDNREKIEKILTFRIPYYVG PLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQS FIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKV KYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQ LKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIK DKDFLDNEENEDILEDIVLTTLTFEDREMIEERLKTYA HLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSG KTILDFLKSDGFANRNFQMQLIHDDSLTFKEDIQKAQVS GQGDSLHEHIANLAGSPAIKKGILQTVKVVDLVKVM GRHKPENIVIEMARENQTTQKGQKNSRERMKRIEEGI KELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYV DQELDINRLSDYDVAIVPQSFLKDDSIDNKVLTRSDK NRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFD NLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILD SRMNTKYDENDKLIREVKVITLKSCLVSDFRKDFQFY KVREINNYHHAHDAYLNAVVGTAIIKKYPKLESEFV YGDYKVYDVRKMIKSEQEIGKATAKYFFYSNIMNFF KTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVR KVLSPQVNIVKKTEVQTGGFSKESILPKRNSDKLIAR KKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKL KSVKELLGITIMERSSSFENPIDFLEAKGYKEVKKDLII KLPKYSLFELENGRKRMLASAGELQKGNELALPSKYV NFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEII EQISEFSKRVLADANLDKVLSAYNKHRDKPIREQAEN	SEQ ID NO: 2

	IIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDAT LIHQSIITGLYETRIDLSQLGGD	
nSpCas9(D10 A)	MDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGN TDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRR KNRICYLQEIFSNEMAKVDDSFHRLSEESFLVEEDKKH ERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKAD LRLIYLALAHMIKFRGHFLIEGDLNPDNSDVKLFIQL VQTYNQLFEENPINASGVDAKAILSARLSKSRLENLI AQLPGEKKNGLFGNLIASLGLTPNFKSDFDLAEDAK LQLSKDTYDDDLNLLAQIGDQYADLFLAAKNLSDAI LLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKAL VRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFI KPILEKMDGTEELLVKNREDLLRKQRTFDNGSIPHQI HLGELHAILRRQEDFYPLKDNREKIEKILTRIPYYVG PLARGNSRFAWMTRKSEETITPWNFEVVVDKGASAQS FIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKV KYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQ LKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLKKIK DKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYA HLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSG KTILDFLKSDGFANRNFQMQLIHDDSLTFKEDIQKAQVS GQGDSLHEHIANLAGSPAIKKGILQTVKVVDLKVVM GRHKPENIVIAMARENQTTQKGQKNSRERMKRIEEGI KELGSQILKEHPVENTQLQNEKLYLYLQNGRDMYV DQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDK NRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFD NLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILD SRMNTKYDENDKLIREVKVITLKSCLVSDFRKDFQFY KVREINNYHHAHDAYLNAVVGTAIIKKYPKLESEFV YGDYKVYDVRKMIKSEQEIGKATAKYFFYSNIMNFF KTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVR KVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIAR KKDWDPKKYGGFDSPTVAYSVLVVAKEKGKSKKL KSVKELLGITIMERSSEKNPIDFLEAKGYKEVKKDLII KLPKYSLELENGRKRMLASAGELQKGNELALPSKYV NFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEII EQISEFSKRVLADANLDKVL SAYNKH RDKPIREQAEN IIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDAT LIHQSIITGLYETRIDLSQLGGD	SEQ ID NO: 3
nSpCas9(H84 0A)	MDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGN TDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRR KNRICYLQEIFSNEMAKVDDSFHRLSEESFLVEEDKKH ERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKAD	SEQ ID NO: 4

	LRLIYLALAHMIKFRGHFLIEGDLNPDNSDVKLFIQL VQTYNQLFEENPINASGVDAKAILSARLSKSRLENLI AQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAK LQLSKDTYDDDLNLLAQIGDQYADLFLAAKNLSDAI LLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKAL VRQQLPKEYKEIFFDQSKNGYAGYIDGGASQEEFYKFI KPILEKMDGTEELLVKNLREDLLRKQRTFDNGSIPHQI HLGELHAILRRQEDFYPLKDNREKIEKILTFRIPYYVG PLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQS FIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKV KYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQ LKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLKIIK DKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYA HLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSG KTILDFLKSDGFANRNFQMQLIHDDSLTFKEDIQKAQVS GQGDSLHEHIANLAGSPAIKKGILQTVKVVDLVKVM GRHKPENIVIAMARENQTTQKGQKNSRERMKRIEEGI KELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYV DQELDINRLSDYDVAIVPQSFLKDDSIDNKVLTRSDK NRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFD NLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILD SRMNTKYDENDKLIREVKVITLKSCLVSDFRKDFQFY KVREINNYHHAHDAYLNAVVG TALIKKYPKLESEFV YGDYKVYDVRKMIKSEQEIGKATAKYFFYSNIMNFF KTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVR KVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIAR KKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKL KSVKELLGITIMERSSEFKNPIDFLEAKGYKEVKKDLII KLPKYSLFELENGRKRMLASAGELQKGNELALPSKYV NFLYLASHYEKLKGSPEDEQKQLFVEQHKHYLDEII EQISEFSKRVLADANLDKVLSAYNKHDKPIREQAEN IIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDT LIHQSTGLYETRIDLSQLGGD	
FnCas9	MNFKILPIAIDLGVKNTGVFSAFYQKGTSLERLDNKN GKVYELSKDSYTLLMNNRTARRHQRRGIDRKQLVKR LFKLIWTEQLNLEWDKDTQQAISFLFNRRGFSFITDGY SPEYLNIVPEQVKAILMDIFDDYNGEDDLDSYLKLATE QESKISEIYNKLMQKILEFKLMKLCTDIKDDKVSTKTL KEITSYEFELLADYLANYESLKTQKFSYTDKQGNLK ELSYHHDKYNIQEFLKRHATINDRILD TLLTDDLDIW NFNFEKFDKNEEKLQNQEDKDHIQAHLHHFVFAV NKIKSEMASGGRHRSQYFQEITNVLDENNHQEGYLKN FCENLHNKKYSNLSVKNLVNLIGNLSNLELKPLRKYF	SEQ ID NO: 5

	NDKIHAKADHWDEQKFTETTYCHWILGEWRVGVKDQ DKKDGAKYSYKDLCNELKQKVTKAGLVDLLELDPC RTIPPYLDNNNRKPPKCQSLILNPKFLDNQYPNWQQY LQELKKLQSIQNYLDSFETDLKVLKSSKDQPYFVEYK SSNQQIASGQRDYKDLDARILQFIFDRVKASDELLNE IYFQAKKLKQKASSELEKLESSKKLDEVIANSQLSQIL KSQHTNGIFEQGTFLHLVCKYYKQQRARDSRLYIMP EYRYDKKLHKYNNNTGRFDDDNQLLTYCNHKPRQKR YQLLNDLAGVLQVSPNFLKDKIGSDDDLFISKWLVEH IRGFKKACEDSLKIQKDNRGLLNHNKINIARNTKGKCE KEIFNLICKIEGSEDKKGNYPKHGLAYELGVLLFGEPNE ASKPEFDRKIKKFNSIYSFAQIQQIAFAERKGNANTCA VCSADNAHRMQQIKITEPVEDNNDKIILSAKAQRLPAI PTRIVDGAVKKMATILAKNIVDDNWQNIKQVLSAKH QLHIPITESNAFEFEPALADVKGKSLKDRRKKALERIS PENIFKDKNNRKEFAKGISAYSGANLTDGDFDGAKEE LDHIIPRSHKKYGTLNDEANLICVTRGDNKNKGNRIFC LRDLADNYKLKQFETTDDLEIEKKIADTIWDANKKDF KFGNYRSFINLTPQEQKAFRHALFLADENPIKQAVIRA INNRRRTFVNGTQRYFAEVLANNIYLRAKKENLNTDK ISFDYFGIPTIGNRGIAEIRQLYEKVDSIDIQAYAKGDK PQASYSHLIDAMLAFCIAADEHRNDGSIGLEIDKNYSL YPLDKNTGEVFTKDIFSQIKITDNEFSDDKLVRKKAIE GFNTHRQMTRDGIYAENYLPILIHKELNEVRKGYTWK NSEEIKIFKGKKYDIQQLNNLVYCLKFVDKPISIDIQIST LEELRNILTTNIAATAEYYYINLKTQKLHEYYIENYN TALGYKKYSKEMEFLRSLAYRSERVKIKSIDDVKQVL DKDSNFIIGKITLPFKKEWQRLYREWQNTTIKDDYEFL KSFFNVKSITKLHKKVRKDFSLPISTNEGKFLVVRKKTW DNNFIYQILNDSDSRADGTKPFIPAFDISKNEIVEAIDS FTSKNIFWLPKNIELQKVDNKNIFAIDTSKWFEVETPS DLRDIGIATIQYKIDNNSRPKVRVKLDYVIDDDSKINY FMNHSLLKSRYPDKVLEILKQSTIIEFESSGFNKTIKEM LGMKLAGIYNETSNN	
St1Cas9	MGSDLVLGLDIGIGSVGVGILNKVTGEIIHKNSRIFPAA QAENNLVRRRTNRQRRRLARRKKHRRVRLNRLFEESEG LITDFTKISINLNPYQLRVKGLTDELSNEELFIALKNMV KHRGISYLDASDDGNSSVGDYAQIVKENSQLETKT PGQIQLERYQTYGQLRGDFTVEKDGGKHLINVFPTS AYRSEALRILQTQQEFNPQITDEFINRYLEILTGKRKYY HGPNEKSRTDYGRYRTSGETLDNIFGILIGKCTFYPD EFRAAKASYTAQEFNLLNDLNNLTVPTETKKSKEQK NQIINYVKNEKAMGPAKLFKYIAKLLSCDVADIKGYR	SEQ ID NO: 6

	IDKSGKAEIHTFEAYRKMKTLETLDIEQMDRETLDKL AYVLTNLNTEREGIQEALEHEFADGSFSQKQVDEL VQF RKANSSIFGKGWHNFSVKLMMELIPELYETSEEQMTIL TRLGKQKTTSSSNKTKYIDEKLLTEEIYNPVVAKSVRQ AIKIVNAAIKEYGDFDNIVIEMARETNEDDEKKAIQKI QKANKDEKDAAMLKAANQYNGKAELPHSVFHGHKQ LATKIRLWHQQGERCLYTGKTISIHDLINNSNQFEVDH ILPLSITFDDSLANKVLVYATANQEKGQRTPYQALDS MDDAWSFRELKAFVRESKTLSNKKKEYLLTEEDISKF DVRKKFIERNLVDTRYASRVVLNALQEHFRAHKIDTK VSVVRGQFTSQLRRHWGIEKTRDTYHHHAVDALIAA SSQLNLWKKQKNTLVSYSEDQLLDIETGELISDDEYK ESVFKAPYQHFVDTLKSKEFEDSILFSYQVDSKFNRKI SDATIYATRQAKVGKDKADETYVLGKIKDIYTQDGY DAFMKIYKKDKSKFLMYRHDPQTFEKVIEPILENYPN KQINEKGKEVPCNPFLKYKEEHGYIRKYSKKGNGPEI KSLKYYDSKLGNHIDITPKDSNNKVVLQSVSPWRADV YFNKTTGKYEILGLKYADLQFEKGTGTYKISQEKYND IKKKEGVDS DSEFKFTLYKNDLLL VKDTETKEQQLFR FLSRTMPKQKHVELKPYDKQKFEGGEALIKVLGNV ANSGQCKKGLGKSNISIYKVRTDVLGNQHIIKNEGDK PKLDF	
St3Cas9	MTKPYSIGLDIGTNSVGWAVTTDNYKVPSKKMKVLG NTSKKYIKKNLLGVLLFDSGITAEGRRLKRTARRRYT RRRNRLYLQEIFSTEMATLDDAFFQRLDDSFLVPDDK RDSKYPIFGNLVEEKAYHDEFPTIYHLRKYLADSTKK ADLRLVYLALAHMIKYRGHFLIEGEFNSKNNDIQKNF QDFLDTYNAIFESDLSLENSKQLEEIVKDKISKLEKDD RILKLFPGEKNSGIFSEFLKLIVGNQADFRKCFNLDEK ASLHFSKESYDEDLETLLGYIGDDYSDVFLKAKKLYD AILLSGFLT VTDNETEAPLSSAMIKRYNEHKEDLALLK EYIRNISLKTYNVFKDDTKNGYAGYIDGKTNQEDFY VYLKKLLAEFEGADYFLEKIDREDFLRKQRTFDNGSIP YQIHLQEMRAILDKQAKFYPPFLAKNKERIEKILTFRIPY YVGPLARGNSDFAWSIRKRNEKITPWNFEDVIDKESS AEAFAINRMTSFDLYLPEEKVLPKHSLLYETFNVYNELT KVRFIAESMRDYQFLDSKQKKDIVRLYFKDKRKVTD KDIEYLHAIYGYDGIELKGIEKQFNSSLSTYHDLLNIIN DKEFLDDSSNEAIIIEIIHTLTIFEDREMIKQRLSKFENIF DKSVLKKLSRRHYTGWGKLSAKLINGIRDEKSGNTIL DYLIDDGISNRNFMQLIHDDALSFKKKIQKAQIIGDED KGNIKEVVKSLPGSPAIAKKGILQSIKIVDELVKVMGGR KPESIVVEMARENQYTNQGKSNSQQRLKRLEKSLKEL	SEQ ID NO: 7

	GSKILKENIPAKLSKIDNNALQNDRLYLYYLQNGKDM YTGDDLDIDRLSNYDIDHIIPQAFLKDNSIDNKVLVSS ASNRGKSDDVPSLEVVKRKTFWYQLLKSKLISQRKF DNLTKAERGGLSPEDKAGFIQRQLVETRQITKHVARL LDEKFNNKKDENNRVRTVKIITLKSTLVSQFRKDFEL YKVBREINDFHHAHDAYLNAVVASALLKKYPKLEPEF VYGDYPKYNSFRERKSATEKVYFYSNIMNIFKKSISLA DGRVIERPLIEVNEETGESVWNKESDLATVRRVLSYP QVNVVKKVEEQNHGLDRGKPKGLFNANLSSKPKPNS NENLVGAKEYLDPKKYGGYAGISNSFTVLVKGTIEKG AKKKITNVLEFQGISILDRINYRKDKLNFLLEKGYKDI ELIIELPKYSLFELSDGSRRMLASILSTNNKRGEIHKGN QIFLSQKFVKLLYHAKRISNTINENHRKYVENHKKKEFE ELFYIILEFNENYVGAKKNGKLLNSAFQSWQNHSIDE LCSSFIGPTGSEKGLFELTSRGSAADFEFLGVKIPRYR DYTPSSLLKDATLIHQSVTGLYETRIDLAKLGEG	
NmCas9	MAAFKPNSINYILGLDIGIASVGWAMVEIDEEENPIRLI DLGVRVFERAEPKGTGDSLAMARRLARSVRRLTRRR AHRLLRTRRLKREGVLQAANFDENGLIKSLPNTPWQ LRAAALDRKLTPLEWSAVLLHLIKHRGYLSQRKNEGE TADKELGALLKGVAGNAHALQTGDFRTPAELALNKF EKESGHIRNQRSDYSHTFSRKDLQAEILLFEKQKEFG NPHVSGGLKEGIETLLMTQRPALSGDAVQKMLGHCT FEPAEPKAAKNTYTAERFIWLTCLNNLRILEQGSRPL TDTERATLMDEPYRKSCLTYAQARKLLGLEDTAFFK GLRYGKDNAEASTLMEMKAYHAISRALEKEGLKDKK SPLNLSPELQDEIGTAFSLFKTDEDITGRLKDRIQPEILE ALLKHISFDKFVQISLKALRRIVPLMEQGKRYDEACAE IYGDHYGKKNTEEKIYLPPIPADEIRNPVLRALSQAR KIVINGVRRYGGSPARIHIETAREVGKSFKDRKEIEKRQ EENRKDREKAAAKFREYFPNFVGEPKSKDILKLRLYE QQHGKCLYSGKEINLGRLENEKGYVEIDHALPFSRTWD DSFNKVLVLGSENQNKGNQTPYEYFNGKDNSREWQ EFKARVETSRFPRSKKQRILLQKFDEDEGFKERNLNDTR YVNRFLCQFVADRMRLTGKGKKRVFASNGQITNLLR GFWGLRKVRAENDRHHALDAVVVACSTVAMQQKIT RFVRYKEMNAFDGKTIDKETGEVLHQKTHFPQPWEFF AQEVMIRVFGKPDGKPEFEEADTLEKLRTLLAEKLSS RPEAVHEYVTPLFVSRAPNRKMSGQGHMETVKSAGR LDEGVSVLRVPLTQLKLDLEKMVNREREPKLYEAL KARLEAHKDDPAKAFAEPFYKYDKAGNRTQQVKAV RVEQVQKTGVWVRNHNGIADNATMVRVDVFEKGDK YYLVPIYSWQVAKGILPDRAVVQGKDEEDWQLIDDSF	SEQ ID NO: 8

	NFKFSLHPNDLVEVITKKARMFQYFASCHRG TG NINIR IHDLDHKIGKNGILEGIGVKTALSFQKYQIDELGKEIRP CRLKKRPPVR	
SaCas9	MKRNYILGLDIGITSVGYGIIDYETRDVIDAGVRLFKE ANVENNEGRRSKRGARRLKRRRRHRIQ RVKKLLFDY NLLTDHSELSGINPYEARVKGLSQKLSEEEFSAALLHL AKRRGVHNVNEVEEDTGNELSTKEQISRNSKALEEKY VAELQLERLKKDGEVRGSINRFKTS DYVKEAKQLLKV QKAYHQLDQSFIDTYIDLLETRRTYYEGPGEGSPFGW KDIKEWYEMLMGHCTYFPEELRSVKYAYNADLYNAL NDLNNLVITRDENEKLEYEKFQIIE NVFKQKKKPTLK QIAKEILVNEEDIKGYRVTSTGKPEFTNLKVYHDIKDIT ARKEIIEAELLDQIAKILTIYQSSEDIQEELTNLNSLT QEEIEQISNLKGYTGTHNLSLKAINLILDELWHTNDNQ IAIFNRLKLVKKVDLSQQKEIPTTLVDDFILSPVVKRS FIQSIKVINAIIKKYGLPNDIIELAREKNSKDAQKMINE MQQRNRQTNERIEEII RTTGKENAKYLIEKIKLHDMQE GKCLYSLEAIPLEDLLNNPFNYEVDHII PRSVSFDNSFN NKVLVKQEENSKKGNRTPFQYLSSSDSKISYETFKKHI LNLAKGKGRISKTKKEYLLEERDINRFSVQKDFINRL VDTRYATRGLMNL LRSYFRVNNLDVKVKSINGGFTSF LRRKWKFKKERNKGYKHHAEDALI ANADFI FKEWK KLDKAKKVMENQMFE EKQAESMPEIETE QEYKEIFIT PHQIKHIKDFKDYKYSHRVDKKPNRELINDTLYSTRK DDKGNTLIVNNLNGLYDKDNDKLKKLINKSPEKLLM YHHPQTYQKLKLIMEQYGDEKNPLYKY YEETGNYL TKYSKKDNGPVIKKIKYYGNKLN AHL DITDDYPNSRN KVVKLSLKP YRFDVYLDNGVYKFVTVKNLDVIKEN YYEVNSKCYEEAKKLKKISNQAEFIASFYNNDLIKING ELYRVIGVNNDLLNRIEVNMIDITYREYLENMNDKRP PRIIKTIASKTQSIKKYSTDILGNLYEVKSKKHPQIIKKG	SEQ ID NO: 9
AsCpf1	MTQFEGFTNLYQVSKTLRFELIPQGKTLKHIQE QGFIE EDKARN DHYKELKPIIDRIYKTYADQCLQLVQLDWEN LSAAIDSYRKEKTEETR NALIEEQATYRNAIH DYFIGR TDNLTD AINKRHA EIYKGLFKAELFNGKVLKQLGTVT TTEHENALLRSFDKFTTYFSGFYENRKNVFS AEDISTAI PHRIVQDNFPKFKENCHIFTRLITAVPSLREHFENVKK AIGIFVSTSIEEVFSFPFYNQLLTQTQIDLYNQLLGGISR EAGTEKIKGLNEVLNLAIQKNDETAHIIASLPHRFIPLF KQILSDRNTLSFILEEFKSDEEVIQS FCKYKTLLRNENV LETAEALFNE LNSIDLTHIFISHKKLETISSALCDHWD T LRNALYERRISELTGKITKSAKEKVQRSLKHEDINLQEI ISAAGKELSEAFKQKTSEILSHAHAALDQPLPTTLKKQ	SEQ ID NO: 10

	EEKEILKSQ LDSLLGLYHLLDWFAVDESNEVDPEFSA RLTGIKLEMPSLSFY NKARNYATKKPYSVEKFCLNF QMPTLASGWDVNKEKNNGAILFVKNGLYYLGIMPKQ KGRYKALSFEPTSEKTEGFDKMYDYFPDAAKMIPKC STQLKAVTAHFQTHHTPIILLSNNFIEPLEITKEIYDLNN PEKEPKKFQTAYAKKTGDQKGYREALCKWIDFTRDF LSKYTKTTSIDLSSLRPSSQYKDLGEYYAELNPLLYHIS FQRIAEKEIMDAVETGKLYLFQIYNKDFAKGHHGKPN LHTLYWTGLFSPENLAKTSIKLNGQAEFYRPKSRMK RMAHRLGEKMLNKKLKDQKTPIDTLYQELYDYVNH RLSHDLSDEARALLPNVITKEVSHEIHKDRRFTSDKFFF HVPITLNYQAANSPSKFNQRVNAYLKEHPETPIIGIDR GERNLIYITVIDSTGKILEQRS LNTIQQFDYQKKLDNRE KERVERAARQAWSVVGTIKDLKQGYLSQVIHEIVDLMIH YQAVVVLENLNF GFKSKRTGIAEKAVYQQFEKMLID KLNCLVLKDYP AEKVGGVLNPYQLTDQFTSFAKMGT QSGFLFYVPAPYTSKIDPLTGFVDPFVWKTIKNHESRK HFLEGDFDLHYDVKTGDFILHFKMNRNLSFQRGLPGF MPAWDIVFEKNETQFDAKGTPFIAGKRIVPVIENTHRFT GRYRDLYPANELIALLEEKGIVFRDGSNILPKLLEND SHAIDTMVALIRSVLQMRNSNAATGEDYINSPVRDLN GVCFDSRFQNP EWPMADANGAYHIALKGQLLLNHL KESKDLKLQNGISNQDWLAYIQELRN	
LbCpf1	MAASKLEKFTNCYSLSKTLRFKAIPVGKTQENIDNKR LLVEDEKRAEDYKGVKKLLDRYYLSFINDVLHSIKLK NLNNYISLFRKKTRTEKENKELENLEINLRKEIAKAFK GAAGYKSLFKKDIIETILPEAADDKDEIALVNSFNGFT TAFTGFFDNRENMFSEEAKSTSIAFR CINENLTRYISN MDIFEKVDAIFDKHEVQEIKEKILNSDYDVEDFFEGEF FNFVLTQEGIDVYNAIIGGFVTESGEKIKGLNEYINLYN AKTKQALPKFKPLYKQVLS DRESLSFYGEGYTSDEEV LEVFRNTLNKNSEIFSSIKKLEKLFKNFDEYSSAGIFVK NGPAISTISKDIFGEWNLIRDKWNAEYDDIHLKKKAV VTEKYEDDRRKSFKKIGSFSLEQLQEYADADLSVVEK LKEIIIQKVDEIYKVYGSSEKLFDA DVFLEKSLKKNDA VVAIMKDLLDSVKSFENYIKAFFGEGKETNRDES FYG DFVLAYDILLKVDHIYDAIRNYVTQKPYSKDKFKLYF QNPQFMGGWDKDKETDYRATILRYGSKYYLAIMDK KYAKCLQKIDKDDVNGNYEKINYKLLPGPNKMLPKV FFSKKWMAYYNPSEDIQKIYKNGTFKKGDMFNLNDC HKLIDFFKDSIS RYPKWSNAYDFNFSETEKYKDIAGFY REVVEQGYKVSFESASKKEVDKLVEEGKLYMFQIYN KDFSDKSHGTPNLHTMYFKLLFDENN HQGIRLSGGAE	SEQ ID NO: 11

	LFMRRASLKKEELVVHPANSPIANKNPDNPKKTTTLS YDVYKDKRFSEDQYELHIPIAINKCPKNIFKINTEVRVL LKHDDNPYVIGIDRGERNLLYIVVVDGKGNIVEQYSL NEIINNFNIGIRIKTDYHSLLDKKEKERFEARQNWTSIE NIKELKAGYISQVVHKICELVEKYDAVIALEDLNSGFK NSRVKVEKQVYQKFEKMLIDKLNYMVDKKSNPCAT GGALKGYQITNKFESFKSMSTQNGFIFYIPAWLTSKID PSTGFVNLLKTKYTSIADSKKFISSEFDRIMYVPEEDLFE FALDYKNFSRTDADYIKKWKLYSYGNRIRIFAAAKKN NVFAWEEVCLTSAYKELFNKYGINYQQGDIRALLCEQ SDKAFYSSFMALMSLMLQMRNSITGRTDVDFLISPVK NSDGIFYDSRNYEAQENAILPKNADANGAYNIARKVL WAIGQFKKAEDEKLDKVKIAISNKEWLEYAQTSVK	
FnCpf1	MSIYQEFVNKYSLSKTLRFELIPQGKTLENIKARGLILD DEKRAKDYKKAKQIIDKYHQFFIEEILSSVCISEDLLQN YSDVYFKLKKSDDDNLQKDFKSAKDTIKKQISEYIKD SEKFKNLFNQNLIDAKKGQESDLILWLKQSKDNGIELF KANSDITDIDEALEIISFKGWTTFYFKGFHENRKNVYS SNDIPTSIIYRIVDDNLPKFLENKAKYESLKDKAPEAIN YEQIKKDLAEELTFDIDYKTSEVNQRVFSLDEVFEIAN FNNYLNQSGITKFNTIIGGKVFNGENTKRKGINEYINL YSQQINDKTLKKYKMSVLFKQILSDTESKSFVIDKLED DSDVVTMQSFYEQIAAFKTVEEKSIKETLSLLFDDLK AQKLDLSKIYFKNDKSLTDLSQQVFDDYSVIGTAVLE YITQQIAPKNLDNPSKKEQELIAKKTEKAKYLSLETIK LAL EEFNKH RDIDKQCRFEEILANFAAIPMIFDEIAQNK DNLAQISIKYQNQGKKDLLQASAEDDVKAIKDLLDQT NNLLHKLKIFHISQSEDKANILDKDEHFYLVFEECYFE LANIVPLYNKIRNYITQKPYSDEKFKLNFENSTLANGW DKNKEPDNTAILFIKDDKY YLGVMNKKNNKIFDDKAI KENKGEGYKKIVYKLLPGANKMLPKVFFSAKSIKFYN PSEDILRIRNHSTHTKNGSPQKGYEKFENIEDCRKFID FYKQSISKHPEWKDFGFRFSDTQRYNSIDEFYREVENQ GYKLT FENISESYIDSVVNQGKLYLFQIYNKDFSAYSK GRPNLHTLYWKALFDERNLQDVVYKLNGEAELEFYRK QSIPKKITHPAKEAIAANKNKNPNPKKESVF EYDLIKDKR FTEDKFFFHCPITINFKSSGANKFNDEINLLLKEKANDV HILSIDRGERHLAYYTLVDGKGNIKQDTFNIIGNDRM KTNYHDKLAAIEKDRDSARKDWKKINNIKEMKEGYL SQVVHEIAKL VIEYNAIVVFEDLNFGFKRGRFKVEKQ VYQKLEKMLIEKLNLYL VKDNEFDKTGGVLRAYQLT APFETFKKMGKQTGIIYYVPAGFTSKICPVTGFVNQLY PKYESVSKSQEFFSKFDKICYNLDKGYFEFSFDYKNFG	SEQ ID NO: 12

	DKAAKGKWTIASFGSRLINFRNSDKNHNWDTREVP TKELEKLLKDYSIEYGHGECIKAAICGESDKKFFAKLT SVLNTILQMRNSKTGTELDYLISPVADVNGNFFDSRQ APKNMPQDADANGAYHIGLKGLMLLGRIKNNQEGK KLNLVIKNEEYFEFVQNRNN	
VQRCas9	MDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGN TDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRR KNRICYLQEIFSNEMAKVDDSFHRLVESFLVEEDKKH ERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKAD LRLIYLALAHMIKFRGHFLIEGDLNPDNSDVKLFIQL VQTYNQLFEENPINASGVDAKAILSARLSKSRLENLI AQLPGEKKNGLFGNLIASLGLTPNFKSNFDLAEDAK LQLSKDTYDDDLNLLAQIGDQYADLFLAAKNLSDAI LLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKAL VRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFI KPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQI HLGELHAILRRQEDFYFPLKDNREKIEKILTRIPYYVG PLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQS FIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKV KYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQ LKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIK DKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYA HLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSG KTILDFLKSDGFANRNFMQLIHDDSLTFKEDIQKAQVS GQGDSLHEHIANLAGSPAIIKKGILQTVKVVDDELVKVM GRHKPENIVIAMARENQTTQKGQKNSRERMKRIEEGI KELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYV DQELDINRLSDYDVHIVPQSFLKDDSIDNKVLTRSDK NRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFD NLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILD SRMNTKYDENDKLIREVKVITLKSCLVSDFRKDFQFY KVREINNYHHAHDAYLNAVVGTAIIKKYPKLESEFV YGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFF KTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVR KVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIAR KKDWDPKKYGGFVSPTVAYSVLVVAKEVGKSKKL KSVKELLGITIMERSSEKPNIDFLEAKGYKEVKKDLII KLPKYSLELENGRKRMLASAGELQKGNELALPSKYV NFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEII EQISEFSKRVILADANLDKVL SAYNKH RDKPIREQAEN IIHLFTLTNLGAPAAFKYFDTTIDRKQYRSTKEVL DAT LIHQ SITGLYETRIDLSQLGGD	SEQ ID NO: 13

EQRCas9	MDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGN TDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRR KNRICYLQEIFSNEMAKVDDSFHRLVESFLVEEDKKH ERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKAD LRLIYLALAHMIKFRGHFLIEGDLNPDNSDVKLFIQL VQTYNQLFEENPINASGVDAKAILSARLSKSRLENLI AQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAK LQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAI LLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKAL VRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFI KPILEKMDGTEELLVKNLREDLLRKQRTFDNGSIPHQI HLGELHAILRRQEDFYFLKDNREKIEKILTFRIPYYVG PLARGNSRFAWMTRKSEETITPWNFEEVVDKGASASQS FIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKV KYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQ LKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIK DKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYA HLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSG KTILDFLKSDGFANRNFQMQLIHDDSLTFKEDIQKAQVS GQGDSLHEHIANLAGSPAIIKKGILQTVKVVDELVKVM GRHKPENIVIEMARENQTTQKGQKNSRERMKRIEEGI KELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYV DQELDINRLSDYDVHIVPQSFLKDDSIDNKVLTRSDK NRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFD NLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILD SRMNTKYDENDKLIREVKVITLKSCLVSDFRKDFQFY KVREINNYHHAHDAYLNAVVGTAIIKKYPKLESEFV YGDYKVYDVRKMIKSEQEIGKATAKYFFYSNIMNFF KTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVR KVLSPQVNIVKKTEVQTGGFSKESILPKRNSDKLIAR KKDWDPKKYGGFESPTVAYSVLVVAKEVGKSKKL KSVKELLGITIMERSSEFKNPIDFLEAKGYKEVKKDLII KLPKYSLELENGRKRMLASAGELQKGNELALPSKYV NFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEII EQISEFSKRVLADANLDKVL SAYNKHRDKPIREQAEN IIHLFTLTNLGAPAAFKYFDTTIDRKQYRSTKEVL DAT LIHQ SITGLYETRIDLSQLGGD	SEQ ID NO: 14
VRERCas9	MDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGN TDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRR KNRICYLQEIFSNEMAKVDDSFHRLVESFLVEEDKKH ERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKAD LRLIYLALAHMIKFRGHFLIEGDLNPDNSDVKLFIQL VQTYNQLFEENPINASGVDAKAILSARLSKSRLENLI	SEQ ID NO: 15

	AQLPGEKKNGLFGNLIASLGLTPNFKSNFDLAEDAK LQLSKDTYDDDLNLLAQIGDQYADLFLAAKNLSDAI LLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKAL VRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFI KPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQI HLGELHAILRRQEDFYFPLKDNREKIEKILTRIPYYVG PLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQ S FIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKV KYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQ LKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIK DKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYA HLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSG KTILDFLKSDGFANRNFQMQLIHDDSLTFKEDIQKAQVS GQGDSLHEHIANLAGSPAIIKKGILQTVKVVDLVKVM GRHKPENIVIAMARENQTTQKGQKNSRERMKRIEEGI KELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYV DQELDINRLSDYDVHIVPQSFLKDDSIDNKVLTRSDK NRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFD NLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILD SRMNTKYDENDKLIREVKVITLKSCLVSDFRKDFQFY KVREINNYHHAHDAYLNAVVGITALIKKYPKLESEFV YGDYKVYDVRKMIKSEQEIGKATAKYFFYSNIMNFF KTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVR KVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIAR KKDWDPKKYGGFVSPTVAYSVLVVAKEVEGKSKKL KSVKELLGITIMERSSEKKNPIDFLEAKGYKEVKKDLII KLPKYSLELENGRKRMLASARELQKGNELALPSKYV NFLYLASHYEKLKGSPEDEQKQLFVEQHKHYLDEII EQISEFSKRVLADANLDKVL SAYNKHDKPIREQAEN IIHLFTLTNLGAPAAFKYFDTTIDRKEYRSTKEVL DAT LIHQ SITGLYETRIDLSQLGGD	
Cas9-NG	MDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGN TDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRR KNRICYLQEFSNEMAKVDDSFHRLEESFLVEEDKKH ERHPIFGNIVDEVAYHEKYPTIYHLRKKLV DSTDKAD LRLIYLALAHMIKFRGHFLIEGDLNPDNSDVKLFIQL VQTYNQLFEENPINASGVDAKILSARLSKSRLENLI AQLPGEKKNGLFGNLIASLGLTPNFKSNFDLAEDAK LQLSKDTYDDDLNLLAQIGDQYADLFLAAKNLSDAI LLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKAL VRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFI KPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQI HLGELHAILRRQEDFYFPLKDNREKIEKILTRIPYYVG	SEQ ID NO: 16

	PLARGNSRFAWMTRKSEETITPWNFEVVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFQMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDLVKVMGRHKPENIVIAMARENQTTQKGQKNSRERMKRIEEGKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRLVETRQITKHVAQILD SRMNTKYDENDKLIREVKVITLKSCLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVGTAIIKKYPKLESEFVYGDYKVYDVRKMIKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESIRPKRNSDKLIARKKDWDPKKYGGFVSPTVAYSVLVVAKEVGKSKKLKSVKELLGITIMERSSEFKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASARFLQKGNELALPSKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIEQISEFSKRVILADANLDKVL SAYNKHDKPIREQAENIIHLFTLTNLGAPRAFKYFDTTIDRKVYRSTKEVL DATLIHQ SITGLYETRIDLSQLGGD	
xCas9	MDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGN TDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKNRICYLQEIFS NEMAKVDDSFHRL EESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRLENLIAQLPGEKKNGLFGNLIASLGLTPNFKSNFDLAEDTKLQLSKD TYDDDLNLLAQIGDQYADLFLAAKNLS DAILSDILRVNTEITKAPLSASMIKLYDEHHQDLTLLKALVRQQLP EKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGIIPHQIHLGELHAILRRQEDFY PFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEKVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGDQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSG	SEQ ID NO: 17

	KTILDFLKSDGFANRNFIQLIHDDSLTFKEDIQKAQVS GQGDSLHEHIANLAGSPAIKKGILQTVKVVDDELVKVM GRHKPENIVIAMARENQTTQKGQKNSRERMKRIEEGI KELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYV DQELDINRLSDYVDHIVPQSFLKDDSIDNKVLTRSDK NRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFD NLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILD SRMNTKYDENDKLIREVKVITLKSCLVSDFRKDFQFY KVREINNYHHAHDAYLNAVVG TALIKKYPKLESEFV YGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFF KTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVR KVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIAR KKDWDPKKYGGFDSPTVAYSVLVVAKEVGKSKKL KSVKELLGITIMERSSEFEKNPIDFLEAKGYKEVKDLII KLPKYSLEFENGRKRMLASAGVLQKGNELALPSKY VNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEI IEQISEFSKRVLADANLDKVL SAYNKH RDKPIREQAE NIIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDA TLIHQSITGLYETRIDLSQLGGD	
eCas9	MDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGN TDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRR KNRICYLQEIFS NEMAKVDDSFHRLEESFLVEEDKKH ERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKAD LRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQL VQTYNQLFEENPINASGVDAKAILSARLSKSRLENLI AQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAK LQLSKD TYDDDLNLLAQIGDQYADLFLAAKNLSDAI LLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKAL VRQQLP EKYKEIFFDQSKNGYAGYIDGGASQEEFYKFI KPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQI HLGELHAILRRQEDFY PFLKDNREKIEKILTFRIPYYVG PLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQS FIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKV KYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQ LKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIK DKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYA HLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSG KTILDFLKSDGFANRNFMQLIHDDSLTFKEDIQKAQVS GQGDSLHEHIANLAGSPAIKKGILQTVKVVDDELVKVM GRHKPENIVIAMARENQTTQKGQKNSRERMKRIEEGI KELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYV DQELDINRLSDYVDHIVPQSFLADDSIDNKVLTRSDK NRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFD	SEQ ID NO: 18

	NLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILD SRMNTKYDENDKLIREVKVITLKS KLVSDFRKDFQFY KVREINNYHHAHDAYLNAVVG TALIKKYPAL ESEFV YGDYKVYDVRKMI AKSEQEIGKATAKYFFYSNIMNFF KTEITLANGEIRKAPLIETNGETGEIVWDKGRDFATVR KVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIAR KKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKL KSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLII KLPKYSLFEL ENGRKRMLASAGELQKG NELALPSKYV NFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEII EQISEFSKR VILADANLDKVL SAYNKH RDKPIREQAEN IIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVL DAT LIHQ SITGLYETRIDLSQLGGD	
SpCas9-HF1	MDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGN TDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRR KNRICYLQEIFS NEMAKVDDSFHRL EESFLVEEDKKH ERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKAD LRLIYLALAHMIKFRGHFLIEGDLNPDNSDV DKLFIQL VQTYNQLFEENPINASGVDAKAILSARLSKSRLENLI AQLPGEKKNGLFGNLI ALSLGLTPNFKS NFDLAEDAK LQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAI LLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKAL VRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFI KPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQI HLGELHAILRRQEDFY PFLKDNREKIEKILTFRIPYYVG PLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQS FIERMATAFDKNLPNEKVLPKHSLLYEYFTVYNELTKV KYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQ LKEDYFKKIECFDSVEISGVEDR FNASLGTYHDLLKIIK DKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYA HLFDDKVMKQLKRRRYTGWGALS RKLINGIRDKQSG KTILDFLKSDGFANRNFMALIHDDSLTFKEDIQKAQVS GQGDSLHEHIANLAGSPA IKKGILQTVKVVD ELVKVM GRHKPENIV IEMARENQTTQKGQKNSRERMKRIEEGI KELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYV DQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDK NRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFD NLTKAERGGLSELDKAGFIKRQLVETRAITKHVAQILD SRMNTKYDENDKLIREVKVITLKS KLVSDFRKDFQFY KVREINNYHHAHDAYLNAVVG TALIKKYPKLESEFV YGDYKVYDVRKMI AKSEQEIGKATAKYFFYSNIMNFF KTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVR KVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIAR	SEQ ID NO: 19

	KKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKL KSVKELLGITIMERSSSFENPIDFLEAKGYKEVKKDLII KLPKYSLFELENGRKRMLASAGELQKGNELALPSKYV NFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEII EQISEFSKRVLADANLDKVLSAYNKHRDKPIREQAEN IIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVL DAT LIHQ SITGLYETRIDLSQLGGD	
HypaCas9	MDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGN TDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRR KNRICYLQEIFS NEMAKVDDSFHRL EESFLVEEDKKH ERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKAD LRLIYLALAHMIKFRGHFLIEGDLNPDNSDVKLFIQL VQTYNQLFEENPINASGVDAKAILSARLSKSRLENLI AQLPGEKKNGLFGNLI ALSGLTPNFKSNFDLAEDAK LQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAI LLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKAL VRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFI KPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQI HLGELHAILRRQEDFY PFLKDNREKIEKILTFRIPYYVG PLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQS FIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKV KYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQ LKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIK DKDFLDNEENEDILEDIVLTTLTFEDREMIEERLKTYA HLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSG KTILDFLKSDGFANRAFAALIADDSLTFKEDIQKAQVS GQGDSLHEHIANLAGSPA IKGILQTVKVVDLVKVM GRHKPENIVIEMARENQTTQKGQKNSRERMKRIEEGI KELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYV DQELDINRLSDYDV DHIVPQSFLKDDSIDNKVLTRSDK NRGKSDNVPSEE VVKMKMKNYWRQLLNAKLITQRKFD NLTKAERGGLSEL DKAGFIKRQLVETRQITKHVAQILD SRMNTKYDENDKLIREVKVITLKS KLVSDFRKDFQFY KVREINNYHHAHDAYLNAVVG TALIKKYPKLESEFV YGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFF KTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVR KVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIAR KKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKL KSVKELLGITIMERSSSFENPIDFLEAKGYKEVKKDLII KLPKYSLFELENGRKRMLASAGELQKGNELALPSKYV NFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEII EQISEFSKRVLADANLDKVLSAYNKHRDKPIREQAEN	SEQ ID NO: 20

	IIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDAT LIHQSIITGLYETRIDLSQLGGD	
HiFiCas9	MDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGN TDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRR KNRICYLQEIFSNEMAKVDDSFHRLVESFLVEEDKKH ERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKAD LRLIYLALAHMIKFRGHFLIEGDLNPDNSDVKLFIQL VQTYNQLFEENPINASGVDAKAILSARLSKSRLENLI AQLPGEKKNGLFGNLIASLGLTPNFKSNFDLAEDAK LQLSKDTYDDDLNLLAQIGDQYADLFLAAKNLSDAI LLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKAL VRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFI KPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQI HLGELHAILRRQEDFYPLKDNREKIEKILTRIPYYVG PLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQS FIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKV KYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQ LKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIK DKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYA HLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSG KTILDFLKSDGFANANFMQLIHDDSLTFKEDIQKAQVS GQGDSLHEHIANLAGSPAIKKGILQTVKVVDLVKVM GRHKPENIVIAMARENQTTQKGQKNSRERMKRIEEGI KELGSQILKEHPVENTQLQNEKLYLYLQNGRDMYV DQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDK NRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFD NLTKAERGGLSELDKAGFIKRLVETRQITKHVAQILD SRMNTKYDENDKLIREVKVITLKSCLVSDFRKDFQFY KVREINNYHHAHDAYLNAVVGTAIIKKYPKLESEFV YGDYKVYDVRKMIKSEQEIGKATAKYFFYSNMNFF KTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVR KVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIAR KKDWDPKKYGGFDSPTVAYSVLVVAKEVGKSKKL KSVKELLGITIMERSSEKPNIDFLEAKGYKEVKKDLII KLPKYSLELENGRKRMLASAGELQKGNELALPSKYV NFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEII EQISEFSKRVLADANLDKVLSAYNKHDKPIREQAEN IIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDAT LIHQSIITGLYETRIDLSQLGGD	SEQ ID NO: 21
sniper-Cas9	MDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGN TDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRR KNRICYLQEIFSNEMAKVDDSFHRLVESFLVEEDKKH ERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKAD	SEQ ID NO: 22

	LRLIYLALAHMIKFRGHFLIEGDLNPDNSDVKLFIQL VQTYNQLFEENPINASGVDAKAILSARLSKSRLENLI AQLPGEKKNGLFGNLIASLGLTPNFKSNFDLAEDAK LQLSKDTYDDDLNLLAQIGDQYADLFLAAKNLSDAI LLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKAL VRQQLPPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFI KPILEKMDGTEELLVKNREDLLRKQRTFDNGSIPHQI HLGELHAILRRQEDFYPLKDNREKIEKILTFRIPYYVG PLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQS FIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKV KYVTEGMRKPASLSGEQKKAIVDLLFKTNRKVTVKQ LKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIK DKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYA HLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSG KTILDFLKSDGFANRNFQMQLIHDDSLTFKEDIQKAQVS GQGDSLHEHIANLAGSPAIIKKGILQTVKVVDLVKVM GRHKPENIVIEIARENQTTQKGQKNSRERMKRIEEGIK ELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVD QELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKN RGKSDNPVSEEVVKKMKNYWRQLLNANLITQRKFDN LTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDS RMNTKYDENDKLIREVKVITLKSCLVSDFRKDFQFYK VREINNYHHAHDAYLNAVVGTAIIKKYPKLESEFVY GDYKVYDVRKMIKSEQEIGKATAKYFFYSNIMNFFK TEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRK VLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARK KDWDPPKKYGGFDSPTVAYSVLVVAKEVGKSKKLK SVKELLGITIMERSSEKPNIDFLEAKGYKEVKKDLIIK LPKYSLFELENGRKRMLASAGELQKGNELALPSKYVN FLYLASHYEKLKGPEDNEQKQLFVEQHKHYLDEIIE QISEFSKRVLADANLDKVLSAYNKHDKPIREQAENII HLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLI HQSITGLYETRIDLSQLGGD	
spG	MDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGN TDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRR KNRICYLQEIFSNEMAKVDDSFHRLEESFLVEEDKKH ERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKAD LRLIYLALAHMIKFRGHFLIEGDLNPDNSDVKLFIQL VQTYNQLFEENPINASGVDAKAILSARLSKSRLENLI AQLPGEKKNGLFGNLIASLGLTPNFKSNFDLAEDAK LQLSKDTYDDDLNLLAQIGDQYADLFLAAKNLSDAI LLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKAL VRQQLPPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFI	SEQ ID NO: 23

	KPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQI HLGELHAILRRQEDFYFPLKDNREKIEKILTFRIPYYVG PLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQS FIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKV KYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQ LKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIK DKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYA HLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSG KTILDFLKSDGFANRNFMQLIHDDSLTFKEDIQKAQVS GQGDSLHEHIANLAGSPAIKKGILQTVKVVDLVKVM GRHKPENIVEMARENQTTQKGQKNSRERMKRIEEGI KELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYV DQELDINRLSDYVDHIVPQSFLKDDSIDNKVLTRSDK NRGKSDNVPSEEVVKMKMKNYWRQLLNAKLITQRKFD NLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILD SRMNTKYDENDKLIREVKVITLKS KLVSDFRKDFQFY KVREINNYHHAHDAYLNAVVG TALIKKYPKLESEFV YGDYKVYDVRKMIKSEQEIGKATAKYFFYSNIMNFF KTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVR KVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIAR KKDWDPKKYGGFLWPTVAYSVLVVAKEKGKSKKL KSVKELLGITIMERSSSF EKNPIDFLEAKGYKEVKDLII KLPKYSLFELENGRRMLASAKQLQKGNELALPSKY VNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEI IEQISEFSKRVLADANLDKVLSAYNKH RDKPIREQAE NIIHLFTLTNLGAPAAF KYFDTTIDRKQYRSTKEVLDA TLIHQSITGLYETRIDLSQLGGD	
SpRY	MDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGN TDRHSIKKNLIGALLFDSGETAERTRLKRTARRRYTRR KNRICYLQEIFS NEMAKVDDSFHRL EESFLVEEDKKH ERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKAD LRLIYLALAHMIKFRGHFLIEGDLNPDNSDV DKLFIQL VQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLI AQLPGEKKNGLFGNLIASLGLTPNFKSNFDLAEDAK LQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAI LLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKAL VRQQLP EKYKEIFFDQSKNGYAGYIDGGASQEEFYKFI KPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQI HLGELHAILRRQEDFYFPLKDNREKIEKILTFRIPYYVG PLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQS FIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKV KYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQ LKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIK	SEQ ID NO: 24

	DKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYA HLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSG KTILDFLKSDGFANRNFMQLIHDDSLTFKEDIQKAQVS GQGDSLHEHIANLAGSPAIKKGILQTVKVVDDELVKVM GRHKPENIVIAMARENQTTQKGQKNSRERMKRIEEGI KELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYV DQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDK NRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFD NLTKAERGGLSELDAKAGFIKRQLVETRQITKHVAQILD SRMNTKYDENDKLIREVKVITLKSCLVSDFRKDFQFY KVREINNYHHAHDAYLNAVVGTAIIKKYPKLESEFV YGDYKVYDVRKMIKSEQEIGKATAKYFFYSNIMNFF KTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVR KVLSMPQVNIVKKTEVQTGGFSKESIRPKRNSDKLIAR KKDWDPKKYGGFLWPTVAYSVLVVAKVEKGKSKKL KSVKELLGITIMERSSEKKNPIDFLEAKGYKEVKKDLII KLPKYSLFELENGKRMLASAKQLQKGNELALPSKY VNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEI IEQISEFSKRVLADANLDKVL SAYNKH RD KPIREQAE NIIHLFTLTRLGAPRAFKYFDTTIDPKQYRSTKEVLDA TLIHQSITGLYETRIDLSQLGGD	
KKH SaCas9	MGKRNILGLDIGITSVGYGIIDYETRDVIDAGVRLFK EANVENNEGRRSKRGARRLKRRRRHRIQRVKKLLFD YNLLTDHSELGINPYEARVKGLSQKLSEEEFSAALLH LAKRRGVHNVNEVEEDTGNELSTKEQISRNSKALEEK YVAELQLERLKKDGEVRGSINRFKTSYVKEAKQLLK VQKAYHQLDQSFIDTYIDLLETRRTYYEGPGEGSPFG WKDIKEWYEMLMGHCTYFPEELRSVKYAYNADLYN ALNDLNNLVITRDENEKLEYEYEFQIENVFKQKKKPT LKQIAKEILVNEEDIKGYRVTSTGKPEFTNLKVYHDIK DITARKEIIEAELLDQIAKILTIYQSSEDIQEELTNLNS ELTQEEIEQISNLKGYTGTHNLSLKAINLILDELWHTN DNQIAIFNRLKLVKKVDLSQQKEIPTTLVDDFILSPVV KRSFIQSIKVINAIIKKYGLPNDIIIELAREKNSKDAQKM INEMQKRNRQTNERIEEII RTTGKENAKYLIEKIKLHD MQEGKCLYSLEAIPLEDLLNNPFNYEVDHII PRSVSFD NSFNKVLVKQEENSKKGNRTPFQYLSSSDSKISYETF KKHILNLAGKGRISKTKKEYLLEERDINRFSVQKDFI NRNLVDTRYATRGLMNLLRSYFRVNNLDVKVKSING GFTSFLRRKWKFKKERNKGYKHHAE DALIANADFIF KEWKKLDKAKKVMENQMFE EKQAESMPEIETE QEY KEIFITPHQIKHIKDFKDYKYSHRVDKKPNRKLINDTL YSTRKDDKGNTLIVNNLNGLYDKDNDKLKKLINKSPE	SEQ ID NO: 25

	KLLMYHHDHPQTYQKLKLIMEQYGDEKNPLYKYEEET GNYLTKYSSKDNNGPVIKKIKYYGNKLNLAHLDITDDYP NSRNKVVKLSLKPYPYRFDVYLDNGVYKFVTVKNLDVI KKENYYEVNSKCYEEAKKLKKISNQAEFASFYKNDL IKINGELYRVIGVNNDLLNRIEVNMIDITYREYLENMN DKRPPHIIKTIASKTQSIKKYSTDILGNLYEVKSKKHPQ IIKKG	
CjCas9	MARILAFDIGISSIGWAFSENDELKDCGVRIFTKVENP KTGESLALPRRLARSARKRLARRKARLNHLKHLIANE FKLNYEDYQSFDESLAKAYKGSLISPYELRFRALNELL SKQDFARVILHIAKRRGYDDIKNSDDKEKGAILKAIKQ NEEKLANYQSVGEYLYKEYFQKFKEKSKEFTNVRNK KESYERCIAQSFLKDELKLIFKKQREFGFSFSKKFEEEV LSVAFYKRALKDFSHLVGNCSSFTDEKRAPKNSPLAF MFVALTRIINLLNNLKNTEGILYTKDDLNALLNEVLK NGTLTYKQTKLLGLSDDYEFKGEKGTIFYEFKYYKE FIKALGEHNLSQDDLNEIAKDITLIKDEIKLKKALAKY DLNQNQIDSLSKLEFKDHLNISFKALKLVTPLMLEGK KYDEACNELNLKVAINEDKKDFLPAFNETYYKDEVT NPVVLRAIKEYRKVLNALLKKYGVHKINIELAREVG KNHSQRAKIEKEQNENYKAKKDAAELECEKLGLKINSK NILKLRLFKEQKEFCAYSGEKIKISDLQDEKMLEIDHIY PYSRSFDDSYMKNVLVFTKQNQEKLNQTPFEAFGND AKWQKIEVLAKNLPTKKQKRILDKNYKDKEQKNFKD RNLNDTRYIARLVNLYTKDYLDLPLSDDENTKLNDT QKGSKVHVEAKSGMLTSALRHTWGFSKDRNNHLH HAIDAVIIAYANNSIVKAFSDFKKEQESNSAELYAKKI SELDYKNKRKFFEPFSGFRQKVLDKIDEIFVSKPERKK PSGALHEETFRKEEEFYQSYGGKEGVLKALELGKIRK VNGKIVKNGDMFRVDIFKHKKTNKFYAVPIYTMDF LKVLPNKAVARSKKGEIKDWILMDENYEFCSLYKDS LILIQTKDMQEPEFVYYNAFTSSTVSLIVSKHDNKFET LSKNQKILFKNANEKEVIAKSIGIQNLKVFEKYIVSAL GEVTKAEFRQREDFKK	SEQ ID NO: 26
Cas9-NRRH	MDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGN TDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRR KNRICYLQEIFSNEMAKVDDSFHRLAESFLVEEDKKH ERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKAD LRLIYLALAHMIKFRGHFLIEGDLNPDNSDVKLFIQL VQTYNQLFEENPINASGVDAKAILSARLSKSRLENLI AQLPGEKKNGLFGNLIALSLGLTPNFKSDFDLAEDAK LQLSKDTYDDDLNLLAQIGDQYADLFLAAKNLSDAI LLSDILRVNTEITKAPLSASMVKRYDEHHQDLTLLKA	SEQ ID NO: 27

	LVRQQLPKEYKEIFFDQSKNGYAGYIDGGASQEEFYK FIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGIIPH QIHLGELHAILRRQGDFYPFLKDNREKIEKILTRIPYY VGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGAS AQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNEL TKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVT VKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDL KIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLK TYAHLFDDKVMKQLKRLRYTGWGRLSRKLINGIRDK QSGKTILDFLKSDGFANRNFMLIHDDSLTFKEDIQKA QVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDLV KVMGGHKPENIVIEMARENQTTQKGQKNSRERMKRI EEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRD MYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLT RSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQ RKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHV AQILDSRMNTKYDENDKLIREVKVITLKSCLVSDFRK DFQFYKVREINNYHHAHDAYLNAVVGTAIIKKYPKL ESEFVYGDYKVYDVRKMIKSEQEIGKATAKYFFYSN IMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDF ATVRKVLSPQVNIVKKTEVQTGGFSKESILPKGNSD KLIARKKDWDPKKYGGFNSPTAAYSVLVVAKEVGK SKKLKSVKELLGITIMERSSEKKNPIGFLEAKGYKEVK KDLIIKLPKYSLELENGRKRMLASAGVLHKGNELAL PSKYVNFLYLASHYEKLKGSPEQNEQQLFVEQHKH YLDEIIEQISEFSKRVILADANLDKVL SAYNKH RDKPIR EQAENIIHLFTLTNLGVPAAFKYFDTTIDKKRYTSTKE VL DATLIHQ SITGLYETRIDLSQLGGD	
Cas9-NRCH	MDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGN TDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRR KNRICYLQEIFS NEMAKVDDSFHRL EESFLVEEDKKH ERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKAD LRLIYLALAHMIKFRGHFLIEGDLNPDNSDVKLFIQL VQTYNQLFEENPINASGVDAKAILSARLSKSRLENLI AQLPGEKKNGLFGNLI ALSGLTPNFKSNFDLAEDAK LQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAI LLSDILRVNTEITKAPLSASMVKRYDEHHQDLTLLKA LVRQQLPKEYKEIFFDQSKNGYAGYIDGGASQEEFYK FIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGIIPH QIHLGELHAILRRQGDFYPFLKDNREKIEKILTRIPYY VGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGAS AQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNEL TKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVT	SEQ ID NO: 28

	VKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDL KIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLK TYAHLFDDKVMKQLKRLRYTGWGRLSRKLINGIRDK QSGKTILDFLKSDGFANRNFMQLIHDDSLTFKEDIQKA QVSGQGDSLHEHIANLAGSPAIIKGILQTVKVVDLV KVMGGHKPENIVIEMARENQTTQKGQKNSRERMKRI EEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRD MYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLT RSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQ RKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHV AQILDSRMNTKYDENDKLIREVKVITLKSCLVSDFRK DFQFYKVREINNYHHAHDAYLNAVVGTAIIKKYPKL ESEFVYGDYKVYDVRKMIKSEQEIGKATAKYFFYSN IMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDF ATVRKVLSPQVNIVKKTEVQTGGFSKESILPKGNSD KLIARKKDWDPKKYGGFNSPTVAYSVLVVAKEVGK SKKLKSVKELLGITIMERSSEKKNPIDFLEAKGYKEVK KDLIKLPKYSLFELENGRKRMLASAGVLQKGNELAL PSKYVNFLYLASHYEKLKGSPEDNEQQLFVEQHKH YLDEIIEQISEFSKRVILADANLDKVL SAYNKHRDKPIR EQAENIIHLFTLTNLGAPAAFKYFDTTINRKQYNTTKE VLDTLIRQSITGLYETRIDLSQLGGD	
Cas9-NRTH	MDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGN TDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRR KNRICYLQEIFSNEMAKVDDSFHRLSEESFLVEEDKKH ERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKAD LRLIYLALAHMIKFRGHFLIEGDLNPDNSDVKLFIQL VQTYNQLFEENPINASGVDAKAILSARLSKSRLENLI AQLPGEKKNGLFGNLIASLGLTPNFKSNFDLAEDAK LQLSKD TYDDLDNLLAQIGDQYADLFLAAKNLSDAI LLSDILRVNTEITKAPLSASMVKRYDEHHQDLTLLKA LVRQQLPKEYKEIFFDQSKNGYAGYIDGGASQEEFYK FIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGIIPH QIHLGELHAILRRQGDFYPFLKDNREKIEKILTFRIPIY VGPLARGNSRFAWMTRKSEETITPWNFEVVDKGAS AQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNEL TKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVT VKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDL KIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLK TYAHLFDDKVMKQLKRLRYTGWGRLSRKLINGIRDK QSGKTILDFLKSDGFANRNFMQLIHDDSLTFKEDIQKA QVSGQGDSLHEHIANLAGSPAIIKGILQTVKVVDLV KVMGGHKPENIVIEMARENQTTQKGQKNSRERMKRI	SEQ ID NO: 29

	EEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRD MYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLT RSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQ RKFDNLTKAERGGELSELDKAGFIKRQLVETRQITKHV AQILDSRMNTKYDENDKLIREVKVITLKSCLVSDFRK DFQFYKVREINNYHHAHDAYLNAVVGTAIIKKYPKL ESEFVYGDYKVYDVRKMIKSEQEIGKATAKYFFYSN IMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDF ATVRKVLSPQVNIVKKTEVQTGGFSKESILPKGNSD KLIARKKDWDPPKKYGGFNSPTVAYSVLVVAKEVGK SKKLKSVKELLGITIMERSSEKPNPIGFLEAKGYKEVK KDLIIKLPKYSLFELENGRKRMLASASVLHKGNELALP SKYVNFLYLASHYEKLKGSSDNKQKQLFVEQHKHY LDEIIQISEFSKRVLADANLDKVL SAYNKHDKPIRE QAENIIHLFTLTNLGASAAFKYFDTTIGRKL YTSTKEV LDATLIHQ SITGLYETRIDLSQLGGD	
ScCpf1	MQTLFENFTNQYPVSKTLRFELIPQGKTKDFIEQKGLL KKDEDRAEKYKKVKNIIDEYHKDFIEKSLNGLKLDGL EKYKTLYLKQEKDDDKKAFDKEKENLRKQIANAFR NNEKFKTLFAKELIKNDLMSFACEEDKKNVKEFEAFT TYFTGFHQNRANMYVADEKRTAIASRLIHENLPKFID NIKIFEKMKKEAPELLSPFNQTLKDMKDVIKGTTL EEI FSLDYFNKTLTQSGIDIYNSVIGGRTPEEGKTKIKGLNE YINTDFNQKQTDKKKRQPKFKQLYKQILSDRQSLSFIA EAFKNDTEILEAIEKFYVNELLHFSNEGKSTNVLDAIK NAVSNLESFNLTKMYFRSGASLTDVSRKVFGIEWSIIN RALDNYYATTYPIKPREKSEKYEERKEKW LKQDFNVS LIQTAIDEYDNETVKGKNSGKVIADYFAKFCDDKETD LIQKVNEG YIAVKDLLNTPCPEN EKLGSNKDQVKQIK AFMDSIMDIMHFVRPLSLKDTDKEKDETFYSLFTPLY DHLTQTIALYNKVRNYLTQKPYST EKIKNFENSTLLG GWDLNKETDNTAIILRKDNLYYLGIMDKRHNRIFRNV PKADKKDFCYEKMVYKLLPGANKMLPKVFFSQSRIQ EFTPSAKLLENYANETHKKGDNFNLNHCHKLIDFFKD SINKHEDWKNFDFRFSATSTYADLSGFYHEVEHQGYK ISFQSVADSFIDDLVNEGKLYLFQIYNKDFSPFSKGKPN LHTLYWKMLFDENNLKD VVYKLNGEAEVFYRKKSIA EKNTTIHKANESIINKNPDNPKATSTFN YDIVKDKRYTI DKFQFHIPITMNFKAEGIFNMNQ RVNQFLKANPDINII GIDRGERHLLYYALINQKGKILKQDTLNVIANEKQKV DYHNLLDKKEGDRATARQEWGVIETIKELKEGYLSQ VIHKLTDLMIENNAIIVMEDLNFGFKRGRQKVEKQVY QKFEKMLIDKLN YLVDKNKKANELGGLLNAFQLANK	SEQ ID NO: 30

	FESFQKMKGKQNGFIFYVPAWNTSKTDPATGFIDFLKP RYENLNQAKDFFEKFDSIRLNSKADYFEFAFDKNFTE KADGGRTKWTVCTTNEDRYAWNRLNNNRGSQEKY DITAEKSLFDGKVDYKSGKDLKQQIASQESADFFKA LMKNLSITLSLRHNNGEKGDNEQDYILSPVADSKGRF FDSRKADDDMPKNADANGAYHIALKGLWCLEQISKT DDLKKVKLAISNKEWLEFVQTLKG	
PcCpf1	MDSLKDFTNLYPVSKTLRFELKPVGKTLENIEKAGILK EDEHRAESYRRVKKIIDTYHKVFIDSSLENMAKMGIE NEIKAMLQSFCELYKKDHRTEGEDKALDKIRAVLRGL IVGAFTGVCGRRENTVQNEKYESLFKEKLIKEILPDFV LSTEAEPLPFSVEEATRSKKEFDSFTSYFAGFYENRKN YSTKPQSTAIAYRLIHENLPKFIDNILVFQKIKEPIAKEL EHIRADFSAGGYIKKDERLEDIFSLNYYIHVLSQAGIEK YNALIGKIVTEGDGEMKGLNEHINLYNQQRGREDRLP LFRPLYKQILSDREQLSYLPESFEKDEELLRALKEFYD HIAEDILGRTQQLMTSISEYDLSRIYVRNDSQLTDISKK MLGDWNAIYMARERAYDHEQAPKRITAKYERDRIKA LKGEESISLANLNSCIAFLDNVRDCRVDTYLSLTLGQKE GPHGLSNLVENVFASYHEAEQLLSFPYPEENNLIQDK DNVVLIKNLLDNISDLQRFLKPLWGMGDEPKDERFY GEYNYIRGALDQVIPLYNKVRNYLTRKPYSTRKVKLN FGNSQLLSGWDRNKEKDNNSCVILRKGGQNFYLAIMNN RHKRSFENKMLPEYKEGEPYFEKMDYKFLPDPNKML PKVFLSKKGIIEYKPSPKLLEQYGHGTHKKGDTFSMD DLHELIDFFKHSIEAHEDWKQFGFKFSDTATYENVSSF YREVEDQGYKLSFRKVSESYVYSLIDQGKLYLFQIYN KDFSPCSKGTPLNHTLYWRMLFDERNLADVYKLDG KAEIFFREKSLKNDHPTHAPAGKPIKKSRQKKGEESLF EYDLVKDRRYTMDKFQFHPITMNFKCSAGSKVNDM VNAHIREAKDMHVIGIDRGERNLLYICVIDSRGTILDQI SLNTINDIDYHDLLESRDKDRQQEHRNWQTIEGIELK QGYLSQAVHRIAELMVAYKAVVALEDLNMGFKRGR QKVESVYQQFEKQLIDKLNLYLVDKKKRPEDIGLLR AYQFTAPFKSFKEMGKQNGFLFYIPAWNTSNIDPTTGF VNLFHVQYENVDKAKSFFQKFDSISYNPKKDWFEFAF DYKNFTKKAEGSRSMWILCTHGSRIKNFRNSQKNGQ WDSEEFALTEAFKSLFVRYEIDYTADLKTIVDEKQK DFFVDLLKLFKLTVMRNSWKEKDLDYLISPVAGAD GRFFDTREGNKSPLKADANGAYNIALKGLWALRQI RQTSEGGKLLAISNKEWLQFVQERSYEKD	SEQ ID NO: 31
BpCpf1	MLLYENYTKRNQITKSLRLELRPQGKTLRNIKELNLE QDKAIYALLERLKPVIDEGIKDIARDTLKNCELSFEKL	SEQ ID NO: 32

	YEHFLSGDKKAYAKESERLKKEIVKTLIKNLPEGIGKI SEINSAKYLNGVLYDFIDKTHKDSEEKQNILSDILETK GYLALFSKFLTSRITTLEQSMPCRVIENFEIYAANIPKM QDALERGAVSFAIEYESICSDYNNQILSQEDIDSYNR LISGIMDEDGAKEKGINQTISEKNIKIKSEHLEEKPFRL KQLHKQILEEREKAFTIDHIDSDEEVVQVTKEAFEQTK EQWENIKKINGFYAKDPGDITLFIVVGPNQTHVLSQLI YGEHDRIRLLLEEYEKNTLEVLPRRTKSEKARYDKFV NAVPPKVAKESHTFDGLQKMTGDDRLFILYRDELAR NYMRIKEAYGTFERDILKSRRGIKGNRDVQESLVSFY DELTKFRSALRIINSGNDEKADPIFYNTFDGIFEKANRT YKAENLCRNYVTKSPADDARIMASCLGTPARLRTHW WNGEENFAINDVAMIRRGDEYYYFVLTPDVKPVDLK TKDETDQIFVQRKGAKSFLGLPKALFKCILEPYFESP EHKNDKNCVIEEYVSKPLTIDRRAYDIFKNGTFKKTNI GIDGLTEEKFKDDCRYLIDVYKEFIAVYTRYSCFNMS GLKRADEYNDIGEFSDDVDTRLCTMEWIPVSFERIND MVDKKEGLLFLVRSMFLYNRPKPYERTFIQLFSDSN MEHTSMLLNSRAMIQYRAASLPRRVTHKKGSILVALR DSNGEHIPMHIREAIYKMKNNFDISSEDFIMAKAYLAE HDVAIKKANEDIIRNRRYTEDKFFLSLSYTKNADISAR TLDYINDKVEEDTQDSRMAVIVTRNLKDLTYVAVVD EKNNVLEEKSLNEIDGVNYRELLKERTKIKYHDKTRL WQYDVSSKGLKEAYVELAVTQISKLATKYNAVVVVE SMSSTFKDKFSFLDEQIFKAPEARLCARMSDLSFNTIK EGEAGSISNPIQVSNNNGNSYQDGVYIFLNNAYTRTLC PDTGFVDVFDKTRLITMQSKRQFFAKMKDIRIDDGEM LFTFNLEEYPTKRLLDRKEWTVKAGDGSYFDKDKGE YVYVNDIVREQIIPALLEDKAVFDGNMAEKFLDKTAIS GKSVELIYKWFANALYGIITKKDGEKIYRSPITGTEIDV SKNTTYNFGKKFMFKQEYRGDGDFLDAFLNYMQAQ DIAV	
LiCpf1	MEDYSGFVNIYSIQKTLRFELKPVGKTLEHIEKKGFLK KDKIRAEDYKAVKKIIDKYHRAYIEEVFDSVLHQKKK KDKTRFSTQFIKEIKEFSELYYKTEKNIPDKERLEALSE KLRKMLVGAFKGEFSEEVAEKYKNLFSKELIRNEIEKF CETDEERKQVSNFKSFTTYFTGFHSNRQNIYSDEKKST AIGYRIIHQNLPKFLDNLKIIESIQRRFKDFPWSDLKKN LKKIDKNIKLTEYFSIDGFVNVLNQKGIDAYNTILGGK SEESGEKIQGLNEYINLYRQKNNIDRKNLPNVKILFKQI LGDRETKSFIPEAFPDDQSVLNSITEFAKYLKLDKKKK SIIAELKKFLSSFNRYEYLDGIYLANDNSLASISTFLFDD WSFIKKSVSFKYDESVGDPKKKIKSPLKYEKEKEKWL	SEQ ID NO: 33

	KQKYTTISFLNDAIESYSKSQDEKRVKIRLEAYFAEFK SKDDAKKQFDLLERIEEAYAIVEPLLGAEYPRDRNLK ADKKEVGKIKDFLDSIKSLQFFLKPLLSAEIFDEKDLGF YNQLEGYYEEIDSIGHLYNKVRNYLTGKIYSKEKFKL NFENSTLLKGWDENREVANLCVIFREDQKY YLGVMD KENNTILSDIPKVKPNELFYEKMVYKLIPTPHMQLPRII FSSDNL SIYNPSKSILKIREAKSFKEGKNFKLKDCHKFI DFYKESISK NEDWSRFDKFSKTSSYENISEFYREVER QGYNLDFKKVSKFYIDSLVEDGKLYLFQIYNKDFSIFS KGKPNLHTIYFRSLFSKENLKD VCLKLNGEAEMFFRK KSINYDEKKKREGHHPELFEKLKYPILKDKRYSEDKF QFHLPISLNFKSKERLNFNLKVNEFLKRNKDINIIGIDR GERNLLYLVMINQKGEILKQTLLDSMQSGKGRPEINY KEKLQEKEIERDKARKSWGTVENIKELKEGYLSIVIHQ ISKLMVENNAIVVLEDLNIGFKRGRQKVERQVYQKFE KMLIDKLNFLVFKENKPTEPGGVLKAYQLTDEFQSFE KLSKQTGFLFYVPSWNTSKIDPRTGFIDFLHPAYENIE KAKQWINKFDSIRFNSKMDWFEFTADTRKFSENLML GKNRVWVICTTNVERYFTSKTANSSIQYNSIQITEKLK ELFVDIPFSNGQDLKPEILRKND AVFFKSLLFYIKTTLS LRQNNGKKGEEKDFILSPVVD SKGRFFNSLEASDDEP KDADANGAYHIALKGLMNLLVLNETKEENLSRPKWK IKNKDWLEFVWERNR	
PmCpf1	MKTQHFFEDFTSLYSLSKTIRFELKPIGKTLENIKKNGL IRRDEQRLDDYEKLKKVIDEYHEDFIANILSSFSFSEEIL QSYIQNLSESEARAKIEKTMRDTLAKAFSEDERYKSIF KKELVKKDIPVWCPAYKSLCKKFDNFTTSLVPFHENR KNLYTSNEITASIPYRIVHVNLPKFIQNIEALCELQKKM GADLYLEMMENLRNVWPSFVKTPDDL CNLKTYNHL MVQSSISEYNRFVGGYSTEDG TKHQGINEWINIYRQR NKEMRLPGLVFLHKQILAKVDSSSFISDTLEND DQVFC VLRQFRKLFWNTVSSKEDDAASLKDLCGLSGYDPEA IYVSDAHLATISKNIFDRWNYISDAIRRKTEVLMPRKK ESVERYAEKISKQIKKRQSYSLAELDDLLAHYSEESLP AGFSLLSYFTSLGGQKYL VSDGEVILYEEGSNIWDEV L IAFRDLQVILDKDFTEKKLGKDEEAVSVIKKALDSALR LRKFFDLLSGTGAEIRRDSSFYALYTDRMDKLKGLLK MYDKVRNYLTKKPYSIEKFKLHFDNPSLLSGWDKNK ELNNLSVIFRQNGYYL GIMTPKGKNLFKTLPKLGAE EMFYEKMEYKQIAEPMLMLPKVFFPKKTKPAFAPDQS VVDIYNKKTFKTGQKGFNKKDL YRLIDFYKEALT VHE WKLNFNFSFPTEQYRNIGE FFDEVREQAYKVS MNVP ASYIDEAVENGKLYLFQIYNKDFSPYSKGIPNLHTLYW	SEQ ID NO: 34

	KALFSEQNQSRVYKLCGGGELFYRKASLHMQDTTVH PKGISIHKKNLNKKGETSLFNVDLVKDKRFTEDKFFFH VPISINYKNKKITNVNQMVVDYIAQNDDLQIIGIDRGE RNLLYISRIDTRGNLLEQFSLNVIESDKGDLRTDYQKIL GDREQERLRRRQEWKSIESIKDLKDGYSQVVHKICN MVVEHKAIVVLENLNLFSMKGRKKVEKSVYEKFERM LVDKLNYLVVDKKNLSNEPGGLYAAYQLTNPLFSFEE LHRYPQSGILFFVDPWNTSLTDPSTGFVNLLGRINYTN VGDARKFFDRFNIRYDGGKGNILFDLDLSRFDVVRVET QRKLWTLTTFGSRIAKSKKSGKWMVERIENLSLCFLE LFEQFNIGYRVEKDLKKAILSQDRKEFYVRLIYLFNLM MQIRNSDGEEDYILSPALNEKNLQFDSRLIEAKDLPVD ADANGAYNVARKGLMVVQRIKRGDHESIHRIGRAQW LRYVQEGIVE	
Lb2Cpf1	MYYESLTKQYPVSKTIRNELIPIGKTLDNIRQNNILESD VKKRQNYEHVKGILDEYHKQLINEALDNCTLPCLKIA AEIYLKNQKEVSDREDFNKTQDLLRKEVVEKLKAHE NFTKIGKKDILDLEKLPSISEDDYNALESFRNFYTYFT SYNKVRENLYSDKEKSSTVAYRLINENFPKFLDNVKS YRFVKTAGILADGLGEEEQDSL FIVETFNKTLTQDGID TYNSQVGKINSSINLYNQKNQKANGFRKIPKMKMLY KQILSDREESFIDEFQSDEVLDNVESYGSVLIESLKSSK VS AFFDALRESKGKNVYVKNDLAKTAMSNIVFENWR TFDDLLNQEYDLANENKKKDDKYFEKRQKELKKNKs YSLEHLCNLSEDS CNLIENYIHQISDDIENIIINNETFLRI VINEHDRSRKLAKNRKAVKAIKDFLDSIKVLERELKLI NSSGQELEKDLIVYSAHEELLVELKQVDSL YNMTRNY LTKKPFSTEKVKLNFNRRSTLLNGWDRNKETDNLGVLL LKDGKYYLGIMNTSANKAFVNPPVAKTEKVFKKVDY KLLPVPNQMLPKVFFAKSNIDFYNPSSEIYSNYKKGTH KKGNMFSLEDCHNLIDFFKESISKHEDWSKFGFKFSDT ASYNDISEFYREVEKQGYKLTYTDIDETYINDLIERNE LYLFQIYNKDFSMYSGKGLNLHTLYFMMLFDQRNID DVVYKLNGEAEVFYRPASISEDELIHKAGEEIKNKNP NRARTKETSTFSYDIVKDKRYSKDKFTLHIPITMNFV DEVKRFND AVNSAIRIDENVNVIGIDRGERNLLYVVVI DSKGNILEQISLNSIINKEYDIETDYHALLDEREGGRDK ARKDWNTVENIRD LKAGYLSQVVNVVAKLVLKYNAI ICLEDLNF GFKRGRQKVEKQVYQKFEKMLIDKLNLYLV IDKSREQTSPKELGGALNALQLTSKFKSFKELGKQSGV IYYVPAYLTSKIDPTTG FANLFYMKCENVEKSKRFFD GFD FIRFNALENVFEFGFDYRSFTQRACGINSKWTVCT NGERIIKYRNPDKNNMFDEKVVVVTD E MKNLFEQYK	SEQ ID NO: 35

	IPYEDGRNVKDMIISNEEAIFYRRLYRLLQQTLMQMRN STSDGTRDYIISPVKNKREAYFNSELSDGSVPKDADAN GAYNIARKGLWVLEQIRQKSEGEKINLAMTNAEWLE YAQTHLL	
PbCpf1	MENIFDQFIGKYSLSKTLRFELKPVGKTEDFLKINKVF EKDQTIDDSYNQAKFYFDSLHQKFIDAALASDKTSELS FQNFADVLEKQNKIILDKKREMGALRKRDKNVAVGID RLQKEINDAEDIIQKEKEKIYKDVRTLFDNEAESWKTY YQEREVDGKKITFSKADLKQKGADFLTAAGILKVLKY EFPEEKEKEFQAKNQPSLFVEEKENPGQKRYIFDSFDK FAGYLTKFQQTKKNLYAADGTSTAVATRIADNFIIH QNTKVFRDKYKNNHTDLGFDEENIFEIERYKNCLLQR EIEHIKNENSYNKIIGRINKKIKEYRDQKAKDTKLTKS DFPFFKNLDKQILGEVEKEKQLIEKTREKTEEDVLIERF KEFIENNEERFTAACKLMNAFCNGEFESEYEGIYLKN KAINTISRRWFVSDRDFELKLPQQKSKNKSEKNEPKV KKFISIAEIKNAVEELDGDIFKAVFYDKKIIAQGGSKLE QFLVIWKYEFEYLFRDIERENGEKLLGYDSCLKIAKQL GIFPQEKEAREKATAVIKNYADAGLGIFQMMKYFSLD DKDRKNTPGQLSTNFYAEYDGYKDFEFIKYYNEFRN FITKKPFDEDKIKLNFENGALLKGWDENKEYDFMGVI LKKEGRLYLGIMHKNNHRKLFQSMGNAKGDNANRYQ KMIYKQIADASKDVPRLLTSSKAMEKFKPSQEILRIK KEKTFKRESKNFSLRDLHALIEYYRNCIPQYSNWSFYD FQFQDTGKYQNIKEFTDDVQKYGYKISFRDIDDEYINQ ALNEGKMYLFEVVNKDIYNTKNGSKNLHTLYFEHILS AENLNDPVFKLSGMAEIFQRQPSVNEREKITTQKNQCI LDKGDRAKYRRYTEKKIMFHMSLVLNTGKGEIKQV QFNKIINQRISSDNEMRVNVIGIDRGEKNLLYYSVVK QNGEIIQASLNEINGVNYRDKLIEREKERLKNRQSWK PVVKIKDLKKGYISHVIHKICQLIEKYSAIVVLEDLNM RFKQIRGGIERSVYQQFEKALIDKLGVLVFKDNRDLR APGGVLNGYQLSAPFVSFEKMRKQTGILFYTQAEYTS KTDPIGFRKNVYISNSASLDKIKEAVKKFDAIGWDG KEQSYFFKYNPYNLADEKYKNSTVSKAWAIFASAPRI RRQKGEDGYWKYDRVKVNEEFELLLKVNWFVNPKA TDIKQEIIKKEKAGDLQGEKELDGRLRNFWHSFIYLFN LVLELRNSFSLQIKIKAGEVIAVDEGVDFIASPVKPFIT TPNPYIPSNLCWLAVENADANGAYNIARKGVMILKKI REHAKKDPEFKLPNLFISNAEWDEAARDWGKYAGT TALNLDH	SEQ ID NO: 36
PeCpf1	MSNFFKNFTNLYELSKTLRFELKPVGDTLTNMKDHLE YDEKLQTFCLKDQNIDDAYQALKPQFDEIHEEFITDSLE	SEQ ID NO: 37

	SKKAKEIDFSEYLDLFQEKKELNDSEKKLRNKGIFTN KAGEKWKKEKYPQYEWKKGSKIANGADILSCQDML QFIKYKNPEDEKIKNYIDDTLKGFFTYFGGFNQNRAN YYETKKEASTAVATRIVHENLPKFCDNVIQFKHIIKRK KDGTVEKTERKTEYLNAYQYLKNNNKITQIKDAETEK MIESTPIAEKIFDVYYFSSCLSQKQIEEYNRIIGHYNLLI NLYNQAKRSEGKHLSENEKKYKDLPKFKTLYKQIGC GKKKDLFYTIKCDTEEEANKSRNEGKESHVSVEEIINKA QEAINKYFKSNNDCEINTVPDFINYILTKENYEGVY WSKAAMNTISDKYFANYHDLQDRLKEAKVFQKADK KSEDDIKIPEAIELSGLFGVLDLADWQTTLFKSSILSN EDKLIKITDSQTPSEALLKMIFNDIEKNMESFLKETNDII TLKKYKGNKEGTEKIKQWFDYTLAINRMLKYFLVKE NKIKGNSLDTNISEALKTLIYSDDAEWFKWYDALRNY LTQKPQDEAKENKLKLNFDNPSLAGGWDVNKECSNF CVILKDKNEKKYLAIMKKGENTLFQKEWTEGRGKNL TKKSNPLFEINNCEILSKMEYDFWADVSKMIPKCSTQL KAVVNHFQKQSDNEFIFPIGYKVTSGEKFREECKISKQD FELNNKVFNNKELSVTAMRYDLSSTQEKQYIKAFQKE YWELLFKQEKRDTKLTNNEIFNEWINFCNKKYSELLS WERKYKDALTWINFCKYFLSKYPKTTLFNYSFKESE NYNSLDEFYRDVDICSYKLNINTTINKSILDRLVEEGK LYLFEIKNQDSNDGKSIGHKNNLHTIYWNAIFENFDNR PKLNGEAEIFYRKAISKDKLGIVKGKKTNGTEIKNY RFSKEKFILHVPITLNFCSNNEYVNDIVNTKFYNFSNL HFLGIDRGEKHLAYYSLVNKNGEIVDQGTNLNLPFTDK DGNQRSIKKEKYFYNKQEDKWEAKEVDCWNYNDLL DAMASNRDMARKNWQRIGTIKEAKNGYVSLVIRKIA DLAVNNERPFAFIVLEDLNTGFKRSRQKIDKSVYQKFE LALAKKLNFLVDKNAKRDEIGSPTKALQLTPPVNNYG DIENKKQAGIMLYTRANYSQTDPATGWRKTIYLKA GPEETTYKKDGKIKNKSVDQIETFTDIGFDGKDYYF EYDKGEFVDEKTGEIKPKKWRLYSGENGKSLDRFRGE REKDKYEWKIDKIDIVKILDDLFDNFKNISLLKQLKE GVELTRNNEHGTGESLRFAINLIQQIRNTGNNERDNDF ILSPVRDENGKHFDSREYWDKETKGEKISMPSSGDAN GAFNIARKGIIMNAHILANSKDLSLFVSDEEWDLHL NNKTEWKKQLNIFSSRKAMAKRKK	
PdCpf1	MENYQEFTNLFQLNKTLRFELKPIGKTCELLEEGKIFA SGSFLEKDKVRADNVSYVKEIDKKHKIFIEETLSSFSI SNDLLKQYFDCYNELKAFKKDCKSDEEEVKKTALRN KCTSIQRAMREAIQAFKSPQKLLAIKNLIENVFKA DENVQHFSEFTSYFSGFETNRENFYSDDEEKSTSIAYRL	SEQ ID NO: 38

	VHDNLPIFIKNIYIFEKLKEQFDAKTLSEIFENYKLYVA GSSLDEVFSLEYFNNTLTQKGIDNYNAVIGKIVKEDKQ EIQGLNEHINLYNQKHKDRRLPFFISLKKQILSDREALS WLPDMFKNDSEVIKALKGFYIEDGFENNVLTPLATLL SSLDKYNLNGIFIRNNEALSSLSQNVYRNFSIDEAIDAN AELQTFNNYELIANALRAKIKKETKQGRKSFEKYEEYI DKKVKAIDSLSIQEINELVENYVSEFNSNSGNMMPRKVE DYFSLMRKGDGFSNDLIENIKTKLSAAEKLLGTKYQE TAKDIFKKDENSKLKELLDATKQFQHFIKPLLGTGEE ADRDLVFYGDFLPLYEKFEELTLLYNKVRNRLTQKPY SKDKIRLCFNKPKLMTGWVDSKTEKSDNGTQYGGYL FRKKNEIGEYDYFLGISSKAQLFRKNEAVIGDYERLDY YQPKANTIYGSAYEGENSYKEDKKRLNKVIIAYIEQIK QTNIKKSIIESISKYPNISDDDKVTPSSLLEKIKKVSIDSY NGILSFKSFQSVNKEVIDNLLKTISPLKNKAEFLDLINK DYQIFTEVQAVIDEICKQKTFIYFPISNVELEKEMGDK DKPLCLFQISNKDLSFAKTFSANLRKKRGAENLHTML FKALMEGNQDNLDLGSGAIFYRAKSLDGNKPTHAN EAIKCRNVANKDKVSLFTYDIYKNRRYMENKFLFHLS IVQNYKAANDSAQLNSSATEYIRKADDLHIIGIDRGER NLLYYSVIDMKGNIVEQDSLNIIRNNDLETDYHDLDD KREKERKANRQNWEAVEGIKDLKKGYLSQAVHQIAQ LMLKYNAIIALEDLGQMFVTRGQKIEKAVYQQFEKSL VDKLSYLVDKKRPYNELGGILKAYQLASSITKNNSDK QNGFLFYVPAWNTSKIDPVTGFTDLLRPKAMTIKEAQ DFFGAFDNISYNDKGYFEFETNYDKFKIRMKSAQTRW TICTFGNRIKRKKDKNYWNYEEVELTEEFKKLFKDSNI DYENCNLKEEIQNKDNRKFFDDLIKLLQLTLQMRNSD DKGNDYIISPVANAEGQFFDSRNGDKKLPLDADANGA YNIARKGLWNIRQIKQTKNDKKLNLSISSTEWLDVFR EKPYLK	
MbCpf1	MLFQDFTHLYPLSKTVRFELKPIDRTLEHIHAKNFLSQ DETMADMHQKVKVILDDYHRDFIADMMGEVKLTKL AEFYDVYLKFRKNPKDDELQKQLKDLQAVLRKEIVK PIGNNGGKYKAGYDRLFGAKLFDGKELGDLAKFVIA QEGESSPKLAHLAHFEKFSTYFTGFHDNRKNMYSDED KHTAIA YRLIHENLPRFIDNLQILT TTIKQKHSALYDQIIN ELTASGLDVSLASHLDGYHKLLTQEGITAYNTLLGGIS GEAGSPKIQGINELINSHHNQHCHKSERIAKLRPLHKQI LSDGMSVSFLPSKFADDSEMCQAVNEFYRHYADVFA KVQSLFDGFDHQQKDGIIYVEHKNLNELSKQAFGDFA LLGRVLDGYVVDVNVNPEFNERFAKAKTDNAKAKLTK EKDKFIKGVHSLASLEQAIEHYTARHDDSVQAGKLG	SEQ ID NO: 39

	QYFKHGLAGVDNPIQKIHNNHSTIKGFLERERPAGER ALPKIKSGKNPEMTQLRQLKELLDNALNVAHFAKLLT TKTTLDNQDGNFYGEFGVLYDELAKIPTLYNKVRDYL SQKPFSTEKYKLNFGNPTLLNGWDLNKEKDNFGVILQ KDGCCYYLALLDKAHKKVFDNAPNTGKSIYQKMIYKY LEVRKQFPKVFFSKEAIAINYHPSKELVEIKDKGRQRS DDERLKLRYFILECLKIHPKYDKKFEGAIGDIQLFKKD KKGREVPISEKDLFDKINGIFSSKPKLEMEDFFIGEFKR YNPSQDLVDQYNIYKKIDSNDNRKKENFYNNHPKFK KDLVRYYYESMCKHEEWEESEFFSKKLQDIGCYVDV NELFTEIETRRLNYKISFCNINADYIDELVEQQQLYLFQ IYNKDFSPKAHGKPNLHTLYFKALFSEDNLADPIYKLN GEAQIFYRKASLDMNETTIHRAGEVLENKNPDNPKKR QFVYDIKDKRYTQDKFMLHVPITMNFVQGMТИKEF NKKVNQSIQQYDEVNVIGIDRGERHLLYLTVINSGEI LEQCSLNDITTASANGTQMTTPYHKILDKREIERLNAR VGWGEIETIKELKSGYLSHVVHQISQLMLKYNAIVVL EDLNFQFKRGRFKVEKQIYQNFENALIKKLNHLVLKD KADDEIGSYKNALQLTNNFTDLKSIGKQTGFLFYVPA WNTSKIDPETGFVDLLKPRYENIAQSQAFFGKFDKICY NADKDYFEFHIDYAKFTDKAKNSRQIWTICSHGDKRY VYDKTANQNKGAAKGINVNDELKSLFARHHINEKQP NLVMDICQNNDKEFHKSLMYLLKTLALRYSNASSD EDFILSPVANDEGVFFNSALADDTQPQNADANGAYHI ALKGLWLLNELKNSDDLNVKLAIDNQTWLNFAQNR	
EeCpf1	MNGNRSIVYREFVGVIPVAKTLRNLRPVGHTQEHIQ NGLIQEDELQEKSTELKNIMDDYYREYIDKSLSGVT DLDFTLFELMNLVQSSPSKDNKKALEKEQSKMREQI CTHLQSDSNYKNIFNAKLLKEILPDFIKNYNQYDVKD KAGKLETLALFNGFSTYFTDFFEKRKNVFTKEAVSTSI AYRIVHENSILFLANMTSYKKISEKALDEIEVIEKNNQ DKMGDWELNQIFNPDFYNMVLIQSGIDFYNEICGVVN AHMNLYCQQTKNNYNLFKMRKLHKQILAYTSTSFEV PKMFEDDMSVYNVAVNAFIDETEKGNIIGKLKDIVNKY DELDEKRIYISKDFYETLSCFMSGNWNLITGCVENFYD ENIHAKGKSKEEKVKKAVKEDKYKSINDVNDLVEKYI DEKERNEFKNSNAKQYIREISNIITDTETAHLEYDDHIS LIESEEKADEMKKRLDMYMNMYHWAKAFIVDEVLD RDEM FYSDIDDIYNILENIVPLYNRVRNYVTQKPYSK KIKLNFQSPTLANGWSQSKEFDNNAIILIRDNKYYLAIF NAKNKPKDKIIQGNSDKKNDNDYKKMVYNLLPGAN KMLPKVFLSKKGIETFKPSDYIISGYNAHKHIKTSNF DISFCRDLIDYFKNSIEKHAEWRYEFKFSATDSYSDIS	SEQ ID NO: 40

	EFYREVEMQGYRIDWTYISEADINKLDEEGKIYLFQIY NKDFAENSTGKENLHTMYFKNIFSEENLKDIIIKLNGQ AELFYRRASVKNPVKHKKDSVLVNKTYKNQLDNGD VVRIPDDIYNEIYKMYNGYIKESDLSEAAKEYLDKV EVRTAQKDIVKDYRYTVDKYFIHTPITINYKVTARNN VNDMVVKYIAQNDDIHVIGIDRGERNLIYISVIDSHGNI VKQKSYNILNNYDYKKKLVEKEKTREYARKNWKSIG NIKELKEGYISGVVHEIAMLIVEYNAILAMEDLNYGFK RGRFKVERQVYQKFESMLINKLNYFASKEKSVDEPGG LLKGYQLTYVPDNIKNLGKQCGVIFYVPAAFSTKIDPS TGFISAFNFKSISTNASRKQFFMQFDEIRYCAEKDMFSF GFDYNNFDTYNITMGKTQWTVYTNGERLQSEFNAR RTGKTKSINLTETIKLLEDNEINYADGHDIRIDMEKM DEDKKSEFFAQLLSLYKLTVMRNSYTEAAEQENGIS YDKIISPVINDEGEFFDSNYKESDDKECKMPKDADA NGAYCIALKGLYEVLKIKSEWTEGDFDRNCLKLPHAE WLDFIQNKRYE	
CmtCpf1	MNNYDEFTKLYPIQKTIRFELKPQGRTEHLETFNFFE EDRDRAEKYKILKEAIDEYHKKFIDEHLTNMSLDWNS LKQISEKYYKSREEKDKKVFLSEQKRMQRQEIVSEFKK DDRFDLFSKKLFSSELLKEEYKKGNGHQEIDALKSFDK FSGYFIGLHENRKNMYSYGDEITAISNRIVNENFPKFL DNLQKYQEARKKYPEWIIKAESALVAHNIKMDVEFSL EYFNKVLNQEGIQRYNLALGGYVTKSGEKMMLND ALNLAHQSEKSSKGRIHMTPLFKQILSEKESFSYIPDV TEDSQLLPSIGGFFAQIENDKDGNIFDRALELISSYAEY DTERIYIRQADINRVSNVIFGEWGTGGLMREYKADSI NDINLERTCKKVDKWLDSEKFDLSDVLEAIKRTGNND AFNEYISKMRTAREKIDAARKEMKFISEKISGDEESIHI KTL LDSVQQFLHFFNLFKARQDIPLDGAFYAEFDEVH SKLFAIVPLYNKVRNYLTKNLNTKKIKLNFKNPTLA NGWDQNKVYDYASLIFLRDGNYYLGIINPKRKKNIKF EQSGNGPFYRKMVYKQIPGPNKNLPRVFLTSTKGKK EYKPSKEIIEGYEADKHIRGDKFDLDFCHKLIDFFKESI EKHKDWSKFNFYFSPTESYGDISEFYLDVEKQGYRMH FENISAETIDEYVEKGD LFLFQIYNKDFVKAATGKKD MHTIYWNAAFSPENLQDVVVKLNGEAELFYRDKSDI KEIVHREGEILVNRTYNGRTPVPDKIHKKLTDYHNGR TKDLGEAKEYLDKVRYFKAHYDITKDRRYLNDKIYF HVPLTLNFKANGKKNLNMVIEKFLSDEKAHIIGIDRG ERNLLYYSIIDRSGKIIDQQSLNVIDGFDYREKLNQREI EMKDARQSWNAIGKIKDLKEGYLSKAVHEITKMAIQ YNAIVVMEELNYGFKRGRFKVEKQIYQKFENMLIDK	SEQ ID NO: 41

	MNYLVFKDAPDESPGGVLNAYQLTNPLESFAKLGKQ TGILFYVPAAAYTSKIDPTTGFVNLNTSSKTNAQERKE FLQKFESISYSAKDGGIFAFADYRKFGTSKTDHKNV WTAYTNGERMRYIKEKKRNELFDPSKEIKEALTSSGIK YDGGQNILPDILRSNNGLIYTMYSFIAAIQMRVYDG KEDYIISPIKNSKGEFFRTDPKRRELPIDADANGAYNIA LRGELTMRAIAEKFPDSEKMAKLELKHKDWFEFMQ TRGD	
BsCpf1	MYYQNLTKKYPVSKTIRNELPIGKTLENIRKNNILESD VKKRKQDYEHVKGIMDEYHKQLINEALDNYMLPSLNQ AAEIYLLKKHVDVEDREEFKKTQDLLRREVTGRLKEHE NYTKIGKKDILDLEKLPSISEEDYNALESFRNFYTYFT SYNKVRENLYSDEEKSSTVAYRLINENLPKFLDNIKS AFVKAAGVLADCEIEEQDALFMVETFNMTLTQEID MYNYQIGKVNSAINLYNQKNHKVEEFKKIPKMKVLY KQILSDREEVFIGEFKDDETLLSSIGAYGNVLMTYLKS EKINIFFDALRESEGKNVYVKNDSLKTMSNIVFGSWS AFDELLNQEYDLANENKKKDDKYFEKRQKELKKNKS YTLEQMSNLSKEDISPIENYIERISEDIEKICIYNGEFEKI VVNEHDSSRKLKSNIAVKVIKDYLDSEIKELHDIKLI NGSGQELEKNLVVYVGQEEALEQLRPVDSLNLTRN YLTKKPFSTEKVKLNFNKSTLLNGWDKNKETDNLGIL FFKDGKYYLGIMNTTANKAFVNPPAAKTENVFKKVD YKLLPGSNKMLPKVFFAKSNIGYYNPSTELYSNYKKG THKKGPSFSIDDCNLDIFFKESIKKHEDWSKFGFEFS DTADYRDISEFYREVEKQGYKLTFTDIDESYINDLIEK NELYLFQIYNKDFSEYSKGKLNHLTYFMMLFDQRNL DNVVYKLNGEAEVFYRPASIAENELVIHKAGEGIKKN NPNRAKVKETSTFSYDIVKDKRYSKYKFTLHIPITMNF GVDEVRRFNDVINNALRTDDNVNVIGIDRGERNLLYV VVINSEKILEQISLNSIINKEYDIETNYHALLDEREDD RNKARKDWNTEINIKELKTGYLSQVVNVVAKLVLY NAIICLEDLNFQFKRGRQKVEKQVYQKFEKMLIEKLN YLVIDKSREQVSPEKMGGALNALQLTSKFKSFAELGK QSGIYYVPAYLTSKIDPTTGFVNLFYIKYENIEKAKQF FDGFDIFRNFKNKDDMFESFDYKSFTQKACGIRSKWIV YTNGERIIKYPNPEKNNLFDEKVINVTDEIKGLFKQYRI PYENGEDIKEIIISKAADFYKRLFRLHQLQMRNSTS DGTRDYIISPVKNDRGEFFCSEFSEGTPMKDADANGA YNIARKGLWVLEQIRQKDEGEKVNLSMTNAEWLKYA QLHLL	SEQ ID NO: 42
BhCas12b	MGIHGVPAAAATRSFILKIEPNEEVKKGLWKTHEVLNH GIAYYMNILKLIRQEAIYEHHEQDPKNPKKVSKEIQA	SEQ ID NO: 43

	ELWDFVLKMQKCNSFTHEVDKDEVFNILRELYEELVP SSVEKKGEANQLSNKFLYPLVDPNSQSGKGTASSGRK PRWYNLKIAGDPSWEEEEKKKWEEDKKKDP LAKILGK LAEYGLIPLFIPYTD SNEPIVKEIKWMEKSRNQSVRRL DKDMFIQALERFLSWESWNLKVKEEY EKVEKEYKTL EERIKEDIQALKALEQYEKERQEQLLRDTLNTNEYRLS KRGLRGWREIIQKWLKMDENEPSEKYLEVFKDYQRK HPREAGDYSVYEFLSKKENHFIWRNHPEYPYLYATFC EIDKKKKDAKQQATFTLADPINHPLWVRFEERSGSNL NKYRILTEQLHTEKLKKKLT VQLDRLIYPTESGGWEE KGKVDIVLLPSRQFYNQIFLDIEEKGKHAFTYKDESIK FPLKGT LGGARVQFDRDHLRRYPHKVESGNVGRIYFN MTVNIEPTESPVSKSLKIHRDDFPKV VNFKPKELTEWI KDSKGKKL KSGIESLEIGLRVMSIDLGQRQAAAASIFE VVDQKPDIEGKLFFPIKGT ELYAVHRASFNIKLPGETL VKSREVL RKAREDNLKLMNQKLNFLRNVLHFQQFED ITEREKRVTKWISRQENS DVPLVYQDELIQIRELMYKP YKDWVAF LKQLHKRLEVEIGKEVKHWRKSLSDGRK GLYGISLKNIDEIDRTRKFLLRWSLRPTEPGEVRRLEPG QRFAIDQLNHLNALKEDRLKKMANTIIMHALGYCYD VRKKKWQA KNPACQIILFEDLSNYPY GERSRFENS R LMKWSRREIPRQVALQGEIYGLQVGEVGAQFSSRFHA KTGSPGIRCRVVTKEKLQDN RFFKNLQREGRLTLDKI AVLKEGDL YPDKGGEKFISLSKDRKCVTTHADINAAQ NLQKRFWTRTHGFYKVYCKAYQVDGQTVYIPESKDQ KQKIIEEFGEGYFILKDG VYEWVNAGK LKIKKGSSKQ SSSELVDS DILKDSFDLASELKGEKLMLYRDP SGNVFP SDKWMAAGVFFGKLERILISKLTNQYSISTIEDDSSKQ S	
AkCas12b	MAVKSIVKLRLSECPDILAGMWQLHRATNAGVRY Y TEWVSLMRQEILYSRGP DGGQQCYMTAEDCQRELLR RLNRQLHNGRQDQP GTDADLLAISRRLYEILVLQSIG KRGDAQQIASSFLSPLVDPNSKGGRGEAKSGRKPAWQ KMRDQGDPRWVAAREKYEQRKA VDPSKEILNSLDAL GLRPLFAVFTET YRSQVDWKPLGKSQGVRTWDRDMF QQALERLMSWESWNRRV GEEYARLFQQKMKFEQEH FAEQSHLVKLARALEADMRAASQGFEAKRGTAHQIT RRALRGADR VFEIWKSIPEEALFSQYDEVIRQVQAEKR RDFGSHDLFAKLAEPKYQPLWRADETFLTRYALYNG VLRDLEKARQFATFTLP DACVNPIWTRFESSQGSNLH KYEF LFDHLGPGRHAVRFQRL LVVESEGA KERDSVV VPVAPSGQLDKLV LREEEKSSVALHLHDTARPDGFM AEWAGAKLQYERSTLARKARRDKQGMRSWRRQPSM	SEQ ID NO: 44

	LMSAAQMLEDKQAGDVYLNISVRVKSPSEVRGQRR PPYAALFRIDDKQRRVTVNYNKLSAYLEEHPDKQIPG APGLLSGLRVMSVDLGLRTSASISVFRVAKKEEVEAL GDGRPPHYYPHGTDDLVAVHERSHLIQMPGETETKQ LRKLREERQAVLRPLFAQLALLRLLVRCGAADERIRT RSWQRLTKQGREFTKRLTPSWREALELELTRLEAYCG RVPDDEWSRIVDRTVIALWRRMGKQVRDWRKQVKS GAKVKVKGYQLDVVGGNSLAQIDYLEQQYKFLRRW SFFARASGLVVRADRESHFAVALRQHIEENAKRDRLKK LADRILMEALGYVYEASGPREGQWTAQHPPCQLIILE ELSAYRFSDDRPPSENSKLMAWGHRGILEELVNQAQV HDVLVGTVYAAFSSRFDARTGAPGVRCRRVPARFVG ATVDDSLPLWLTEFLDKHRLDKNLLRPDDVIPTGEGE FLVSPCGEEAARVRQVHADINAAQNLQRRLWQNFDIT ELRLRCDVKMGEGTVLVPRVNNARAKQLFGKKVL VSQDGVTTFFERSQTGGKPHSEKQTDLTDKELELIAEA DEARAKSVVLFRDPSGHIGKGHWIRQREFWSLVKQRI ESHTAERIRVRGVGSSLD	
BsCas12b	MAIRSIKCLKTHTGPEAQNLRKGIWRTHRLNEGVA YYMKMLLLFRQESTGERPKEELQEELICHIREQQQRN QADKNTQALPLDKALEALRQLYELLVPSSVGQSGDA QIISRKFLSPLVDPNSEGGKGTSKAGAKPTWQKKKEA NDPTWEQDYEKWKKRREEDPTASVITTEEYGIRPIFP LYTNTVTDIAWLPLQSNQFVRTWDRDMLQQAIERLLS WESWNKRVQEYAKLKEKMAQLNEQLEGGQEWISL LEQYEENRERELRENMTAANDKYRITKRQMKGWNEL YELWSTFPASASHEQYKEALKRVQQRLRGRFGDAH FQYLMEEKNRLIWKGPNQRIHYFVARNELTKRLEEAK QSATMTLPNARKHPLWVRFDARGGNLQDYILTAEA DKPRSRRFVTFSQLIWPSESGWMEKKDVEVELALS FYQQVKLLKNDKGKQKIEFKDKGSGSTFNGHLGGAK LQLERGDLEKEEKNFEDGEIGSVYLVNVIDFEPLQEVK NGRVQAPYGQVLQLIRRPNEFPKVTTYKSEQLVEWIK ASPQHSAGVESLASGFRVMSIDLGLRAAAATSIFSVEE SSDKNAADFSYWIEGTPLVAVHQRSYMLRLPGEQVE KQVMEKRDERFQLHQRVKFQIRVLAQIMRMANKQY GDRWDELDSLKQAVEQKKSPLDQTDRTFWEGIVCDL TKVLPRNEADWEQAVVQIHRKAEEYVGKAVQAWRK RFAADERKGIAGLSMWNIEELEGLRKLLISWSRRTN PQEVNRFERGHQSHQRLTHIQNVKEDRLKQLSHAIV MTALGYVYDERKQEWCAEYPACQVILFENLSQYRSN LDRSTKENSTLMKWAHRSIPKYVHMQAEPYGIQIGDV RAEYSSRFYAKTGTGIRCKKVRGQDLQGRRFENLQK	SEQ ID NO: 45

	RLVNEQFLTEEQVKQLRPGDIVPDDSGELFMTLTDGS GSKEVVFLQADINAAHNLQKRFWQRYNELFKVSCRVI VRDEEEYLVPKTKSVQAKLGKGLFVKKSDTAWKDV YVWDSQAKLKGGKTTFTTESESPEQLEDFQEIIIEAEEA KGTYRTLFRDPSGVFFPESVWYPQKDFWGEVVKRKL Y GKLRERFLTKAR	
AmCas12b	MNVAVKSIKVKLMLGHLPEIREGLWHLHEAVNLGVR YYTEWLALLRQGNLYRRGKDGAQECYMTAEQCRQE LLVRLRDRQKRNGHTGDPGTDEELLGVARRLYELLV PQSVGKKGQAQMLASGFLSPLADPKSEGKGTSGS RKPAWMGMKEAGDSRWVEAKARYEANKAKDPTKQ VIASLEMYGLRPLFDVFTETYKTIRWMPLGKHQGVRA WDRDMFQQSLERLMSWESWNERVGAEFARLVDRRD RFREKHFTGQEHLVALAQRLEQEMKEASPGFESKSSQ AHRITKRALRGADGIIDDWLKLSEGEVPDRFDEILRKR QAQNPRRFGSHDLFLKLAEPVFQPLWREDPSFLSRWA SYNEVLNKLEDAKQFATFTLPSPCSNPVWARFENAEG TNIFKYDFLFDHFHGKGRHGVRFQRMIVMRDGVPTVE GIVVPIAPSRQLDALAPNDAASPIDVFVGDPAPGAFR GQFGGAKIQYRRSALVRKGRREEKAYLCGFRLPSQRR TGTPADDAGEVFLNLSLRVESQSEQAGRRNPPYA AVF HISDQTRRVIVRYGEIERYLAEHPDTGIPGSRGLTSGLR VMSVDLGLRTSAAISVFRVAHRDELTPDAHGRQPFFF PIHGMDHLVALHERSHLIRLPGETESKKVRSIREQRLD RLNRLRSQMASLRLLVRTGVLDEQKRDRNWERLQSS MERGGERMPSDWWDLFQAQVRYLAQHRDASGEAW GRMVQAAVRTLWRQLAKQVRDWRKEVRRNADKVK IRGIARDVPGGHSALAQLDYLERQYRFLRSWSAFSVQA GQVVRAERDSRFAVALREHIDNGKKDRLKKLADRIL MEALGYVYVTDGRRAGWQAVYPPCQLVLLEELSE YRFSNDRPPSENSQLMVWVSHRGVLEELIHQAQVHDV LVGTIPAAFSSRFDARTGAPGIRCRRVPSIPLKDAPSIPI WLSHYLKQTERDAAALRPGELIPTGDGEFLVTPAGRG ASGVRVVHADINAAHNLQRRLLWENFDLSDIRVRCR REGKDGTVVLPRLTNQRVKERYSGVIFTSEDGVSFTV GDAKTRRRSSASQGEGDDLSDEEQELLA EADDARERS VVLFRDPSGFVNGGRWTAQRAFWGMVHNRIETLLAE RFSVSGAAEKVRG	SEQ ID NO: 46
AaCas12b	MAVKSMKVKLRLDNMPEIRAGLWKLHTEVNAGVRY YTEWLSLLRQENLYRRSPNGDGEQECYKTAEECKAE LLERLRARQVENGHCGPAGSDDELLQLARQLYELLVP QAIGAKGDAQQIARKFLSPLADKDAVGGGLGIAKAGN KPRWVRMREAGEPGWEEEEKAKAEARKSTDRTADVL	SEQ ID NO: 47

	RALADFGKPLMRVYTDSDMSSVQWKPLRKGQAVR TWDRDMFQQAIERMMSWESWNQRVGEAYAKLVEQ KSRFEQKNFVGQEHLVQLVNQLQQDMKEASHGLESK EQTAHYLTGRALRGSDKVFEKWEKLPDAPFDLYDT EIKNVQRRNTRRFGSHDLFAKLAEPKYQALWREDASF LTRYAVYNSIVRKLNHAKMFATFTLPDATAHPIWTRF DKLGGNLHQYTFLFNEFGEGRHAIRFQKLLTVEDGVA KEVDDVTVPISMSAQLDDLLPRDPHELVALYFQDYGA EQHLAGEFGGAKIQYRRDQLNHLHARRGARDVYLN SVRVQSQSEARGERRPPYAAVFRLVGDNHRAVHFD KLSDYLAHPDDGKLGSEGLLSGLRVMSVDLGLRTSA SISVFRVARKDELKPNSEGRVPFCFPIEGNENLVAVHE RSQLKLPGETESKDLRAIREERQRTLRLTQLAYLR LLVRCGSEDVGRRERSWAKLIEQPM DANQMTPDWRE AFEDELQKLKSLYGICGDREWTEAVYESVRRVWRHM GKQVRDWRKDVRSGERP KIRGYQKDVVGGNSIEQIE YLERQYKFLKSWSFSGKVSGQVIRAEKGSRFAITLREH IDHAKEDRLKKLADRIIMEALGYVYALDDER GKGKW VAKYPPCQLILLEELSEYQFNDRPPSENNQLMQWSH RGVFQELLNQAQVHDLLVGTMYAAFSSRFDARTGAP GIRCRRVPARCAREQNPEPFPWWLNKFVAEHKLDGC PLRADDLIPTGEGEFFVSPFSAEEGDFHQIHADLNAAQ NLQRRLWSDFDISQIRLRCDWGEVDGEPVLIPRTTGK RTADSYGNKVFYTKTGVTTYERERGGKRRKVFAQEE LSEEEAELLVEADEAREKSVVLMRDPSGIINRGDWTR QKEFWSMVNQRIEGLVKQIRSRVRLQESACENTGDI	
RfxCas13d	MIEKKKSFAKGMGVKSTLVSGSKVYMTTFAEGSDAR LEKIVEGDSIRSVNEGEAFSAEMADKNAGYKIGNAKF SHPKGYAVVANPLYTGVPVQQDMLGLKETLEKRYFG ESADGNDNICIQVIHNILDIEKILAEYITNAAYAVNNIS GLDKDIIGFGKFSTVYTYDEFKDPEHHRAAFNNNDKLI NAIKAQYDEFDNFLDNPRLG YFGQAFFSKEGRNYIINY GNECYDILALLSGLRHWV VHNNEEESRISRTWLYNLD KNLDNEYISTLNYLYDRITNELTNSFSKNSAANVNYIA ETLGINPAEFAEQYFRFSIMKEQKNLGFNITKLREV ML DRKDMSEIRKNHKVFDSIRTKVYTMMD FVIYRYIEE DAKVAAANKSLPDNEKSLSEKDIFVINLRGSFNDDQK DALYYDEANRIWRKLENIMHNIKEFRGNKTREYKKK DAPRLPRILPAGRDVSAFSKLMYALTMFLDGKEINDL LTTLINKFDNIQSFLKVMPLIGVNAKFVEEYAFFKDSA KIADELRLIKSFARMGEPIADARRAMYIDAIRILGTNLS YDELKALADTFSLDENGK LKKGKHGM RNFIIINNVIS NKR FHYLIRYGDPAHLHEIAKNEAVVKFVLGRIADIQ	SEQ ID NO: 48

	KKQGQNGKNQIDRYYETCIGKDKGKSVSEKVDALTKI ITGMNYDQFDKKRSVIEDTGRENAEREKFKKIISLYLT VIYHILKNIVNINARYVIGFHCVERDAQLYKEKGYDIN LKKLEEKGFSSVTKLCAGIDETAPDKRKDVEKEMAER AKESIDSLESANPKLYANYIKYSDEKKAEEFTRQINRE KAKTALNAYLRNTKWNVIREDLLRIDNKTCTLFRNK AVHLEVARYVHAYINDIAEVNSYFQLYHYIMQRIIMN ERYEKSSGKVSEYFDAVNDEKKYNDRLLKLLCVPFG YCIPRFKNLSIEALFDRNEAAKFDKEKKKVSGN	
LwaCas13a	MKVTKVDGISHKKYIEEGKLVKSTSEENRTSERLSELL SIRLDIYIKNPDNASEEENRIRRENKKFFSNKVLHLKD SVLYLKNRKEKNAVQDKNYSEEDISEYDLKNKNSFSV LKKILLNEDVNSEELEIFRKDVEAKLNKINSLKYSFEE NKANYQKINENNVEKVGKSKRNIIYDYYRESAKRN DYINNVQEAFDKLYKKEDIEKLFFLIENSKKHEKYKIR EYYHKIIGRKNDKENFAKIIYEEIQNVNNIKELIEKIPD MSELKKSQVFYKYLDKEELNDKNIKYAFCHFVEIEM SOLLKNYVYKRLSNISNDKIKRIFEYQNLKKLIENKLL NKLDTYVRNCGKYNYYLQVGEIATSDFIARNRQNEAF LRNIIGVSSVAYFSLRNILETENENGITGRMRGKTVKN NKGEEKYVSGEVDKIYNENKQNEVKENLKMFSYDF NMDNKNEIEDFFANIDEAIISSIRHGIVHFNLELEGKDIF AFKNIAPSEISKMFQNEINEKKLKLKIFKQLNSANVF NYYEKDVIIKYLKNTKFNFVNKNIPFVPSFTKLYNKIE DLRNTLKKFFWSVPKDKEEKDAQIYLLKNIIYGEFLNK FVKNSKVFFKITNEVIKINKQRNQKTGHYKYQKFENIE KTVPVEYLAIQSREMINNQDKEEKNTYIDFIQQIFLKG FIDYLNKNLKYIESNNNDNDNDIFSKIKIKKDNKEY DKILKNYEKHNRNKEIPHEINEFVREIKLGKILKYTENL NMFYLILKLLNHKELTNLKGSLKEYQSANKEETFSDE LELINLLNLDNNRVTEDFELEANEIGKFLDFNENKID RKELKKFDTNKIYFDGENIIKHRAFYNIKKYGMLNLE KIADKAKYKISLKEKKEYSNKKNEIEKNYTMQQNLHR KYARPKKDEKFNDEDYKEYEKAIGNIQKYTHLKNKV EFNELNLLQGLLLKILHRLVGYTSIWERDLRFRLKGEF PENHYIEEIFNFDNSKNVKYKSGQIVEKYINFYKELYK DNVEKRSIYSDKKVKKLKQEKDLYIRNYIAHFNYIP HAEISLLEVLENLRKLLSYDRKLKNAIMKSIVDILKEY GFVATFKIGADKKIEIQTLESEKIVHLKNLKKKKLMTD RNSEELCELVKVMFEYKALE	SEQ ID NO: 49
PspCas13b	MNIPALVENQKKYFGTYSVMAMLNAQTVLDHIQKVA DIEGEQNENNENLWFHPVMSHLYNAKNGYDKQPEKT MFIIERLQSYFPFLKIMAENQREYSNGKYKQNRVEVN	SEQ ID NO: 50

	SNDIFEVLKRAFGVLKMYRDLTNHYKTYEEKLNDGC EFLTSTEQPLSGMINNYTVALRNMNERYGYKTEDLA FIQDKRFKFKDAYGKKKSQVNTGFFLSLQDYNGDT QKKLHLSGVGIALLICLFLDKQYINIFLSRLPIFSSYNA QSEERRIIIRSFGINSIKLPKDRIHSEKSNKSVAMDMLN EVKRCPDELFTTLSAEKQSRFRIISDDHNEVLMKRSSD RFVPLLLQYIDYGKLFDFHIRFHVNMGKLRYLLKADKT CIDGQTRVRVIEQPLNGFGRLEEAETMRKQENGTFGN SGIRIRDFENMKRDDANPANYPYIVDTYTHYLENNK VEMFINDKEDSAPLLPVIEDDRYVVKTIPSCRMSTLEIP AMAFHMFLLFGSKKTEKLIVDVHNRYKRLFQAMQKEE VTAENIASFGIAESDLPQKILDLISGNAHGKDVDADFIRL TVDDMLTDTERRIKRFKDDRKSIRSADNKMGRGFK QISTGKLADFLAKDIVLFQPSVNDGENKITGLNYRIMQ SAIAVYDSGDDYEAKQQFKLMFEKARLIGKGTTEPHP FLYKVFARSIPANAVEFYERYLIERKFYLTGLSNEIKK GNRVDVPFIRRDQNKWKTPAMKTLGRIYSEDLPVELP RQMGFDNEIKSHLKSLPQMEGIDFNNANVTYLIAEYMK RVLDDDFQTFYQWNRNYRYMDMLKGEYDRKGSQKH CFTSVEEREGLWKERASRTERYRKQASNKIRSNRQMR NASSEIETILDKRLSNSRNEYQKSEKVIRRYRVQDAL LFLAKKTLTELADFDGERFKLKEIMPDAEKGILSEIM PMSFTFEKGGKKYTITSEGMKLKNYGDFVFLASDKRI GNLLELVGSDIVSKEDIMEEFNKYDQCRPEISSIVFNLE KWAFTYPELSARVDREEKVDFKSILKILLNNKNINKE QSDILRKIRNAFDHNNYPDKGVVEIKALPEIAMSIIKA FGEYAIMKGSQ	
PguCas13b	MTEQSERPYNGTYTLEDKHFWA AFLNLARHNAYIT LTHIDRQLAYS KADITNDQDVL SFKALWKNFDNDLER KSRLRSLILKHFSFLEGAAYGKKLFESKSSGNKSSKNK ELTKKEKEELQANALSLDNLKSILFDFLQKLKDFRNY YSHYRHSGSSELPLFDGNMLQRLYNVFDVSVQRVKID HEHNDEVDPHYHFNHLVRKGKKDRYGHNDNPSFKH HFVDGEGMVTEAGLLFFVSLFLEKRDAIWMQKKIRGF KGGTETYQQMTNEVFCSRISLPKLLKESLRMDDWM LLDMLNELVRCPKPLYDRLREDDRACFRVPVDILPDE DDTDGGGEDPFKNTLVRHQDRFPYFALRYFDLKKVF TSLRFHIDLGTYHFAIYKKMIGE QPEDRHLTRNLYGFG RIQDFAEEHRPEEWKRLVRDLDYFETGDKPYISQTS PH YHIEKGKIGLRFMPEGQHLWPSPEVGTTTRTGRSKYAQ DKRLTAEAFLSVHELMPMMFYFLLREKYSEEVS AER VQGRIKRVIEDVYAVYDAFARDEINTRDELDA CLADK GIRRGHLPRQMIAILSQEHKDMEEKIRKKLQEMMADT	SEQ ID NO: 51

	DHRLDMLDRQTD RKIRIGRKNAGLPKSGVIADWLVR DMMRFQPVAKDASGKPLNNSKANSTEYRMLQRALA LFGGEKERLTPYFRQMNL TGGNNPHPFLHETR WESHT NILSFYRSYL RARKAFLERIGRSDRVENRPFLLLKEPKT DRQTLVAGWKGEFHLPRGIFTEAVRDCLIEMGHDEV ASYKEVGFMAKAVPLYFERACEDRVQPFYDSPFNVG NSLKPKKGRFLSKEERAEEWERGKERFRDLEAWSYS AARRIEDAFAGIEYASPGNKKKIEQLLRDLSLWEAFES KLKVRADRINLAKLKKEILEAQEHYPYHDFKSWQKFER ELRLVKNQDIITWMMCRDLMEENKVEGLDTGTLYLK DIRPNVQEQGSLNVLNRVKPMRLPVVVYRADSRGHV HKEEAPLATVYIEERDTKLLKQGNFKSFVKDRRLNGL FSFVDTGGLAMEQYPISKLRVEYELAKYQTARVCVFE LTLRLEESLLTRYPHLPDES FREMLESWSDPLLAKWPE LHGKVRLLIAVRNAFSHNQYPMYDEAVFSSIRKYDPS SPDAIEERMGLNIAHRLSEEVKQAKETVERIIQAGSLQ	
RanCas13b	MEKPLLPNVYTLKHKFFWGAFLNIARHNAFITICHINE QLGLKTPSNDDKIVDVVCETWNNILNNDHDLKKSQ LTEILKHFPFLTAMCYHPPKKEGKKKGHQKEQQKEK ESEAQSQA EALNPSKLEALEILVNQLHSLRNYYSHYK HKKPDAEKDIFKHL YKAFDASLRMVKEDYKAHFTVN LTRDFAHLNRKGKNKQDNPDFNRYRFEKDGFFTESGL LFFTNLFLDKRDAYWMLKKVSGFKASHKQREKMTTE VFCRSRILLPKLRLESRYDHNQMLLDMLSELSRCPKLL YEKLSEENKKHFQVEADGFLDEIEEEQNPFKDTLIRHQ DRFPYFALRYLDL NESFKSIRFQVDLGTYHYCIYDKKI GDEQEKRHLTRTLLSFGRLQDFTEINRPQEWKALT KD LDYKETS NQPFISKTTPHYHITDNKIGFRLGTSKELYPS LEIKDGANRIAKYPYNSGFVAHAFISVHELLPLMFYQH LTGKSEDLLKETVRHIQRIYKDFEEERINTIEDLEKANQ GRLPLGAFPKQMLGLLQNKQPD LSEKAKIKIEKLIAET KLLSHRLNTKLKSSPKLGKRREKLIK TGVLADWL VKD FMRFPQVAYDAQNQPIKSSKANSTEFWFIRRALALYG GEKNRLEGYFKQTNLIGNTNPHPFLNKFNWKACRNL VDFYQQYLEQREKFLEAIKNQPWEPYQYCLLLKIPKE NRKNLVKGWEQGGISLPRGLFTEAIRETLSEDMLSKP IRKEIKKHGRVGFISR AITLYFKEKYQDKHQSFYNLSY KLEAKAPLLKREEHYEYWQQNK PQSPTESQRLELHTS DRWKDYLLYKRWQHLEKKLRLYRNQDVMLWLMTL ELTKNHFKELNLNYHQLKLENLAVNVQEADAKLNPL NQTLPMVLPVKVYPATAFGEVQYHKTPIRTVYIREEH TKALKMGNFKALVKDRRLNGLFSFIKEENDTQKHPIS QLRLRRELEIYQSLRVDAFKETLSLEEKLLNKHTSLSS	SEQ ID NO: 52

	LENEFRALLEEWKKEYAASSMVTDEHIAFIASVRNAF CHNQYPFYKEALHAPIPLFTVAQPTTEEKDGLGIAEAL LKVLREYCEIVKSQIGSSLQKKLEELGSS	
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[00266] In some embodiments, the Cas protein is a nCas9. In some embodiments, the nCas9 protein is a nSpCas9-D10A protein or nSpCas9-H840A, comprising an amino acid sequence of SEQ ID NO: 3 or 4, respectively.

[00267] In some embodiments, the first protein-binding RNA motif and the first RNA binding domain, the second protein-binding RNA motif and the second RNA binding domain, and the third protein-binding RNA motif and the third RNA binding domain, are each independently selected from the group consisting of a MS2 phage operator stem-loop and MS2 coat protein (MCP) or an RNA-binding section thereof; a BoxB and N22P or an RNA-binding section thereof; a telomerase Ku binding motif and Ku protein or an RNA-binding section thereof; a telomerase Sm7 binding motif and Sm7 protein or an RNA-binding section thereof; a PP7 phage operator stem – loop and PP7 coat protein (PCP) or an RNA-binding section thereof; a SfMu phage Com stem-loop and Com RNA binding protein or an RNA-binding section thereof; and a non-natural RNA aptamer and corresponding aptamer ligand or an RNA-binding section thereof.

Table 5 Exemplary sequences of protein-binding RNA motifs and RNA binding domains

Name	Sequence	SEQ ID NO:
MS2 coat protein (MCP)	MASNFTQFVLVDNGGTGDVTVAPSNFANGIAEWISSN SRSQAYKVTC SVRQSSA QNRKYTIKVEVPKGAWRSY LNMELTIPIFATNSDCELIVKAMQGLLKDGNPIPSAIAA NSGIY	SEQ ID NO: 53
PP7 coat protein (PCP)	MGSKTIVLSVGEATRTLTEIQSTADRQIFEEKVGPLVGRLRL TASLRQNGAKTAYRVNLKLDQADVVD SGLPKVRYTQVWS HDVTIVANSTEASRKS LYDLTKSLVATSQVEDLVVNLVPL GR	SEQ ID NO: 54
boxB coat protein (N22p)	MGNARTRRRERRAEKQAQWKAAN	SEQ ID NO: 55
MS2	ACATGAGGATCACCCATGT	SEQ ID NO: 56
PP7	GGAGCAGACGATATGGCGTCGCTCC	SEQ ID NO: 57

boxB	GCCCTGAAGAAGGGC	SEQ ID NO: 58
Telomerase Ku binding motif	TTGTGTTTCTACTTATAGATGGCTAAAATCTGAGTT TAGAAAATGCAA	SEQ ID NO: 59
Telomerase Sm7 binding motif	AATTTTGGGA	SEQ ID NO: 60
SfMu	CTGAATGCCTGCGAGCATC	SEQ ID NO: 61
YKU70	MELDPDDVFRDEDEDPENDFFQEKEASKEFVVYLIDA SPKMFCSTCPSEEDKQESHFHIAVSCIAQSLKAHIINR SNDEIAICFFNTREKKNLQDLNGVYVFNVPERDSIDRP TARLIKEFDLIEESFDKEIGSQTGIVSDSRENSLYSALW VAQALLRKGS�KTADKRMFLFTNEDDPFGSMRISVKE DMTRTTLQRAKDAQDLGISIELLPLSQPDKQFNITLFY KDLIGLNSDELTEFMPSVGQKLEDMDQLKKRVLAK RIAKRITFVICDGLSIELNGYALLRPAIPGSITWLDSTTN LPVKVERSYICTDTGAIMQDPIQRIQPYKNQNMFTVE ELSQVKRISTGHLRLLGFKPLSCLKDYHNLKPSTFLYP SDKEVIGSTRAFIALHRSMIQLERFAVAFYGGTTPPRL VALVAQDEIESDGGQVEPPGINMIYLPYANDIRDIDEL HSKPGVAAPRASDDQLKKASALMRRELKDFSVCQF ANPALQRHYAILQAIALDENELRETRDETLPDEEGMN RPAVVKAIEQFKQSIYGDDPDEESDSGAKEKSKKRKA GDADDGKYDYIELAKTGKLDLTVVELKTYLTANNL LVSGKKEVLINRILTHIGK	SEQ ID NO: 62
YKU80	MSSESTTFIVDVSPSMMKNNNVSKSMAYLEYTLLNKS KKSRTDWISCYLANCPVSENSQEIPNVFQIQSFLAPV TTTATIGFIKRLKQYCDQHSHDSSNEGLQSMIQCLLV SLDIKQQFQARKILKQIVVFTDNLDDLITDEEIDLLTE ELSTRILIDCGKDTQEERKKS NWLKLVEAIPNSRIYN MNELLVEITSPATSVVKPVRVFSGELRLGADILSTQTS NPSGSMQDENCLCIKVEAFPATKAVSGLNRKTAVEVE DSQKKERYVGVKSIIEYEIHNEGNNKNVSEDDQSGSS YIPVTISKDSVTKAYRYGADYVVLPSVLVDQTVYESF PGLDLRGFLNREALPRYFLTSESSFITADTRLGCQSDL MAFSALVDVMLENRKIAVARYVSKKDSEVNMCALCP VLIEHSNINSEKKFVKS LTLCRLPFAEDERVTDFPKLLD	SEQ ID NO: 63

	RTTTSGVPLKKETDGHQIDELMEQFVDSMDTDELPEIP LGNYYPQIGEVTTDTTLPLPSLNKDQEENKKDPLRIPT VFVYRQQQVLEWQHQLMINDSREFEPELPDSLKNKI SPYTHKKFDSTKLVEVLGIKKVDKLDSELKTELER EKIPDLETLLKRGEQHSRGSPNNSNN	
Sm7-like protein	GSVIDVSSQRVNVQRPLDALGNSLNSPVIKLGKDREF RGVLKSFDLHMNLVLNDAAEELEDGEVTRRLGT	SEQ ID NO: 64
SfMu Com binding protein	MKSIRCKNCNKLLFKADSFHDHIEIRCPRCKRHIIMLNA CEHPTEKHCGKREKITHSDETVRY	SEQ ID NO: 65

[00268] In some embodiments of the gene editing system described herein, the mgRNA and/or the hgRNA comprises a dual-RNA structure.

[00269] In some embodiments, the dual-RNA structure is formed by a CRISPR RNA (crRNA) and a trans-activating crRNA (tracrRNA), wherein the crRNA comprises the spacer.

[00270] In some embodiments of the gene editing system described herein, the mgRNA comprises a mcrRNA and a first tracrRNA, and the mcrRNA comprises the mgRNA spacer, wherein the hgRNA comprises a hcrRNA and a second tracrRNA, and the hcrRNA comprises the hgRNA spacer, and wherein the first tracrRNA and the second tracrRNA are same or different.

[00271] In some embodiments, the mcrRNA and/or the hcrRNA is capable of binding to the *PCSK9* gene. In some embodiments, the mcrRNA and the hcrRNA are SEQ ID NO: 1112 and SEQ ID NO: 1111, respectively; or SEQ ID NO: 1114 and SEQ ID NO: 1113, respectively; or SEQ ID NO: 1116 and SEQ ID NO: 1115, respectively.

[00272] In some embodiments, the mcrRNA and/or the hcrRNA is capable of binding to the *ANGPTL3* gene. In some embodiments, the mcrRNA and the hcrRNA are SEQ ID NO: 1138 and SEQ ID NO: 1137, respectively; or SEQ ID NO: 1140 and SEQ ID NO: 1139, respectively; or SEQ ID NO: 1142 and SEQ ID NO: 1141, respectively.

[00273] In some embodiments, the tracrRNA is SEQ ID NO: 1117 and 1242.

[00274] In another aspect, the present disclosure provides a polynucleotide encoding the hgRNA and/or the mgRNA disclosed herein.

[00275] In another aspect, the present disclosure provides a polynucleotide encoding all components except the first and the second Cas protein in the gene editing system disclosed herein.

[00276] In another aspect, the present disclosure provides a polynucleotide encoding all components except the mgRNA and hgRNA in the gene editing system described herein.

[00277] In another aspect, the present disclosure provides a polynucleotide encoding all components except the mgRNA, hgRNA, and the first and second Cas proteins in the gene editing system described herein.

[00278] In another aspect, the present disclosure provides a kit comprising a polynucleotide encoding all components except the first and the second Cas protein in the gene editing system disclosed herein, and a polynucleotide encoding the first and/or second Cas protein in the gene editing system disclosed herein. In some embodiments, the first and the second Cas proteins are the same Cas protein.

[00279] In an aspect, the present disclosure provides a vector comprising the polynucleotide described herein. In another aspect, the present disclosure provides a vector comprising the polynucleotide encoding the hgRNA and/or the mgRNA disclosed herein.

[00280] In another aspect, the present disclosure provides a vector comprising the polynucleotide encoding all components except the first and the second Cas protein in the gene editing system disclosed herein.

[00281] In some embodiments, the vector is a plasmid, a viral vector, a non-viral vector or a lipid nanoparticle (LNP) vector.

[00282] In some embodiments, the vector is a polycistronic vector.

[00283] In some embodiments, the vector is an AAV vector.

[00284] In another aspect, the present disclosure provides a kit comprising the vector disclosed above, and a vector comprising the polynucleotide encoding the first and/or second Cas protein in the gene editing system disclosed herein.

[00285] In another aspect, the present disclosure provides a cell comprising the gene editing system disclosed herein.

[00286] In another aspect, the present disclosure provides a cell comprising the polynucleotide disclosed herein. In some embodiments, the cell further comprises a polynucleotide encoding the first and/or second Cas protein in the gene editing system disclosed herein.

[00287] In another aspect, the present disclosure provides a cell comprising the vector disclosed herein. In some embodiments, the cell further comprises a vector comprising a polynucleotide encoding the first and/or second Cas protein in the gene editing system disclosed herein.

[00288] In another aspect, the present disclosure provides a cell comprising the kit disclosed herein.

[00289] In another aspect, the present disclosure provides a composition comprising the gene editing system disclosed herein.

5 [00290] In another aspect, the present disclosure provides a composition comprising the cell disclosed herein.

[00291] In another aspect, the present disclosure provides a method for disrupting or regulating the expression of a gene selected from *PCSK9*, *ANGPTL3*, *ASGR1*, *LPA*, *AGT* and *APOC3* gene in a cell, comprising introducing into the cell the gene editing system disclosed
10 herein.

[00292] In some embodiments, the present disclosure provides a method for disrupting or regulating the expression of *PCSK9* gene in a cell, comprising introducing into the cell the gene editing system disclosed herein.

[00293] In some embodiments, the present disclosure provides a method for disrupting or
15 regulating the expression of *ANGPTL3* gene in a cell, comprising introducing into the cell the gene editing system disclosed herein.

[00294] In some embodiments, the present disclosure provides a method for disrupting or regulating the expression of *ASGR1* gene in a cell, comprising introducing into the cell the gene editing system disclosed herein.

20 [00295] In some embodiments, the present disclosure provides a method for disrupting or regulating the expression of *LPA* gene in a cell, comprising introducing into the cell the gene editing system disclosed herein.

[00296] In some embodiments, the present disclosure provides a method for disrupting or regulating the expression of *AGT* gene in a cell, comprising introducing into the cell the gene
25 editing system disclosed herein.

[00297] In some embodiments, the present disclosure provides a method for disrupting or regulating the expression of *APOC3* gene in a cell, comprising introducing into the cell the gene editing system disclosed herein.

[00298] In another aspect, the present disclosure provides a method for regulating Low-Density Lipoprotein cholesterol (LDL-C) metabolism in a subject, comprising introducing
30 into a cell of the subject the gene editing system disclosed herein.

[00299] In another aspect, the present disclosure provides a method for treating hypercholesterolemia in a subject, comprising introducing into a cell of the subject a therapeutically effective amount of the gene editing system disclosed herein.

[00300] In another aspect, the present disclosure provides a method for lowering LDL-C level in a subject, comprising introducing into a cell of the subject the gene editing system disclosed herein.

5 [00301] In another aspect, the present disclosure provides a method for regulating triglyceride-rich remnant particles and/or lipoprotein(a) (Lp(a)) metabolism in a subject, comprising introducing into a cell of the subject the gene editing system disclosed herein.

[00302] In another aspect, the present disclosure provides a method for regulating blood pressure in a subject, comprising introducing into a cell of the subject the gene editing system disclosed herein.

10 [00303] In another aspect, the present disclosure provides a method for reducing the expression of angiotensinogen in a subject, comprising introducing into a cell of the subject the gene editing system disclosed herein.

[00304] In another aspect, the present disclosure provides a method for treating hypertension in a subject, comprising introducing into a cell of the subject a therapeutically effective amount of the gene editing system disclosed herein.

15 [00305] In another aspect, the present disclosure provides a method for treating cardiovascular disease (CVD) in a subject, comprising introducing into the subject a therapeutically effective amount of the gene editing system disclosed herein. In some embodiments, the present disclosure provides a method for treating CVD, comprising
20 lowering blood lipid level with a method as disclosed herein, and/or lowering the level of circulating lipoprotein particles with a method disclosed herein, and/or lowering blood pressure with a method disclosed herein.

[00306] In some embodiments, the cardiovascular disease is associated with the expression of genes selected from *PCSK9*, *ANGPTL3*, *ASGR1*, *LPA*, *AGT* and *APOC3* gene.

25 [00307] In some embodiments, the cardiovascular disease is selected from atherosclerosis, congestive heart failure, peripheral vascular disease, cerebrovascular disease, rheumatic heart disease, arrhythmia, hypertension, and coronary artery disease.

[00308] In some embodiments, the cell as disclosed herein is a stem cell.

[00309] In some embodiments, the cell as disclosed herein is a pluripotent stem cell.

30 [00310] In some embodiments, the cell as disclosed herein is an embryonic stem cell (ESC).

[00311] In some embodiments, the cell as disclosed herein is an induced pluripotent stem cell (iPSC).

[00312] In some embodiments, the cell as disclosed herein is the cell is a somatic cell.

[00313] In some embodiments, the cell as disclosed herein is the cell is a hepatocyte.

[00314] In some embodiments, the cell as disclosed herein is a primary cell.

[00315] In some embodiments, the cell as disclosed herein is a differentiated cell.

5

BRIEF DESCRIPTION OF THE FIGURES

[00316] Figure 1 illustrates exemplary base editors that can be used in the gene editing systems disclosed herein. The various versions of base editors are denoted as V1, V2, V3, V4, and V5, with constructs denoted as tBE-V1-rA1, tBE-V2-rA1, tBE-V3-rA1, tBE-V4-rA1, tBE-V5-rA1, and tBE-V5-mA3. Figure 1A shows schematic diagrams illustrating the construction and development of various versions of base editors. Figure 1B shows interactions of molecular components in different versions of the base editors. Base editors of V2 to V5 illustrate different strategies to cleave mA3dCDI off. The dCDI domain could be cleaved off from APOBEC through a two-component interaction of the TEV site and a free TEV protease (V2), a N22p-fused TEV protease (V3), or a TEV protease reconstituted by an mgRNA-boxB (V4). In the version 5 (V5) of the base editor, the dCDI is cleaved off from APOBEC through a three-component interaction of TEV site, TEVn, and N22p-TEVc.

[00317] Figure 2 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *PCSK9* gene. Figure 2A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 2B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 2C shows editing frequency at each target site calculated by EditR analysis.

[00318] Figure 3 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *PCSK9* gene. Figure 3A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 3B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 3C shows editing frequency at each target site calculated by EditR analysis.

[00319] Figure 4 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *PCSK9* gene. Figure 4A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 4B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 4C shows editing frequency at each target site calculated by EditR analysis.

[00320] Figure 5 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *PCSK9* gene. Figure 5A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 5B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 5C shows editing frequency at each target site calculated by EditR analysis.

[00321] Figure 6 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *PCSK9* gene. Figure 6A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 6B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 6C shows editing frequency at each target site calculated by EditR analysis.

[00322] Figure 7 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *PCSK9* gene. Figure 7A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 7B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 7C shows editing frequency at each target site calculated by EditR analysis.

[00323] Figure 8 illustrates relative human PCSK9 protein expression induced by a tBE gene editing system with pairs of mgRNA and hgRNA targeting human *PCSK9* gene in human cells. Figure 8A shows protein expression level examined with western blot using GAPDH as the loading control. Figure 8B shows protein expression level examined with ELISA and corresponding editing frequency at indicated sites.

[00324] Figure 9 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting mouse *PCSK9* gene. Figure 9A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 9B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 9C shows editing frequency at each target site calculated by EditR analysis.

[00325] Figure 10 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting mouse *PCSK9* gene. Figure 10A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 10B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites.

[00326] Figure 11 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting mouse *PCSK9*

gene. Figure 11A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding with tBE-V5-mA3 and nCas9. Figure 11B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 11C shows editing frequency at each target site in Figure 10B calculated by EditR analysis. Figure 11D shows editing frequency at each target sites in Figure 11B calculated by EditR analysis.

[00327] Figure 12 illustrates relative mouse PCSK9 protein expression induced by a tBE gene editing system with pairs of mgRNA and hgRNA targeting mouse *PCSK9* gene in mouse cells. Figure 12A shows protein expression level examined with western blot using GAPDH as the loading control in Hepa1-6 cells. Figure 12B shows protein expression level examined with ELISA and corresponding editing frequency at indicated sites in Hepa1-6 cells. Figure 12C shows protein expression level examined with ELISA and corresponding editing frequency at indicated sites in COS-1 cells. Figure 12D shows editing efficiency induced by tBE-V5-mA3 with different pairs of mgRNA/hgRNA at indicated sites in Hepa1-6 cells.

[00328] Figure 13 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *ANGPTL3* gene. Figure 13A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 13B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 13C shows editing frequency at each target site calculated by EditR analysis.

[00329] Figure 14 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *ANGPTL3* gene. Figure 14A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 14B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 14C shows editing frequency at each target site calculated by EditR analysis.

[00330] Figure 15 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *ANGPTL3*. Figure 15A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 15B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 15C shows editing frequency at each target site calculated by EditR analysis.

[00331] Figure 16 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *ANGPTL3* gene. Figure 16A is a schematic diagram illustrating the co-transfection of

mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 16B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites.

[00332] Figure 17 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *ANGPTL3* gene. Figure 17A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 17B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 17C shows editing frequency at each target sites in figure 16B calculated by EditR analysis. Figure 17D shows editing frequency at each target site in figure 17B calculated by EditR analysis.

[00333] Figure 18 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *ANGPTL3* gene. Figure 18A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 18B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 18C shows editing frequency at each target site calculated by EditR analysis.

[00334] Figure 19 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *ANGPTL3* gene. Figure 19A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 19B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 19C shows editing frequency at each target site calculated by EditR analysis.

[00335] Figure 20 illustrates relative human *ANGPTL3* protein expression induced by a tBE gene editing system with pairs of mgRNA and hgRNA targeting human *ANGPTL3* gene in human cells. Figure 20A shows protein expression level examined with ELISA and corresponding editing frequency at indicated sites.

[00336] Figure 21 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting mouse *ANGPTL3* gene. Figure 21A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 21B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 21C shows editing frequency at each target site calculated by EditR analysis.

[00337] Figure 22 illustrates relative mouse *ANGPTL3* protein expression induced by a tBE gene editing system with pairs of mgRNA and hgRNA targeting mouse *ANGPTL3* gene in mouse cells. Figure 22A shows protein expression level examined with western blot using GAPDH as the loading control and corresponding editing frequency at indicated sites.

5 [00338] Figure 23 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *ASGR1* gene. Figure 23A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 23B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure
10 23C shows editing frequency at each target site calculated by EditR analysis.

[00339] Figure 24 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *ASGR1* gene. Figure 24A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 24B shows editing efficiency
15 induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 24C shows editing frequency at each target site calculated by EditR analysis.

[00340] Figure 25 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *ASGR1* gene. Figure 25A is a schematic diagram illustrating the co-transfection of mgRNA and the
20 corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 25B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 25C shows editing frequency at each target site calculated by EditR analysis.

[00341] Figure 26 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *ASGR1*
25 gene. Figure 26A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 26B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 26C shows editing frequency at each target site calculated by EditR analysis.

[00342] Figure 27 illustrates editing efficiencies induced by a tBE gene editing system
30 with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *ASGR1* gene. Figure 27A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 27B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 27C shows editing frequency at each target site calculated by EditR analysis.

35 [00343] Figure 28 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *ASGR1*

gene. Figure 28A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 28B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 28C shows editing frequency at each target site calculated by EditR analysis.

5 [00344] Figure 29 illustrates relative human ASGR1 protein expression induced by a tBE gene editing system with pairs of mgRNA and hgRNA targeting human *ASGR1* gene in human cells. Figure 29A shows protein expression level examined with western blot using GAPDH as the loading control and corresponding editing frequency at indicated sites.

[00345] Figure 30 illustrates editing efficiencies induced by a tBE gene editing system
10 with the indicated pairs of mgRNA and the corresponding hgRNAs targeting mouse *ASGR1* gene. Figure 30A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 30B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 30C shows editing frequency at each target site calculated by EditR analysis.

15 [00346] Figure 31 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting mouse *ASGR1* gene. Figure 31A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 31B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure
20 31C shows editing frequency at each target site calculated by EditR analysis.

[00347] Figure 32 illustrates relative mouse ASGR1 protein expression induced by a tBE gene editing system with pairs of mgRNA and hgRNA targeting mouse *ASGR1* gene in mouse cells. Figure 32A shows protein expression level examined with western blot using GAPDH as the loading control and corresponding editing frequency at indicated sites.

25 [00348] Figure 33 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *LPA* gene. Figure 33A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 33B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure
30 33C shows editing frequency at each target site calculated by EditR analysis.

[00349] Figure 34 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *LPA* gene. Figure 34A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 34B shows editing efficiency
35 induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 34C shows editing frequency at each target site calculated by EditR analysis.

[00350] Figure 35 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *LPA* gene. Figure 35A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 35B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 35C shows editing frequency at each target site calculated by EditR analysis.

[00351] Figure 36 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *LPA* gene. Figure 36A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 36B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 36C shows editing frequency at each target site calculated by EditR analysis.

[00352] Figure 37 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *LPA* gene. Figure 37A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 37B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 37C shows editing frequency at each target site calculated by EditR analysis.

[00353] Figure 38 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *LPA* gene. Figure 38A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 38B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 38C shows editing frequency at each target site calculated by EditR analysis.

[00354] Figure 39 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *LPA* gene. Figure 39A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 39B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 39C shows editing frequency at each target site calculated by EditR analysis.

[00355] Figure 40 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *LPA* gene. Figure 40A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 40B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 40C shows editing frequency at each target site calculated by EditR analysis.

[00356] Figure 41 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *LPA* gene. Figure 41A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 41B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 41C shows editing frequency at each target site calculated by EditR analysis.

[00357] Figure 42 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *LPA* gene. Figure 42A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 42B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 42C shows editing frequency at each target site calculated by EditR analysis.

[00358] Figure 43 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *AGT* gene. Figure 43A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 43B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 43C shows editing frequency at each target site calculated by EditR analysis.

[00359] Figure 44 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *AGT* gene. Figure 44A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 44B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 44C shows editing frequency at each target site calculated by EditR analysis.

[00360] Figure 45 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *AGT* gene. Figure 45A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 45B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 45C shows editing frequency at each target site calculated by EditR analysis.

[00361] Figure 46 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *AGT* gene. Figure 46A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 46B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 46C shows editing frequency at each target site calculated by EditR analysis.

[00362] Figure 47 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *AGT* gene. Figure 47A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 47B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 47C shows editing frequency at each target site calculated by EditR analysis.

[00363] Figure 48 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *AGT* gene. Figure 48A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 48B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 48C shows editing frequency at each target site calculated by EditR analysis.

[00364] Figure 49 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *AGT* gene. Figure 49A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 49B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 49C shows editing frequency at each target site calculated by EditR analysis.

[00365] Figure 50 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *AGT* gene. Figure 50A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 50B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 50C shows editing frequency at each target site calculated by EditR analysis.

[00366] Figure 51 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *AGT* gene. Figure 51A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 51B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 51C shows editing frequency at each target site calculated by EditR analysis.

[00367] Figure 52 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *AGT* gene. Figure 52A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 52B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 52C shows editing frequency at each target site calculated by EditR analysis.

[00368] Figure 53 illustrates relative human AGT protein expression induced by a tBE gene editing system with pairs of mgRNA and hgRNA targeting human *AGT* gene in human cells. Figure 53A shows protein expression level examined with western blot using GAPDH as the loading control. Figure 53B shows protein expression level examined with ELISA and
5 corresponding editing frequency at indicated sites.

[00369] Figure 54 illustrates LNP delivery of a tBE gene editing system targeting the *PCSK9* gene for *in vivo* base editing. Figure 54A is a schematic of an LNP system for tBE-V5-mA3 and key experimental steps. Figure 54B-54D shows *in vivo* editing frequencies (B) induced by LNP containing a tBE system with different detection time periods and the levels of plasma PCSK9 protein (C) and cholesterol levels (D) in the mice injected with LNP
10 expressing tBE system. Figure 54E-54G shows *in vivo* editing frequencies (E) induced by LNP containing a tBE system and the corresponding chemically modified guide RNA and the levels of plasma PCSK9 protein (F) and cholesterol levels (G) in the mice injected with LNP expressing tBE system.

[00370] Figure 55 illustrates several versions of a LigoRNA-based gene editing systems. Figure 55A shows polynucleotide constructs encoding components of six versions of the LigoRNA-based gene editing system that comprises two LigoRNA structures (denoted as V1, V2, V3, V4, V5, and V6). Figure 55B&C are the illustrations of the six versions of the LigoRNA-based gene editing system (denoted as V1, V2, V3, V4, V5, and V6).
15

[00371] Figure 56 illustrates LNP delivery of LigoRNA-tCBE-V5 targeting the *PCSK9* gene for *in vivo* base editing. Figure 56A-56C shows *in vivo* editing frequencies (A) induced by LNP containing tBE system with end modified guide RNA or a LigoRNA-tCBE-V5 system and the levels of plasma PCSK9 protein (B) and cholesterol levels (C) in the mice injected with LNP expressing tBE or LigoRNA-tCBE-V5.
20

[00372] Figure 57 illustrates a dual editing strategy by LigoRNA-tCBE-V5 in different cells. Figure 57A shows co-editing by guide RNA (including two pairs of mgRNA and hgRNA) targeting *PCSK9* and *ANGPTL3*, showing comparable editing efficiency with their respective single editing control. Figure 57B shows the dual editing strategy produced comparable protein level reduction compared to single editing as evidenced by an ELISA
25 assay.
30

[00373] Figure 58 illustrates LNP delivery of a tBE gene editing system targeting the *PCSK9* and *ANGPTL3* gene for *in vivo* base editing. Figure 58A is a schematic of an LNP system for tBE-V5-mA3 and key experimental steps. Figure 58B shows *in vivo* editing efficiencies in mouse liver and mouse hepatocytes induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs (including two pairs of
35 mgRNA and hgRNA). Figure 58C-D shows the levels of plasma PCSK9 protein (C) and ANGPTL3 protein (D) in the mice injected with LNP expressing tBE system.

[00374] Figure 59 illustrates editing efficiencies induced by a tBE gene editing system with the indicated pairs of mgRNA and the corresponding hgRNAs targeting human *APOC3* gene. Figure 59A is a schematic diagram illustrating the co-transfection of mgRNA and the corresponding hgRNA with tBE-V5-mA3 and nCas9. Figure 59B shows editing efficiency induced by tBE-V5-mA3 with indicated pairs of mgRNA/hgRNA at indicated sites. Figure 59C shows editing frequency at each target site calculated by EditR analysis.

[00375] Figure 60 illustrates LNP delivery of a tBE gene editing system targeting the *APOC3* gene for *in vivo* base editing. Figure 60A is a schematic of an LNP system for tBE-V5-mA3 and key experimental steps. Figure 60B-60D shows *in vivo* editing frequencies (B) induced by LNP containing a tBE system with different sgRNA pairs, plasma level of hApoC3 protein (C) detected in ELISA assay, and plasma triglyceride (TG) levels (D) in the mice injected with LNP expressing tBE system. Figure 60E-60G shows the levels of plasma low-density lipoprotein cholesterol (LDL-C) (E), high-density lipoprotein cholesterol (HDL-C) (F) and cholesterol (CHOL) (G).

[00376] Figure 61 illustrates LNP delivery of a tBE gene editing system targeting the *PCSK9* gene for *in vivo* base editing. Figure 61A is a schematic of an LNP system for tBE-V1-mA3 or tBE-V5-mA3 and key experimental steps. Figure 61B shows *in vivo* editing frequencies induced by LNP containing different tBE versions and different doses (mpk, mg of RNA per kg of body weight).

DETAILED DESCRIPTION

[00377] All publications, patents, and patent applications referred to herein are incorporated by reference in their entirety to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

[00378] In the present disclosure, unless otherwise specified, the scientific and technical terms used herein have the meanings generally understood by a person skilled in the art. Although any methods and materials similar or equivalent to those described herein find use in the practice of the present disclosure, the preferred methods and materials are described herein. Accordingly, the terms defined herein are more fully described by reference to the Specification as a whole.

[00379] As used herein, the singular terms “a,” “an,” and “the” include the plural reference unless the context clearly indicates otherwise.

[00380] As used herein, “and/or” refers to and encompasses any and all possible combinations of one or more of the associated listed items, as well as the lack of combinations when interpreted in the alternative (“or”). Moreover, the present invention also

contemplates that in some embodiments of the invention, any feature or combination of features set forth herein can be excluded or omitted.

[00381] Unless the context requires otherwise, the terms “comprise,” “comprises,” and “comprising,” or similar terms are intended to mean a non-exclusive inclusion, such that a
5 recited list of elements or features does not include those stated or listed elements solely, but may include other elements or features that are not listed or stated.

[00382] Unless otherwise indicated, nucleic acids are written left to right in the 5' to 3' orientation, and amino acid sequences are written left to right in amino to carboxy orientation, respectively. A number “n”, when used in the context of an amino acid sequence,
10 refers to the nth amino acid in the amino acid sequence counting from the amino end. For example, “amino acid 15” refers to the 15th amino acid in a certain amino acid sequence. For example, “R15” refers to the 15th amino acid, which is an arginine (R), in a certain amino acid sequence.

[00383] It is to be understood that this disclosure is not limited to the particular
15 methodology, protocols, and reagents described, as these may vary, depending upon the context in which they are used by those skilled in the art.

[00384] As used herein, the term “about” will be understood by persons of ordinary skill in the art and will vary to some extent depending on the context in which it is used. In some
20 embodiments, the term “about” when referring to a value is meant to encompass art-accepted variations. In some embodiments, the term “about” when referring to such values, is meant to encompass variations of $\pm 20\%$ or $\pm 10\%$, more preferably $\pm 5\%$, even more preferably $\pm 1\%$, and still more preferably $\pm 0.1\%$ from the specified value, as such variations are appropriate in the context in which the term “about” is used.

[00385] As used herein, the terms “percent identity” and “% identity,” as applied to
25 nucleic acid or polynucleotide sequences, refer to the percentage of residue matches between at least two nucleic acid or polynucleotide sequences aligned using a standardized algorithm. Such an algorithm may insert, in a standardized and reproducible way, gaps in the sequences being compared in order to optimize alignment between two sequences, and therefore achieve a more meaningful comparison of the two sequences.

[00386] Percent identity between nucleic acid or polynucleotide sequences may be
30 determined using a suite of commonly used and freely available sequence comparison algorithms provided by the National Center for Biotechnology Information (NCBI) Basic Local Alignment Search Tool (BLAST) (Altschul, S. F. et al. (1990) J. Mol. Biol. 215:403-410), which is available from several sources, including the NCBI, Bethesda, Md., and on the
35 Internet at <http://www.ncbi.nlm.nih.gov/BLAST/>.

[00387] Nucleic acid or polynucleotide sequences that do not show a high degree of identity may nevertheless encode similar amino acid sequences due to the degeneracy of the genetic code. It is understood that changes in a nucleic acid sequence can be made using this degeneracy to produce multiple nucleic acid sequences that all encode substantially the same protein. Specifically, degenerate codon substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues (Batzer et al. (1991) *Nucleic Acid Res* 19:5081; Ohtsuka et al. (1985) *J Biol Chem* 260:2605-2608; Cassol et al. (1992); Rossolini et al. (1994) *Mol Cell Probes* 8:91-98). The term “nucleic acid” refers to deoxyribonucleotides or ribonucleotides and polymers thereof in either single- or double-stranded form. Unless specifically limited, the term encompasses nucleic acids containing known analogues of natural nucleotides which have similar binding properties as the reference nucleic acid and are metabolized in a manner similar to naturally occurring nucleotides. The term nucleic acid is used interchangeably with polynucleotide, and (in appropriate contexts) gene, cDNA, and mRNA encoded by a gene.

[00388] As used herein, “percent (%) amino acid sequence identity” with respect to a peptide, polypeptide or protein sequence is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in another peptide or polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Percent amino acid sequence identity in the current disclosure is measured using BLAST software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared.

[00389] An amino acid substitution refers to the replacement of one amino acid in a polypeptide with another amino acid. Amino acid substitutions can be conservative or non-conservative substitutions. Exemplary substitutions are shown in Table 6. Amino acid substitutions may be introduced into a protein of interest and the products screened for a desired activity, for example, retained/improved biological activity.

Table 6

Original Residue	Exemplary Substitutions
Ala (A)	Val; Leu; Ile
Arg (R)	Lys; Gln; Asn
Asn (N)	Gln; His; Asp, Lys; Arg
Asp (D)	Glu; Asn

Cys (C)	Ser; Ala
Gln (Q)	Asn; Glu
Glu (E)	Asp; Gln
Gly (G)	Ala
His (H)	Asn; Gln; Lys; Arg
Ile (I)	Leu; Val; Met; Ala; Phe; Norleucine
Leu (L)	Norleucine; Ile; Val; Met; Ala; Phe
Lys (K)	Arg; Gln; Asn
Met (M)	Leu; Phe; Ile
Phe (F)	Trp; Leu; Val; Ile; Ala; Tyr
Pro (P)	Ala
Ser (S)	Thr
Thr (T)	Val; Ser
Trp (W)	Tyr; Phe
Tyr (Y)	Trp; Phe; Thr; Ser
Val (V)	Ile; Leu; Met; Phe; Ala; Norleucine

[00390] Amino acids may be grouped according to common side-chain properties:

[00391] (1) hydrophobic: Norleucine, Met, Ala, Val, Leu, Ile;

[00392] (2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln;

5 [00393] (3) acidic: Asp, Glu;

[00394] (4) basic: His, Lys, Arg;

[00395] (5) residues that influence chain orientation: Gly, Pro;

[00396] (6) aromatic: Trp, Tyr, Phe.

[00397] The term “nucleic acid” or “polynucleotide” refers to deoxyribonucleic acids
 10 (DNA) or ribonucleic acids (RNA) and polymers thereof in either single- or double-stranded
 form. Unless specifically limited, the term encompasses nucleic acids containing known
 analogues of natural nucleotides that have similar binding properties as the reference nucleic
 acid and are metabolized in a manner similar to naturally occurring nucleotides. Unless

otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (e.g., degenerate codon substitutions), alleles, orthologs, SNPs, and complementary sequences as well as the sequence explicitly indicated. Specifically, degenerate codon substitutions may be achieved by generating sequences in
5 which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues (Batzner et al., *Nucleic Acid Res.* 19:5081 (1991); Ohtsuka et al., *J. Biol. Chem.* 260:2605-2608 (1985); and Rossolini et al., *Mol. Cell. Probes* 8:91-98 (1994)).

[00398] The term “polypeptide” is intended to encompass a singular “polypeptide” as well
10 as plural “polypeptides,” and refers to a molecule composed of monomers (amino acids) linearly linked by amide bonds (also known as peptide bonds). The term “polypeptide” refers to any chain or chains of two or more amino acids, and does not refer to a specific length of the product. Thus, “peptides,” “protein”, or any other term used to refer to a chain or chains of two or more amino acids, are included within the definition of “polypeptide,” and the term
15 “polypeptide” may be used instead of, or interchangeably with any of these terms. The term “polypeptide” is also intended to refer to the products of post-expression modifications of the polypeptide, including without limitation glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, or modification by non- naturally occurring amino acids. A polypeptide may be derived from a
20 natural biological source or produced by recombinant technology, but is not necessarily translated from a designated nucleic acid sequence. It may be generated in any manner, including by chemical synthesis.

[00399] The term “promoter” refers to a nucleic acid sequence recognized by the synthetic machinery of the cell, or introduced synthetic machinery, required to initiate the specific
25 transcription of a polynucleotide sequence.

[00400] As used herein, the term “encode” or “encoding” as it is applied to polynucleotides refers to a polynucleotide which is said to “encode” a polypeptide if, in its native state or when manipulated by methods well known to those skilled in the art, it can be transcribed and/or translated to produce the mRNA for the polypeptide and/or a fragment
30 thereof. The antisense strand is the complement of such a nucleic acid, and the encoding sequence can be deduced therefrom.

[00401] A “guide RNA” (gRNA) refers to a synthetic or expressed RNA sequence that comprises a CRISPR binding motif and a spacer. In some embodiments, the guide RNA is a single guide RNA. In some embodiments, the guide RNA is a dual-RNA structure. In some
35 embodiments, the guide RNA is a dual-RNA structure formed by a ligand-bound CRISPR RNA (crRNA) and a trans-activating crRNA (tracrRNA). In some embodiments, the guide RNA is a LigoRNA. A “spacer” is a DNA-targeting motif, which is a sequence that is

complementary to a target specific DNA region. In some embodiments, the guide RNA is a crRNA-tracrRNA dual RNA structure, and the crRNA comprises the spacer. The CRISPR binding motif of a guide RNA can bind to a Cas enzyme and DNA-targeting motif of the gRNA can guide the complex to a specific target location on a DNA. In some embodiments, the guide RNA is a crRNA-tracrRNA dual RNA structure, and the base-pair structure formed by the crRNA and the tracrRNA comprises the CRISPR binding motif. A guide RNA may further comprise one or more other motifs, such as one or more protein-binding motifs, or the like.

[00402] As used herein, a “fusion protein” is a protein comprising at least two polypeptides that have been joined as a single polypeptide. For example, a fusion protein can comprise two domains that are encoded by separate genes that have been joined so that they are transcribed and translated as a single unit, producing a single polypeptide. In some embodiments, the at least two domains are fused together directly. In some embodiments, the domains are connected by one or more linkers.

[00403] The term “genetic modification” and its grammatical equivalents, as used herein can refer to one or more alterations of a nucleic acid, *e.g.*, the nucleic acid within an organism’s genome. For example, genetic modification can refer to alterations, additions, and/or deletion of genes or portions of genes or other nucleic acid sequences. A genetically modified cell can also refer to a cell with an added, deleted, and/or altered gene or portion of a gene. A genetically modified cell can also refer to a cell with an added nucleic acid sequence that is not a gene or gene portion. Genetic modifications include, for example, both transient knock-in or knock-down mechanisms, and mechanisms that result in permanent knock-in, knock-down, or knock-out of target genes or portions of genes or nucleic acid sequences. Genetic modifications include, for example, both transient knock-in and mechanisms that result in permanent knock-in of nucleic acids sequences. Genetic modifications also include, for example, reduced or increased transcription, reduced or increased mRNA stability, reduced or increased translation, and reduced or increased protein stability.

[00404] “Cleavage” or “cleavable” refers to the breakage of a covalent bond, *e.g.*, of a covalent bond on the backbone of a DNA molecule, or the capability thereof. Cleavage can be initiated by a variety of methods including, but not limited to, enzymatic or chemical hydrolysis of a phosphodiester bond. Both single-stranded cleavage and double-stranded cleavage are possible, and double-stranded cleavage can occur as a result of two distinct single-stranded cleavage events. DNA cleavage can result in the production of either blunt ends or staggered ends.

[00405] Unless otherwise specified, a “nucleotide sequence encoding an amino acid sequence” includes all nucleotide sequences that are degenerate versions of each other and

that encode the same amino acid sequence. The phrase nucleotide sequence that encodes a protein or an RNA may also include introns to the extent that the nucleotide sequence encoding the protein may in some version contain an intron(s).

5 [00406] The term “expression” refers to the transcription and/or translation of a particular nucleotide sequence driven by its promoter.

[00407] The term “effective amount” or “therapeutically effective amount” is used interchangeably herein, and refer to an amount of a compound, formulation, material, or composition, as described herein effective to achieve a particular biological result. The term “endogenous” refers to any material from or produced inside an organism, cell, tissue
10 or system.

[00408] As used herein, a composition refers to any mixture of two or more products, substances, or compounds, including cells.

[00409] The term “subject” means any animal such as a mammal, e.g., a human.

[00410] The term “transfer vector” or “vector” refers to a composition of matter which
15 comprises an isolated nucleic acid and which can be used to deliver the isolated nucleic acid to the interior of a cell. Numerous vectors are known in the art including, but not limited to, linear polynucleotides, polynucleotides associated with ionic or amphiphilic compounds, plasmids, and viruses. Thus, the term “transfer vector” includes an autonomously replicating plasmid or a virus. The term should also be construed to further include non-plasmid and
20 non-viral compounds which facilitate transfer of nucleic acid into cells, such as, for example, a polylysine compound, liposome, and the like. Examples of viral transfer vectors include, but are not limited to, adenoviral vectors, adeno-associated virus vectors, retroviral vectors, lentiviral vectors, and the like.

[00411] As used herein, the term “treat,” “treating,” or “treatment” refers to ameliorating a
25 disease or disorder, e.g., slowing or arresting or reducing the development of the disease or disorder or reducing at least one of the clinical symptoms thereof. For example, in some embodiments, ameliorating a disease or disorder can include obtaining a beneficial or desired clinical result that includes, but is not limited to, any one or more of: alleviation of one or more symptoms, diminishment of extent of disease, preventing or delaying spread of disease,
30 preventing or delaying recurrence of disease, delay or slowing of disease progression, amelioration of the disease state, inhibiting or eliminating the disease or progression of the disease, inhibiting or slowing the disease or its progression, arresting its development, and remission (whether partial or total).

As used herein, "regulation" or "regulate" in relation to gene expression refers to any process that increases, decreases, or alters gene expression. For example, regulation of gene expression may be achieved through the modulation or control of transcription or translation of a genetic material.*Cardiovascular disease (CVD)*

- 5 [00412] Cardiovascular disease (CVD) represents a broad category of disorders that affect the heart and blood vessels, encompassing conditions such as coronary artery disease, heart failure, stroke, and peripheral vascular disease. As a leading cause of morbidity and mortality globally, CVD poses significant public health challenges. The intricate interplay of risk factors, including hypertension, dyslipidemia, diabetes, and genetic predispositions,
- 10 contributes to the multifactorial nature of CVD. The clinical manifestations of CVD range from atherosclerosis-related events, such as myocardial infarction and stroke, to chronic conditions affecting cardiac function and overall cardiovascular health. Since CVD encompasses a broad spectrum of conditions, ongoing research continues to uncover new facets of its complex etiology.
- 15 [00413] Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a prohormone-protein convertase in the subtilisin (S8) family of serine proteases (Seidah et al., 100(3) Proc. Nat'l Acad. Sci. 928-33 (2003)). PCSK9 is a key regulator of LDL metabolism and a popular LLT target; that the expression or upregulation of PCSK9 is associated with increased plasma levels of LDL cholesterol, that the corresponding inhibition or lack of expression of PCSK9
- 20 is associated with reduced LDL cholesterol plasma levels; and that decreased levels of LDL cholesterol are associated with sequence variations in PCSK9 have been found to confer protection against coronary heart disease; Cohen, 2006 N. Engl. J. Med. 354:1264-1272. Loss of function mutations in PCSK9 are associated with reduced LDL-C and risk of coronary heart disease and no apparent adverse health consequences. Till now, treatments with
- 25 monoclonal antibodies, small interfering RNAs, and antisense oligonucleotides targeting PCSK9 mRNA or protein are already approved. Notably, introducing nonsense mutations in PCSK9 through a lipid nanoparticle (LNP) delivery system resulted in reduction of PCSK9 protein and LDL-C levels in mice, showing the potential of this approach for therapeutic interventions.
- 30 [00414] Angiopoietin-like protein 3 (ANGPTL3) is another attractive target for lipid lowering. In vitro analysis of recombinant protein showed that ANGPTL3 directly inhibits lipoprotein lipase (LPL) activity, indicating that it is a lipid metabolism modulator that regulates very low density lipoprotein (VLDL) triglyceride levels through the inhibition of LPL activity (Shimizu et al., 2002, J Biol Chem 277(37):33742-33748). By mainly
- 35 affecting triglyceride-rich lipoproteins, ANGPTL3 reduction might prove complementary to LDL cholesterol lowering with PCSK9 blockade. Targeting ANGPTL3 protein is already

approved for the treatment of homozygous familial hypercholesterolemia, which reducing LDL-C in these patients in an LDLR-independent mechanism.

[00415] ASGR1 is the predominant isoform of the asialoglycoprotein receptor, a liver-specific receptor mediating the endocytosis and lysosomal degradation of a variety of desialylated glycoproteins. A large-scale genetic study identified that the loss-of-function ASGR1 variants were associated with low cholesterol and a reduced risk of CVD.

[00416] Lipoprotein(a) (Lp(a)) represents a unique subclass of circulating lipoprotein particles. The metabolism of Lp(a) particles is distinct from that of LDL-C, and currently approved lipid-lowering drugs do not provide substantial reductions in Lp(a), a causal risk factor for CVD. The clinical phase III outcomes study with Pelacarsen targeting the *LPA* gene indicating its strong candidacy as a CVD treatment target.

[00417] AGT, the upstream precursor in the renin-angiotensin-aldosterone system (RAAS) pathway, plays a pivotal role in blood pressure regulation. Inhibiting AGT synthesis in the liver could lead to durable reductions in AGT protein and, consequently, in the vasoconstrictor angiotensin II. Recognizing the importance of AGT as a therapeutic target, especially for hypertension, demonstrates its potential impact on reducing the leading cause of cardiovascular diseases, including valvular heart disease and atrial fibrillation.

[00418] Aside from the *PCSK9* and *ANGPTL3* genes associated with lowering LDL-C, the importance of *APOC3* in the prevention and treatment of cardiovascular diseases is also gradually gaining attention. *APOC3* encodes a protein component of triglyceride (TG)-rich lipoproteins (TRLs) including very low density lipoproteins (VLDL), high density lipoproteins (HDL) and chylomicrons. The encoded protein plays a role in the metabolism of these TRLs through multiple modes. This protein has been shown to promote the secretion of VLDL1, inhibit lipoprotein lipase enzyme activity, and delay catabolism of TRL remnants. Mutations in this gene are associated with low plasma triglyceride levels and reduced risk of ischemic cardiovascular disease, and hyperalphalipoproteinemia, which is characterized by elevated levels of high density lipoprotein (HDL) and HDL cholesterol in human patients.

[00419]

30 Gene Editing Systems

[00420] Gene editing systems are known in the art, and include but are not limited to, zinc finger nucleases, transcription activator-like effector nucleases (TALENs); clustered regularly interspaced short palindromic repeats (CRISPR)/Cas systems, and meganuclease systems. Gene editing tools offer a versatile approach for targeting specific genes, enabling precise repair or disruption to address conditions such as familial hypercholesterolemia,

dyslipidemia or established CVD. Somatic genome editing has the potential to be a one-time therapy for individuals.

[00421] “CRISPR” or “CRISPR/Cas” as used herein refers to a set of clustered regularly interspaced short palindromic repeats, or a system comprising such a set of repeats. “Cas”, as
5 used herein, refers to a CRISPR-associated protein. The CRISPR/Cas gene editing system, denoting clustered regularly interspaced short palindromic repeats and associated proteins, comprises a prokaryotic immune system prevalent in approximately 40% of eubacteria genomes and 90% of archaea genomes. Initially identified as a defense mechanism against
10 foreign genetic elements, this system has been repurposed for gene editing in eukaryotes like mice and primates. In this modified application, a designed CRISPR and suitable Cas proteins are introduced into the target cells. The CRISPR locus, characterized by alternating repeats and spacers, plays a pivotal role. In the natural prokaryotic setting, these spacers typically contain sequences from foreign genetic elements. However, in eukaryotic gene editing, spacers are derived from the target gene sequence. Constitutively expressed CRISPR
15 locus RNA is processed into small RNAs by Cas proteins, guiding other Cas proteins to silence specific genes at the RNA or DNA level. While the arrangement and structure of CRISPR and Cas genes vary across bacterial species, the CRISPR/Cas9 system, involving a nuclease with dual cutting sites, has gained prominence in eukaryotic gene editing. Utilizing this system enables precise modifications such as addition, replacement, or deletion of base
20 pairs in the target gene, or reversible gene silencing through RNA interference mechanisms. Notably, the Cas9 protein, often derived from *Streptococcus pyogenes*, is a central player in this versatile and powerful gene editing tool.

[00422] The combination of CRISPR-Cas9 and cytidine deaminases leads to the development of cytosine base editors (CBEs), allowing programmable cytosine to thymine
25 (C-to-T) substitution. This technology has demonstrated successful and efficient editing across various species, holding great potentials in clinical applications. Notably, the base editing process circumvents reliance on DNA double-strand breaks (DSB), thereby minimizing unwanted nucleotide insertions/deletions (indels) and avoiding DNA damage responses (DDRs). The importance of safety and efficiency in gene editing tools for clinical
30 applications is underscored by previous studies revealing that Cas9 nuclease-induced DSBs can activate a p53-mediated DDR pathway, leading to cell death. It is also noted that APOBEC/AID family members can trigger C-to-T base substitutions in single-stranded DNA (ssDNA) regions, which are formed randomly during various cellular processes including DNA replication, repair and transcription. Thus, the specificity of previous base editing
35 systems is compromised, limiting the applications of base editors for therapeutic purposes. In the present disclosure, inventors use a new base editing system, transformer base editor (tBE), which can specifically edit cytosine in target regions with no observable off-target mutations.

Transformer base editor (tBE) system

[00423] The term “base editor (BE),” or “nucleobase editor (NBE)” refers to an agent comprising a polypeptide that is capable of making a modification to a base (e.g., A, T, C, G, or U) within a nucleic acid sequence (e.g., DNA or RNA).

5 [00424] In some embodiments, a base editor as used herein is a cytosine base editor (CBE), which comprises a combination of a CRISPR system and cytidine deaminase. A CBE effectuates a programmable cytosine to thymine (C-to-T) substitution. Because the base editing process does not depend on the generation of DNA double strand break (DSB), unwanted nucleotide insertions/deletions (indels) or DNA damage responses (DDR) can be
10 largely avoided.

[00425] In some embodiments, a highly specific base editing system, transformer base editor (tBE), is used, which can edit cytosine in target regions with no observable off-target mutations. In some embodiments, the tBE is any one of the base editors described in WO2020156575A1, incorporated herein by reference in its entirety. For instance, the tBE can
15 be any base editor as illustrated in Figure 1.

[00426] In some embodiments, the transformer base editor (tBE) system may contain a cytidine deaminase inhibitor (dCDI) domain and a split-TEV protease (e.g., as illustrated in Figure 1A, V5). Thus, tBE remains inactive at off-target sites with a cleavable fusion of dCDI domain and eliminates unintended off-target mutations. Only when binding at on-target sites,
20 tBE is transformed to cleave off the dCDI domain and catalyzes targeted deamination for precise editing. Specifically, tBE uses one main guide RNA (mgRNA, normally 20 nt) to bind at the target genomic site and one helper guide RNA (hgRNA, normally 10 to 20 nt) to bind at a nearby region (ideally upstream to the target genomic site). The binding of two gRNAs can guide the components of tBE system to correctly assemble at the target genomic
25 site for base editing (Figure 1B). tBE can specifically edit cytosine in target regions with no observable off-target mutations, e.g., inducing a premature stop codon to repress, such as PCSK9 protein expression, or breaking the GU-AG rule to disrupt splicing site.

[00427] In some embodiments, the tBE system is used to disrupt *PCSK9*, *ANGPTL3*, *ASGR1*, *LPA*, *AGT* or *APOC3* gene. In some embodiments, the tBE system is used to disrupt
30 one or more genes selected from *PCSK9*, *ANGPTL3*, *ASGR1*, *LPA*, *AGT*, and *APOC3* genes. In some embodiments, the tBE system is used to disrupt *PCSK9* gene, which leads to reduced level of Low-Density Lipoprotein cholesterol and thereby leads to therapeutic effects against CVD. In some embodiments, the tBE system is used to disrupt *ANGPTL3* gene, which leads to reduced level of Low-Density Lipoprotein cholesterol, reduced level of triglyceride-rich
35 remnant particles, and/or reduced level of lipoprotein(a) (Lp(a)), and thereby leads to therapeutic effects against CVD. In some embodiments, the tBE system is used to disrupt *ASGR1* gene, which leads to reduced level of Low-Density Lipoprotein cholesterol and

thereby leads to therapeutic effects against CVD. In some embodiments, the tBE system is used to disrupt *LPA* gene, which leads to reduced level of triglyceride-rich remnant particles, and/or reduced level of lipoprotein(a) (Lp(a)), and thereby leads to therapeutic effects against CVD. In some embodiments, the tBE system is used to disrupt *AGT* gene, which leads to reduced vasoconstrictor angiotensin (Ang) II, and thereby leads to therapeutic effects against CVD. In some embodiments, the tBE system is used to disrupt *APOC3* gene, which leads to reduced triglyceride-rich lipoproteins and reduced level of LDL-C, and thereby leads to therapeutic effects against CVD.

[00428] In some embodiments, the base editors and base editing methods described herein can be applied to perform high-specificity and high-efficiency base editing in the genome of various eukaryotes. In some embodiments, the tBE comprises a Cas9 nickase (D10A), which is less toxic to cells than Cas9 nuclease, because Cas9 nickase activates a lower level of p53-mediated DDR. Besides, tBE achieves highly specific and efficient base editing at most sites.

[00429] In an aspect, the present disclosure provides a gene editing system comprising a main guide RNA (mgRNA) and a helper guide RNA (hgRNA), or at least one DNA polynucleotide encoding the mgRNA and/or the hgRNA, wherein the mgRNA comprises an mgRNA spacer of about 20 nucleotides (about 20 nt) that binds to a target site on a target gene and the hgRNA comprises an hgRNA spacer of about 10 to about 20 nt that binds to a site that is close to the target site that the mgRNA spacer binds to.

[00430] In some embodiments, the target gene as described herein includes one or more genes selected from *PCSK9*, *ANGPTL3*, *ASGR1*, *LPA*, *AGT* and *APOC3* genes.

[00431] In some embodiments, the gene editing system comprises an mgRNA comprising an mgRNA spacer selected from SEQ ID NOs: 213-236, 317-328, and 1128, and an hgRNA comprising an hgRNA spacer of about 10 to about 20 nt, e.g., 7 nt to 23 nt, 8 nt to 22 nt, 9 nt to 21 nt, and 10 nt to 20 nt, that binds to a site close to the target site that the mgRNA spacer binds to. In some embodiments, the gene editing system comprises an hgRNA comprising an hgRNA spacer selected from SEQ ID NOs: 237-316, 329-402, 1129, and 1130. In some embodiments, the gene editing system comprises an mgRNA targeting *PCSK9* gene.

[00432] In some embodiments, the gene editing system comprises an mgRNA comprising an mgRNA spacer selected from SEQ ID NOs: 403-429, and 550-552, and an hgRNA comprising an hgRNA spacer of about 10 to about 20 nt, e.g., 7 nt to 23 nt, 8 nt to 22 nt, 9 nt to 21 nt, and 10 nt to 20 nt, that binds to a site close to the target site that the mgRNA spacer binds to. In some embodiments, the gene editing system comprises an hgRNA comprising an hgRNA spacer selected from SEQ ID NOs: 430-549, and 553-562. In some embodiments, the gene editing system comprises an mgRNA targeting *ANGPTL3* gene.

[00433] In some embodiments, the gene editing system comprises an mgRNA comprising an mgRNA spacer selected from SEQ ID NOs: 563-584, and 677-684, and an hgRNA comprising an hgRNA spacer of about 10 to about 20 nt, e.g., 7 nt to 23 nt, 8 nt to 22 nt, 9 nt to 21 nt, and 10 nt to 20 nt, that binds to a site close to the target site that the mgRNA spacer binds to. In some embodiments, the gene editing system comprises an hgRNA comprising an hgRNA spacer selected from SEQ ID NOs: 585-676, and 685-716. In some embodiments, the gene editing system comprises an mgRNA targeting *ASGR1* gene.

[00434] In some embodiments, the gene editing system comprises an mgRNA comprising an mgRNA spacer selected from SEQ ID NOs: 717-750, and an hgRNA comprising an hgRNA spacer of about 10 to about 20 nt, e.g., 7 nt to 23 nt, 8 nt to 22 nt, 9 nt to 21 nt, and 10 nt to 20 nt, that binds to a site close to the target site that the mgRNA spacer binds to. In some embodiments, the gene editing system comprises an hgRNA comprising an hgRNA spacer selected from SEQ ID NOs: 751-924. In some embodiments, the gene editing system comprises an mgRNA targeting *LPA* gene.

[00435] In some embodiments, the gene editing system comprises an mgRNA comprising an mgRNA spacer selected from SEQ ID NOs: 925-961, and an hgRNA comprising an hgRNA spacer of about 10 to about 20 nt, e.g., 7 nt to 23 nt, 8 nt to 22 nt, 9 nt to 21 nt, and 10 nt to 20 nt, that binds to a site close to the target site that the mgRNA spacer binds to. In some embodiments, the gene editing system comprises an hgRNA comprising an hgRNA spacer selected from SEQ ID NOs: 962-1105. In some embodiments, the gene editing system comprises an mgRNA targeting *AGT* gene.

[00436] In some embodiments, the gene editing system comprises an mgRNA comprising an mgRNA spacer selected from SEQ ID NOs: 1249-1251, and an hgRNA comprising an hgRNA spacer of about 10 to about 20 nt, e.g., 7 nt to 23 nt, 8 nt to 22 nt, 9 nt to 21 nt, and 10 nt to 20 nt, that binds to a site close to the target site that the mgRNA spacer binds to. In some embodiments, the gene editing system comprises an hgRNA comprising an hgRNA spacer selected from SEQ ID NOs: 1252-1265. In some embodiments, the gene editing system comprises an mgRNA targeting *APOC3* gene.

[00437] In some embodiments, the present disclosure provides a gene editing system comprising a main guide RNA (mgRNA) and a helper guide RNA (hgRNA), or at least one DNA polynucleotide encoding the mgRNA and/or the hgRNA, wherein the mgRNA comprises an mgRNA spacer and the hgRNA comprises an hgRNA spacer, wherein the nucleic acid sequences of the mgRNA spacer and the hgRNA spacer comprise the sequences respectively as set forth in Table 7A-7F. In some embodiments, the present disclosure provides a gene editing system comprising a main guide RNA (mgRNA) and a helper guide RNA (hgRNA), or at least one DNA polynucleotide encoding the mgRNA and/or the

hgRNA, wherein the nucleic acid sequences of the mgRNA and the hgRNA comprise the sequences respectively as set forth in Table 8A-8C.

[00438] Table 7A the mgRNA spacer and the hgRNA spacer binding to *PCSK9* gene

mgRNA	Sequence	hgRNA
mg-hPCSK9-GU1	CCCGCACCUUGGCGCAGCGG (SEQ ID NO: 213)	hg-hPCSK9-GU1-U1 UCCCGGCUGCGGGUUCGCCC (SEQ ID NO: 237)
		hg-hPCSK9-GU1-U2 CACCGCACCGUCCCGGCUGC (SEQ ID NO: 238)
		hg-hPCSK9-GU1-U3 GAAACAGCACCGCACCGUCC (SEQ ID NO: 239)
		hg-hPCSK9-GU1-U1 GGGUUCGCCC (SEQ ID NO: 277)
		hg-hPCSK9-GU1-U2 UCCCGGCUGC (SEQ ID NO: 278)
		hg-hPCSK9-GU1-U3 CGCACCGUCC (SEQ ID NO: 279)
mg-hPCSK9-TGG-1	CAGCGGCCACCGAGACCGCC (SEQ ID NO: 214)	hg-hPCSK9-TGG1-U1 UCCUGCGCACGGGCGCCCGC (SEQ ID NO: 240)
		hg-hPCSK9-TGG1-U1 GGGCGCCCGC (SEQ ID NO: 280)
mg-hPCSK9-AG6	ACGGAUCCUGGCCCAUGCA (SEQ ID NO: 215)	hg-hPCSK9-AG6-U1 AGCACCACCACGUAGGUGCC (SEQ ID NO: 241)
		hg-hPCSK9-AG6-U2 CUCCUUCAGCACCACCACGU (SEQ ID NO: 242)
		hg-hPCSK9-AG6-U1 CGUAGGUGCC (SEQ ID NO: 281)
		hg-hPCSK9-AG6-U2 ACCACCACGU (SEQ ID NO: 282)
	UAGGUGCCAGGCAACCUCCA	hg-hPCSK9-M5-U1

mg-hPCSK9-M5	(SEQ ID NO: 216)	GCGCUCUGACUGCGAGAGGU (SEQ ID NO: 243)
		hg-hPCSK9-M5-U2 UGCGCUCUGACUGCGAGAGG (SEQ ID NO: 244)
		hg-hPCSK9-M5-U3 CAGUGCGCUCUGACUGCGAG (SEQ ID NO: 245)
		hg-hPCSK9-M5-U1 UGCGAGAGGU (SEQ ID NO: 283)
		hg-hPCSK9-M5-U2 CUGCGAGAGG (SEQ ID NO: 284)
		hg-hPCSK9-M5-U3 UGACUGCGAG (SEQ ID NO: 285)
mg-hPCSK9-AG7	GAUCCUGGCCCAUGCAAGG (SEQ ID NO: 217)	hg-hPCSK9-AG7-U1 AGCACCACCACGUAGGUGCC (SEQ ID NO: 246)
		hg-hPCSK9-AG7-U2 CUCCUUCAGCACCACCACGU (SEQ ID NO: 247)
		hg-hPCSK9-AG7-U1 CGUAGGUGCC (SEQ ID NO: 286)
		hg-hPCSK9-AG7-U2 CGUAGGUGCC (SEQ ID NO: 287)
mg-hPCSK9-M6	CAGGUUCCACGGGAUGCUCU (SEQ ID NO: 218)	hg-hPCSK9-M6-U1 CAUCCGCCCGGUACCGUGGA (SEQ ID NO: 248)
		hg-hPCSK9-M6-U2 GGGGCUGGUAUUCAUCCGCC (SEQ ID NO: 249)
		hg-hPCSK9-M6-U3 UGGGGGUCUUACCGGGGGC (SEQ ID NO: 250)
		hg-hPCSK9-M6-U1 GUACCGUGGA (SEQ ID NO: 288)
		hg-hPCSK9-M6-U2 UUCAUCCGCC (SEQ ID NO: 289)
		hg-hPCSK9-M6-U3 ACCGGGGGGC (SEQ ID NO: 290)
mg-hPCSK9-M7	CCAGGUUCCACGGGAUGCUC (SEQ ID NO: 219)	hg-hPCSK9-M7-U1 CAUCCGCCCGGUACCGUGGA (SEQ ID NO: 251)
		hg-hPCSK9-M7-U2 GGGGCUGGUAUUCAUCCGCC

		(SEQ ID NO: 252)
		hg-hPCSK9-M7-U3 UGGGGGUCUUACCGGGGGGC (SEQ ID NO: 253)
		hg-hPCSK9-M7-U1 GUACCGUGGA (SEQ ID NO: 291)
		hg-hPCSK9-M7-U2 UUCAUCCGCC (SEQ ID NO: 292)
		hg-hPCSK9-M7-U3 ACCGGGGGGC (SEQ ID NO: 293)
mg-hPCSK9- AG12	AAGGCCUGCAGAAGCCAGAG (SEQ ID NO: 220)	hg-hPCSK9-AG12-U1 GAUGCUCUGGGCAAAGACAG (SEQ ID NO: 254)
		hg-hPCSK9-AG12-U1 GCAAAGACAG (SEQ ID NO: 294)
mg-hPCSK9- GU22	GCUUACCUGUCUGUGGAAGC (SEQ ID NO: 221)	hg-hPCSK9-GU22-U1 CACCUCAGGAUGGGGAUUAU (SEQ ID NO: 255)
		hg-hPCSK9-GU22-U2 CCACCUCAGGAUGGGGAUA (SEQ ID NO: 256)
		hg-hPCSK9-GU22-U1 AUGGGGAUUAU (SEQ ID NO: 295)
		hg-hPCSK9-GU22-U2 GAUGGGGAUA (SEQ ID NO: 296)
mg-hPCSK9- GU23	UGC UUACCUGUCUGUGGAAG (SEQ ID NO: 222)	hg-hPCSK9-GU23-U1 CACCUCAGGAUGGGGAUUAU (SEQ ID NO: 257)
		hg-hPCSK9-GU23-U1 AUGGGGAUUAU (SEQ ID NO: 297)
mg-hPCSK9- AG26	UGGCCUGCUCGACGAACACA (SEQ ID NO: 223)	hg-hPCSK9-AG26-U1 CGCUGACCACCCUGCCAGG (SEQ ID NO: 258)
		hg-hPCSK9-AG26-U2 GGCCGUGACCACCCUGCC (SEQ ID NO: 259)
		hg-hPCSK9-AG26-U1 CCCUGCCAGG (SEQ ID NO: 298)
		hg-hPCSK9-AG26-U2 CACCCUGCC (SEQ ID NO: 299)
mg-hPCSK9- AG39	GAUGACCUGGAAAGGUGAGG (SEQ ID NO: 224)	hg-hPCSK9-AG39-U1 AAGUCCCCAGGGUCACCGGC (SEQ ID NO: 260)

		hg-hPCSK9-AG39-U1 GGUCACCGGC (SEQ ID NO: 300)
mg-hPCSK9-GU47	UACCUGCCCCAUGGGUGCUG (SEQ ID NO: 225)	hg-hPCSK9-GU47-U1 AGACCUCCCAAGCCCCAGCC (SEQ ID NO: 261)
		hg-hPCSK9-GU47-U1 AGCCCCAGCC (SEQ ID NO: 301)
mg-hPCSK9-GU48	UUACCUGCCCCAUGGGUGCU (SEQ ID NO: 226)	hg-hPCSK9-GU48-U1 AGACCUCCCAAGCCCCAGCC (SEQ ID NO: 262)
		hg-hPCSK9-GU48-U1 AGCCCCAGCC (SEQ ID NO: 302)
mg-hPCSK9-GU49	CUUACCUGCCCCAUGGGUGC (SEQ ID NO: 227)	hg-hPCSK9-GU49-U1 AGACCUCCCAAGCCCCAGCC (SEQ ID NO: 263)
		hg-hPCSK9-GU49-U1 AGCCCCAGCC (SEQ ID NO: 303)
mg-hPCSK9-M13	CAGCUGCCAACCUGCAAAAA (SEQ ID NO: 228)	hg-hPCSK9-M13-U1 ACGGCUGUGGCCAUCCGUGU (SEQ ID NO: 264)
		hg-hPCSK9-M13-U1 CCAUCCGUGU (SEQ ID NO: 304)
mg-hPCSK9-M14	ACAGCUGCCAACCUGCAAAAA (SEQ ID NO: 229)	hg-hPCSK9-M14-U1 ACGGCUGUGGCCAUCCGUGU (SEQ ID NO: 265)
		hg-hPCSK9-M14-U1 CCAUCCGUGU (SEQ ID NO: 305)
mg-hPCSK9-AG51	CCAACCUGCAAAAAGGGCCU (SEQ ID NO: 230)	hg-hPCSK9-AG51-U1 ACGGCUGUGGCCAUCCGUGU (SEQ ID NO: 266)
		hg-hPCSK9-AG51-U1 CCAUCCGUGU (SEQ ID NO: 306)
mg-hPCSK9-AG52	GCCAACCUGCAAAAAGGGCC (SEQ ID NO: 231)	hg-hPCSK9-AG52-U1 ACGGCUGUGGCCAUCCGUGU (SEQ ID NO: 267)
		hg-hPCSK9-AG52-U1 CCAUCCGUGU (SEQ ID NO: 307)
mg-hPCSK9-AG54	UUGGGCCUAGAGUCAAGA (SEQ ID NO: 232)	hg-hPCSK9-AG54-U1 CUCACCCCAAAAGCGUUGU (SEQ ID NO: 268)
		hg-hPCSK9-AG54-U1 AAAGCGUUGU (SEQ ID NO: 308)
	UCCAGUGGGAGCUGCAGCC	hg-hPCSK9-M17-U1

mg-hPCSK9-M17	(SEQ ID NO: 233)	CCUCGUGGCCUCAGCACAGG (SEQ ID NO: 269)
		hg-hPCSK9-M17-U1 UCAGCACAGG (SEQ ID NO: 309)
mg-hPCSK9-GU65	CCUCUUCACCUGCUCCUGAG (SEQ ID NO: 234)	hg-hPCSK9-GU65-U1 CUGACACAGAAAAGCUGUGC (SEQ ID NO: 270)
		hg-hPCSK9-GU65-U1 AAAGCUGUGC (SEQ ID NO: 310)
mg-hPCSK9-M19	CAGGGUCCAGCCCUCCUCGC (SEQ ID NO: 235)	hg-hPCSK9-M19-U1 GACGUGGGAGGUCCCAGGGA (SEQ ID NO: 271)
		hg-hPCSK9-M19-U2 CCAGGACGUGGGAGGUCCCA (SEQ ID NO: 272)
		hg-hPCSK9-M19-U3 GUAGGCCCCCAGGACGUGGG (SEQ ID NO: 273)
		hg-hPCSK9-M19-U4 UGUCUACGGCGUAGGCCCCC (SEQ ID NO: 274)
		hg-hPCSK9-M19-U1 GUCCCAGGGA (SEQ ID NO: 311)
		hg-hPCSK9-M19-U2 GGAGGUCCCA (SEQ ID NO: 312)
		hg-hPCSK9-M19-U3 AGGACGUGGG (SEQ ID NO: 313)
		hg-hPCSK9-M19-U4 GUAGGCCCCC (SEQ ID NO: 314)
mg-hPCSK9-AG68	CGGUCACCUGCCAGAGCCCG (SEQ ID NO: 236)	hg-hPCSK9-AG68-U1 GAGGGCACUGCAGCCAGUCA (SEQ ID NO: 275)
		hg-hPCSK9-AG68-U2 GACGUGGGAGGUCCCAGGGA (SEQ ID NO: 276)
		hg-hPCSK9-AG68-U1 CAGCCAGUCA (SEQ ID NO: 315)
		hg-hPCSK9-AG68-U2 GUCCCAGGGA (SEQ ID NO: 316)
mg-mPCSK9-TGG-1	CCGCAGCCACGCAGAGCAGU (SEQ ID NO: 317)	hg-mPCSK9-TGG-1-U1 AGCAGCAGCGGCGGCAACAG (SEQ ID NO: 329)
		hg-mPCSK9-TGG-1-U2 AGCAACAGCAGCAGCAGCGG

		(SEQ ID NO: 330)
		hg-mPCSK9-TGG-1-U3 AGCAGCAACAGCAGCAGCAG (SEQ ID NO: 331)
		hg-mPCSK9-TGG-1-U1 GCGGCAACAG (SEQ ID NO: 366)
		hg-mPCSK9-TGG-1-U2 GCAGCAGCGG (SEQ ID NO: 367)
		hg-mPCSK9-TGG-1-U3 GCAGCAGCAG (SEQ ID NO: 368)
mg-mPCSK9- AG-3	AGGCCUCCUGAUCCCAAGA (SEQ ID NO: 318)	hg-mPCSK9-AG-3-U1 CUCCAUCAGCACCACAAUGU (SEQ ID NO: 332)
		hg-mPCSK9-AG-3-U2 UUGUCAAUCUGUAGCCUCU (SEQ ID NO: 333)
		hg-mPCSK9-AG-3-U1 ACCACAAUGU (SEQ ID NO: 369)
		hg-mPCSK9-AG-3-U2 UGUAGCCUCU (SEQ ID NO: 370)
mg-mPCSK9- TGG-6	CAGGUUCCAUGGGAUGCUCU (SEQ ID NO: 319)	hg-mPCSK9-TGG-6-U1 GGGAGCGGUCUUCCUCUGUC (SEQ ID NO: 334)
		hg-mPCSK9-TGG-6-U2 UGGGGACCUUACCAGGGGAG (SEQ ID NO: 335)
		hg-mPCSK9-TGG-6-U1 UUCCUCUGUC (SEQ ID NO: 371)
		hg-mPCSK9-TGG-6-U2 ACCAGGGGAG (SEQ ID NO: 372)
mg-mPCSK9- CAG-20	UCUUCGCCCAGAGCAUCCCA (SEQ ID NO: 320)	hg-mPCSK9-CAG-20-U1 GGCCCUGAAGUUGCCCAUG (SEQ ID NO: 336)
		hg-mPCSK9-CAG-20-U2 GCCCCAUGUGGAGUACAUUG (SEQ ID NO: 337)
		hg-mPCSK9-CAG-20-U1 UUGCCCAUG (SEQ ID NO: 373)
		hg-mPCSK9-CAG-20-U2 GAGUACAUUG (SEQ ID NO: 374)
mg-mPCSK9- AG-7	UCGCCUGAUCAAUCAACACG (SEQ ID NO: 321)	hg-mPCSK9-AG-7-U1 GCUGACCACACCUGCCAGGU (SEQ ID NO: 338)

		hg-mPCSK9-AG-7-U2 CGCUGACCACACCUGCCAGG (SEQ ID NO: 339)
		hg-mPCSK9-AG-7-U3 GGCCGCUGACCACACCUGCC (SEQ ID NO: 340)
		hg-mPCSK9-AG-7-U1 CCUGCCAGGU (SEQ ID NO: 375)
		hg-mPCSK9-AG-7-U2 ACCUGCCAGG (SEQ ID NO: 376)
		hg-mPCSK9-AG-7-U3 CACACCUGCC (SEQ ID NO: 377)
mg-mPCSK9- GU-10	CCUACCUCUGGAGCAGAAGC (SEQ ID NO: 322)	hg-mPCSK9-GU-10-U1 AGGCAGCUCGGUCAGCAAGG (SEQ ID NO: 341)
		hg-mPCSK9-GU-10-U2 CAGGCAGCUCGGUCAGCAAG (SEQ ID NO: 342)
		hg-mPCSK9-GU-10-U3 CCAGGCAGCUCGGUCAGCAA (SEQ ID NO: 343)
		hg-mPCSK9-GU-10-U4 CCCAGGCAGCUCGGUCAGCA (SEQ ID NO: 344)
		hg-mPCSK9-GU-10-U1 GUCAGCAAGG (SEQ ID NO: 378)
		hg-mPCSK9-GU-10-U2 GGUCAGCAAG (SEQ ID NO: 379)
		hg-mPCSK9-GU-10-U3 CGGUCAGCAA (SEQ ID NO: 380)
mg-mPCSK9- AG-22	GACCUGGCAUGGUAAAGGAG (SEQ ID NO: 323)	hg-mPCSK9-GU-10-U4 UCGGUCAGCA (SEQ ID NO: 381)
		hg-mPCSK9-AG-22-U1 CAAGGUAACUGGCUGGUCCU (SEQ ID NO: 345)
		hg-mPCSK9-AG-22-U2 CCAAGGUAACUGGCUGGUCC (SEQ ID NO: 346)
		hg-mPCSK9-AG-22-U3 AAGUCCCCAAGGUAACUGGC (SEQ ID NO: 347)
		hg-mPCSK9-AG-22-U4 CCCAAAGUCCCCAAGGUAAC (SEQ ID NO: 348)
		hg-mPCSK9-AG-22-U5

		AUUAGUCCCCAAAGUCCCCA (SEQ ID NO: 349)
		hg-mPCSK9-AG-22-U1 GGCUGGUCCU (SEQ ID NO: 382)
		hg-mPCSK9-AG-22-U2 UGGCUGGUCC (SEQ ID NO: 383)
		hg-mPCSK9-AG-22-U3 GGUAAACUGGC (SEQ ID NO: 384)
		hg-mPCSK9-AG-22-U4 CCAAGGUAAC (SEQ ID NO: 385)
		hg-mPCSK9-AG-22-U5 AAAGUCCCCA (SEQ ID NO: 386)
mg-mPCSK9- GU-11	CUCACCUUGUCUCAUGGGUGC (SEQ ID NO: 324)	hg-mPCSK9-GU-11-U1 UGUGAGGCCAGGGCAGGGGC (SEQ ID NO: 350)
		hg-mPCSK9-GU-11-U2 UUCCUGUGAGGCCAGGGCAG (SEQ ID NO: 351)
		hg-mPCSK9-GU-11-U3 CCUCCUGUGAGGCCAGGGC (SEQ ID NO: 352)
		hg-mPCSK9-GU-11-U4 AAAACCUCCUGUGAGGCCA (SEQ ID NO: 353)
		hg-mPCSK9-GU-11-U5 GGAAAGAAAACCUCCUGUG (SEQ ID NO: 354)
		hg-mPCSK9-GU-11-U1 GGGCAGGGGC (SEQ ID NO: 387)
		hg-mPCSK9-GU-11-U2 GCCAGGGCAG (SEQ ID NO: 388)
		hg-mPCSK9-GU-11-U3 AGGCCAGGGC (SEQ ID NO: 389)
		hg-mPCSK9-GU-11-U4 UGUGAGGCCA (SEQ ID NO: 390)
		hg-mPCSK9-GU-11-U5 CCUCCUGUG (SEQ ID NO: 391)
mg-mPCSK9- CAG-16	UUCAGAGCAGGUGAAGGAGU (SEQ ID NO: 325)	hg-mPCSK9-CAG-16-U1 AGGGCUGGAAUGCAAAAUCA (SEQ ID NO: 355)
		hg-mPCSK9-CAG-16-U2 CUGCUGCCAUGCCCCAGGGC

		(SEQ ID NO: 356)
		hg-mPCSK9-CAG-16-U1 UGCAAAAUCA (SEQ ID NO: 392)
		hg-mPCSK9-CAG-16-U2 GCCCCAGGGC (SEQ ID NO: 393)
mg-mPCSK9- AG-17	GACCUGCCAGAGUCCAGAGA (SEQ ID NO: 326)	hg-mPCSK9-AG-17-U1 GAGCACAUUGCAUCCAGUCA (SEQ ID NO: 357)
		hg-mPCSK9-AG-17-U2 GGAGCACAUUGCAUCCAGUC (SEQ ID NO: 358)
		hg-mPCSK9-AG-17-U3 CCAGAGUGAGGGAUGCCCCA (SEQ ID NO: 359)
		hg-mPCSK9-AG-17-U1 CAUCCAGUCA (SEQ ID NO: 394)
		hg-mPCSK9-AG-17-U2 GCAUCCAGUC (SEQ ID NO: 395)
		hg-mPCSK9-AG-17-U3 GGAUGCCCCA (SEQ ID NO: 396)
mg-mPCSK9- TGG-18	CAGGGUCCAUCCUGCUUCGC (SEQ ID NO: 327)	hg-mPCSK9-TGG-18-U1 CCAGAGUGAGGGAUGCCCCA (SEQ ID NO: 360)
		hg-mPCSK9-TGG-18-U2 CCCAGAGUGAGGGAUGCCCC (SEQ ID NO: 361)
		hg-mPCSK9-TGG-18-U3 GCUGUAGGCUCCAGAGUGA (SEQ ID NO: 362)
		hg-mPCSK9-TGG-18-U4 CGCUGUAGGCUCCAGAGUG (SEQ ID NO: 363)
		hg-mPCSK9-TGG-18-U1 GGAUGCCCCA (SEQ ID NO: 397)
		hg-mPCSK9-TGG-18-U2 GGGAUGCCCC (SEQ ID NO: 398)
		hg-mPCSK9-TGG-18-U3 CCCAGAGUGA (SEQ ID NO: 399)
		hg-mPCSK9-TGG-18-U4 UCCAGAGUG (SEQ ID NO: 400)
mg-mPCSK9- CAG-19	GUUCAGUGACAGCCUCAGGC (SEQ ID NO: 328)	hg-mPCSK9-CAG-19-U1 CUGCCAUCUGCUGCCGGAGC (SEQ ID NO: 364)

		hg-mPCSK9-CAG-19-U2 UAGCUGCUGCCAUCUGCUGC (SEQ ID NO: 365)
		hg-mPCSK9-CAG-19-U1 CUGCCGGAGC (SEQ ID NO: 401)
		hg-mPCSK9-CAG-19-U2 CAUCUGCUGC (SEQ ID NO: 402)
mg-monPCSK9	CAGGTTCCATGGGATGCTCT (SEQ ID NO: 1128)	hg-monPCSK9 GGGGCTGGTATTCATCCGCC (SEQ ID NO: 1129)
		hg-monPCSK9 TTCATCCGCC (SEQ ID NO: 1130)

[00439] Table 7B the mgRNA spacer and the hgRNA spacer binding to *ANGPTL3* gene

mgRNA	Sequence	hgRNA
mg-hANGPTL3-1	GGCCUCCUUCAGUUGGGACA (SEQ ID NO: 403)	hg-hANGPTL3-1-U1 CCAGAGCCAAAAUCAAGAUU (SEQ ID NO: 430)
		hg-hANGPTL3-1-U2 GCCAAAAUCAAGAUUUGCUA (SEQ ID NO: 431)
		hg-hANGPTL3-1-U3 AGAUUUGCUAUGUUAGACGA (SEQ ID NO: 432)
		hg-hANGPTL3-1-U1 AAUCAAGAUU (SEQ ID NO: 490)
		hg-hANGPTL3-1-U2 AGAUUUGCUA (SEQ ID NO: 491)
		hg-hANGPTL3-1-U3 UGUUAGACGA (SEQ ID NO: 492)
mg-hANGPTL3-2	UUUCAAAAACUCAACAUUU (SEQ ID NO: 404)	hg-hANGPTL3-2-U1 GGCCUCCUUCAGUUGGGACA (SEQ ID NO: 433)
		hg-hANGPTL3-2-U2 AGACUUUGUCCAUAAAGACGA (SEQ ID NO: 434)
		hg-hANGPTL3-2-U1 AGUUGGGACA (SEQ ID NO: 493)
		hg-hANGPTL3-2-U2 CAUAAGACGA (SEQ ID NO: 494)
	CUGCAAACCAGUGAAAUCAA	hg-hANGPTL3-3-U1

mg-hANGPTL3-3	(SEQ ID NO: 405)	UUUCAAAAACUCAACAUAUU (SEQ ID NO: 435)
		hg-hANGPTL3-3-U2 AAAACUCAACAUAUUUGAUC (SEQ ID NO: 436)
		hg-hANGPTL3-3-U1 UCAACAUAUU (SEQ ID NO: 495)
		hg-hANGPTL3-3-U2 AUAUUUGAUC (SEQ ID NO: 496)
mg-hANGPTL3-4	ACUACAAGUCAAAAAUGAAG (SEQ ID NO: 406)	hg-hANGPTL3-4-U1 UGAAAUCAAAGAAGAAGAAA (SEQ ID NO: 437)
		hg-hANGPTL3-4-U1 GAAGAAGAAA (SEQ ID NO: 497)
mg-hANGPTL3-5	CAACAAAAAGUGAAAUUUU (SEQ ID NO: 407)	hg-hANGPTL3-5-U1 GAGGUAAGAAUAUGUCACU (SEQ ID NO: 438)
		hg-hANGPTL3-5-U2 CUUGAACUCAACUCAAACU (SEQ ID NO: 439)
		hg-hANGPTL3-5-U3 AACUCAACUCAAACUUGAA (SEQ ID NO: 440)
		hg-hANGPTL3-5-U1 AUAUGUCACU (SEQ ID NO: 498)
		hg-hANGPTL3-5-U2 ACUCAAACU (SEQ ID NO: 499)
		hg-hANGPTL3-5-U3 AAAACUUGAA (SEQ ID NO: 500)
mg-hANGPTL3-6	CAAAAUCAACCUGAAACUCC (SEQ ID NO: 408)	hg-hANGPTL3-6-U1 AAAAUUCUACUUCAACAAAA (SEQ ID NO: 441)
		hg-hANGPTL3-6-U2 CAACAAAAAGUGAAAUUUU (SEQ ID NO: 442)
		hg-hANGPTL3-6-U3 AAAAGUGAAAUUUUAGAAG (SEQ ID NO: 443)
		hg-hANGPTL3-6-U1 UUCAACAAAA (SEQ ID NO: 501)
		hg-hANGPTL3-6-U2 UGAAAUUUU (SEQ ID NO: 502)
		hg-hANGPTL3-6-U3 UAUUUAGAAG

		(SEQ ID NO: 503)
mg-hANGPTL3-7	ACUUUAAGUGAAGUUACUUC (SEQ ID NO: 409)	hg-hANGPTL3-7-U1 CCACAUUGAAAACAUAACA (SEQ ID NO: 444)
		hg-hANGPTL3-7-U2 UUUUUUUAAAAGAUCCACAU (SEQ ID NO: 445)
		hg-hANGPTL3-7-U3 UUAGAAAUUUUUUUUAAA (SEQ ID NO: 446)
		hg-hANGPTL3-7-U1 AACAUAAACA (SEQ ID NO: 504)
		hg-hANGPTL3-7-U2 AGAUCCACAU (SEQ ID NO: 505)
		hg-hANGPTL3-7-U3 UUUUUUUAAA (SEQ ID NO: 506)
mg-hANGPTL3-8	UUUCUACUUACUUUAAGUGA (SEQ ID NO: 410)	hg-hANGPTL3-8-U1 CCACAUUGAAAACAUAACA (SEQ ID NO: 447)
		hg-hANGPTL3-8-U2 UUUUUUUAAAAGAUCCACAU (SEQ ID NO: 448)
		hg-hANGPTL3-8-U3 UUAGAAAUUUUUUUUAAA (SEQ ID NO: 449)
		hg-hANGPTL3-8-U1 AACAUAAACA (SEQ ID NO: 507)
		hg-hANGPTL3-8-U2 AGAUCCACAU (SEQ ID NO: 508)
		hg-hANGPTL3-8-U3 UUUUUUUAAA (SEQ ID NO: 509)
mg-hANGPTL3-9	AAAGUCUGGAUUAUAGAGAGU (SEQ ID NO: 411)	hg-hANGPTL3-9-U1 GGUCUCCACGGUCUGGAGA (SEQ ID NO: 450)
		hg-hANGPTL3-9-U2 UAUAUUGGUCUCCACGGUC (SEQ ID NO: 451)
		hg-hANGPTL3-9-U3 UUGUUUAUAUUGGUCUCCA (SEQ ID NO: 452)
		hg-hANGPTL3-9-U1 GGUCUGGAGA (SEQ ID NO: 510)
		hg-hANGPTL3-9-U2 UCCACGGUC (SEQ ID NO: 511)

		hg-hANGPTL3-9-U3 UGGUCUCCA (SEQ ID NO: 512)
mg- hANGPTL3- 10	AAACAAGAUAAUAGCAUCAA (SEQ ID NO: 412)	hg-hANGPTL3-10-U1 GAAAUUAAUAGAAAAGAAAG (SEQ ID NO: 453)
		hg-hANGPTL3-10-U1 GAAAAGAAAG (SEQ ID NO: 513)
mg- hANGPTL3- 11	AUUAAAACAAUAAAACCAAC (SEQ ID NO: 413)	hg-hANGPTL3-11-U1 UUGUAGAAAAACAAGAUAAU (SEQ ID NO: 454)
		hg-hANGPTL3-11-U2 AAACAAGAUAAUAGCAUCAA (SEQ ID NO: 455)
		hg-hANGPTL3-11-U3 UAGCAUCAAGACCUUCUCC (SEQ ID NO: 456)
		hg-hANGPTL3-11-U1 ACAAGAUAAU (SEQ ID NO: 514)
		hg-hANGPTL3-11-U2 ACAAGAUAAU (SEQ ID NO: 515)
		hg-hANGPTL3-11-U3 ACAAGAUAAU (SEQ ID NO: 516)
mg- hANGPTL3- 12	CAUAGUCAAAUAAAAGAAU (SEQ ID NO: 414)	hg-hANGPTL3-12-U1 CAAAGACCUUCUCCAGACCG (SEQ ID NO: 457)
		hg-hANGPTL3-12-U2 UAGCAUCAAGACCUUCUCC (SEQ ID NO: 458)
		hg-hANGPTL3-12-U1 CUCCAGACCG (SEQ ID NO: 517)
		hg-hANGPTL3-12-U2 CUCCAGACCG (SEQ ID NO: 518)
mg- hANGPTL3- 13	UUCUUCAGUUGAAUGAAUA (SEQ ID NO: 415)	hg-hANGPTL3-13-U1 ACUAGUAUUAAGAACCCAC (SEQ ID NO: 459)
		hg-hANGPTL3-13-U2 AGAAAUUUCUCUAUCUCCA (SEQ ID NO: 460)
		hg-hANGPTL3-13-U3 UCUCUAUCUCCAAGCCAAG (SEQ ID NO: 461)
		hg-hANGPTL3-13-U1 AAGAACCCAC (SEQ ID NO: 519)
		hg-hANGPTL3-13-U2

		CUAUCUCCA (SEQ ID NO: 520)
		hg-hANGPTL3-13-U3 CCAAGCCAAG (SEQ ID NO: 521)
mg- hANGPTL3- 14	AAUGCCUAGAAUCAAUAAAA (SEQ ID NO: 416)	hg-hANGPTL3-14-U1 AUGUUCACCUCUGUUUAAAA (SEQ ID NO: 462)
		hg-hANGPTL3-14-U2 CUGAUGGCAUACAUGCCACU (SEQ ID NO: 463)
		hg-hANGPTL3-14-U1 CUGUUUAAAA (SEQ ID NO: 522)
		hg-hANGPTL3-14-U2 ACAUGCCACU (SEQ ID NO: 523)
mg- hANGPTL3- 15	CUCAAGUUUUUCAUGUCUAC (SEQ ID NO: 417)	hg-hANGPTL3-15-U1 UGUACCACCAUUUUAACAG (SEQ ID NO: 464)
		hg-hANGPTL3-15-U2 AACAGAGGUGAACAUACAAG (SEQ ID NO: 465)
		hg-hANGPTL3-15-U1 UUUAUAACAG (SEQ ID NO: 524)
		hg-hANGPTL3-15-U2 AACAUACAAG (SEQ ID NO: 525)
mg- hANGPTL3- 16	UUUACCUGAUUAACAUCAC (SEQ ID NO: 418)	hg-hANGPTL3-16-U1 GAGUAAGUUGAACUAACUAC (SEQ ID NO: 466)
		hg-hANGPTL3-16-U2 CUAAUACGUAAGAGUAAAGU (SEQ ID NO: 467)
		hg-hANGPTL3-16-U3 AAUCUCCUAAUACGUAAG (SEQ ID NO: 468)
		hg-hANGPTL3-16-U1 AACUAACUAC (SEQ ID NO: 526)
		hg-hANGPTL3-16-U2 AUGAGUAAAGU (SEQ ID NO: 527)
		hg-hANGPTL3-16-U3 AUACGUAAG (SEQ ID NO: 528)
mg- hANGPTL3- 17	GACUACCUGAAUUAUAUGAA (SEQ ID NO: 419)	hg-hANGPTL3-17-U1 CACGUUUCAUUGAAGUUUUG (SEQ ID NO: 469)
		hg-hANGPTL3-17-U2 GUAGUUCUCCACGUUUCAU

		(SEQ ID NO: 470)
		hg-hANGPTL3-17-U1 UGAAGUUUUG (SEQ ID NO: 529)
		hg-hANGPTL3-17-U2 CACGUUUUCAU (SEQ ID NO: 530)
mg- hANGPTL3- 18	AUUAAUGUCCAUGGACUACC (SEQ ID NO: 420)	hg-hANGPTL3-18-U1 CACGUUUUCAUUGAAGUUUUG (SEQ ID NO: 471)
		hg-hANGPTL3-18-U2 GUAGUUCUCCCACGUUUUCAU (SEQ ID NO: 472)
		hg-hANGPTL3-18-U1 UGAAGUUUUG (SEQ ID NO: 531)
		hg-hANGPTL3-18-U2 CACGUUUUCAU (SEQ ID NO: 532)
mg- hANGPTL3- 19	UUAAUUCAACAUCGAAUAGA (SEQ ID NO: 421)	hg-hANGPTL3-19-U1 UGAUUUCAUUCAUUAUAUUC (SEQ ID NO: 473)
		hg-hANGPTL3-19-U1 CAUUAUAUUC (SEQ ID NO: 533)
mg- hANGPTL3- 20	CACAAAACUUCAAUGAAACG (SEQ ID NO: 422)	hg-hANGPTL3-20-U1 UGAUUUCAUUCAUUAUAUUC (SEQ ID NO: 474)
		hg-hANGPTL3-20-U2 CAUUAUAUUCAGGUAGUCCA (SEQ ID NO: 475)
		hg-hANGPTL3-20-U1 CAUUAUAUUC (SEQ ID NO: 534)
		hg-hANGPTL3-20-U2 AGGUAGUCCA (SEQ ID NO: 535)
mg- hANGPTL3- 21	GUUCUCCCACGUUUCAUUGA (SEQ ID NO: 423)	hg-hANGPTL3-21-U1 AUGUAGUCCCCUUAACCAUCA (SEQ ID NO: 476)
		hg-hANGPTL3-21-U2 GUGAAUGAAUGAUUGAAUGU (SEQ ID NO: 477)
		hg-hANGPTL3-21-U1 CUUACCAUCA (SEQ ID NO: 536)
		hg-hANGPTL3-21-U2 GAUUGAAUGU (SEQ ID NO: 537)
mg- hANGPTL3- 22	CAACCAAAAUUCUCCUGAAA (SEQ ID NO: 424)	hg-hANGPTL3-22-U1 AUAAUUAGAUUGCUUCACUA (SEQ ID NO: 478)

		hg-hANGPTL3-22-U1 UGCUCACUA (SEQ ID NO: 538)
mg- hANGPTL3- 23	AGCAAUCUAAUUAUGUUUUA (SEQ ID NO: 425)	hg-hANGPTL3-23-U1 UUUUUAAAACUUUUUUUUUC (SEQ ID NO: 479)
		hg-hANGPTL3-23-U2 UUUUCUUUUUCAGGAGAAUUU (SEQ ID NO: 480)
		hg-hANGPTL3-23-U3 UUUUCAGGAGAAUUUUGGUU (SEQ ID NO: 481)
		hg-hANGPTL3-23-U1 UUUUCUUUUUC (SEQ ID NO: 539)
		hg-hANGPTL3-23-U2 AGGAGAAUUU (SEQ ID NO: 540)
		hg-hANGPTL3-23-U3 AAUUUUGGUU (SEQ ID NO: 541)
mg- hANGPTL3- 24	UACGAAUUGAGUUGGAAGAC (SEQ ID NO: 426)	hg-hANGPTL3-24-U1 UUUUUAAAACUUUUUUUUUC (SEQ ID NO: 482)
		hg-hANGPTL3-24-U2 UUUUCUUUUUCAGGAGAAUUU (SEQ ID NO: 483)
		hg-hANGPTL3-24-U3 UUUUCAGGAGAAUUUUGGUU (SEQ ID NO: 484)
		hg-hANGPTL3-24-U1 UUUUCUUUUUC (SEQ ID NO: 542)
		hg-hANGPTL3-24-U2 AGGAGAAUUU (SEQ ID NO: 543)
		hg-hANGPTL3-24-U3 AAUUUUGGUU (SEQ ID NO: 544)
mg- hANGPTL3- 25	AAGAUACCUGAAUAACCCUC (SEQ ID NO: 427)	hg-hANGPTL3-25-U1 CAGAUAAUAGCUAAUAAUGU (SEQ ID NO: 485)
		hg-hANGPTL3-25-U1 CUAAUAAUGU (SEQ ID NO: 545)
mg- hANGPTL3- 26	CCUCCUAAAGGAGAUAGAU (SEQ ID NO: 428)	hg-hANGPTL3-26-U1 GUUUGUUAUAUUUACCAUUU (SEQ ID NO: 486)
		hg-hANGPTL3-26-U2 UCUGGCUUAGAUUUUGCUCU (SEQ ID NO: 487)
		hg-hANGPTL3-26-U1

		UUUACCAUUU (SEQ ID NO: 546)
		hg-hANGPTL3-26-U2 AUUUUGCUCU (SEQ ID NO: 547)
mg- hANGPTL3- 27	UGCCACCACCAGCCUCCUAA (SEQ ID NO: 429)	hg-hANGPTL3-27-U1 GUUUGUUUAUUAUUUACCAUUU (SEQ ID NO: 488)
		hg-hANGPTL3-27-U2 UCUGGCUUAGAUUUUGCUCU (SEQ ID NO: 489)
		hg-hANGPTL3-27-U1 UUUACCAUUU (SEQ ID NO: 548)
		hg-hANGPTL3-27-U2 AUUUUGCUCU (SEQ ID NO: 549)
mg- mANGPTL3-1	GGCCUCCUGCAGCUGGGUCA (SEQ ID NO: 550)	hg-mANGPTL3-1-U1 AAAAUCAAGAUUUGCUAUGU (SEQ ID NO: 553)
		hg-mANGPTL3-1-U1 UUUGCUAUGU (SEQ ID NO: 558)
mg- mANGPTL3-2	ACUACAAGUAAAAACGAGG (SEQ ID NO: 551)	hg-mANGPTL3-2-U1 AACCAAUGAAAUCAAGAAG (SEQ ID NO: 554)
		hg-mANGPTL3-2-U2 UGAAAUCAAAGAAGAGGAAA (SEQ ID NO: 555)
		hg-mANGPTL3-2-U1 AUCAAAGAAG (SEQ ID NO: 559)
		hg-mANGPTL3-2-U2 GAAGAGGAAA (SEQ ID NO: 560)
mg- mANGPTL3-3	AGCCCUUCAACACAAGGUCA (SEQ ID NO: 552)	hg-mANGPTL3-3-U1 GAAGAACAUGUCAGUAGAAC (SEQ ID NO: 556)
		hg-mANGPTL3-3-U2 GUAGAACUGAACUCAAGCU (SEQ ID NO: 557)
		hg-mANGPTL3-3-U1 UCAGUAGAAC (SEQ ID NO: 561)
		hg-mANGPTL3-3-U2 ACUCAAGCU (SEQ ID NO: 562)

[00440] Table 7C the mgRNA spacer and the hgRNA spacer binding to *ASGR1* gene

mgRNA	Sequence	hgRNA
mg-hASGR1-1	GUAUCAAGACCUUCAGCAUC (SEQ ID NO: 563)	hg-hASGR1-1-U1 CUCAGUCUUGACUCAGUCCC (SEQ ID NO: 585)
		hg-hASGR1-1-U1 ACUCAGUCCC (SEQ ID NO: 631)
mg-hASGR1-2	CCUUCAGCAUCUGGACAAUG (SEQ ID NO: 564)	hg-hASGR1-2-U1 CUCAGUCUUGACUCAGUCCC (SEQ ID NO: 586)
		hg-hASGR1-2-U1 ACUCAGUCCC (SEQ ID NO: 632)
mg-hASGR1-3	CCAUCAGCUCAGAAAAGGUG (SEQ ID NO: 565)	hg-hASGR1-3-U1 CGCCAGCCCUAUCAUGACCA (SEQ ID NO: 587)
		hg-hASGR1-3-U2 GUAUCAAGACCUUCAGCAUC (SEQ ID NO: 588)
		hg-hASGR1-3-U1 AUCAUGACCA (SEQ ID NO: 633)
		hg-hASGR1-3-U2 CUUCAGCAUC (SEQ ID NO: 634)
mg-hASGR1-4	CAUCAGCUCAGAAAAGGUGA (SEQ ID NO: 566)	hg-hASGR1-4-U1 CGCCAGCCCUAUCAUGACCA (SEQ ID NO: 589)
		hg-hASGR1-4-U2 GUAUCAAGACCUUCAGCAUC (SEQ ID NO: 590)
		hg-hASGR1-4-U1 AUCAUGACCA (SEQ ID NO: 635)
		hg-hASGR1-4-U2 CUUCAGCAUC (SEQ ID NO: 636)
mg-hASGR1-5	CCUCACCUUUUCUGAGCUGA (SEQ ID NO: 567)	hg-hASGR1-5-U1 GCCAAAUUCUCGCCUUGCAG (SEQ ID NO: 591)
		hg-hASGR1-5-U2 UAGGAGCUGUGGCUGGGGGG (SEQ ID NO: 592)
		hg-hASGR1-5-U3 GAGUAGGAGCUGUGGCUGGG (SEQ ID NO: 593)
		hg-hASGR1-5-U1 CGCCUUGCAG (SEQ ID NO: 637)
		hg-hASGR1-5-U2 GGCUGGGGGG

		(SEQ ID NO: 638)
		hg-hASGR1-5-U3 UGUGGCUGGG (SEQ ID NO: 639)
mg- hASGR1-6	GGUGGCCUGCAAGAGGAGG (SEQ ID NO: 568)	hg-hASGR1-6-U1 GUCCGGAGCAGAGACGCUGC (SEQ ID NO: 594)
		hg-hASGR1-6-U2 GAGCAGGAGGAGGCGAGGUC (SEQ ID NO: 595)
		hg-hASGR1-6-U3 AGGGAGAGCAGGAGGAGGCG (SEQ ID NO: 596)
		hg-hASGR1-6-U1 GAGACGCUGC (SEQ ID NO: 640)
		hg-hASGR1-6-U2 AGGCGAGGUC (SEQ ID NO: 641)
		hg-hASGR1-6-U3 GGAGGAGGCG (SEQ ID NO: 642)
mg- hASGR1-7	CUCCUGCAGCGUCUCUGCUC (SEQ ID NO: 569)	hg-hASGR1-7-U1 UGACACCCCUCCUCUUGCA (SEQ ID NO: 597)
		hg-hASGR1-7-U2 CUGACACCCCUCCUCUUGC (SEQ ID NO: 598)
		hg-hASGR1-7-U1 UCCUCUUGCA (SEQ ID NO: 643)
		hg-hASGR1-7-U2 CUCCUCUUGC (SEQ ID NO: 644)
mg- hASGR1-8	GAUCCCAAAGUGGGUGCCCC (SEQ ID NO: 570)	hg-hASGR1-8-U1 UCGCCUCCUCCUGCUCUCCC (SEQ ID NO: 599)
		hg-hASGR1-8-U2 CGCCUCCUCCUGCUCUCCCU (SEQ ID NO: 600)
		hg-hASGR1-8-U3 CCUCAGCCUCCUGCUGCUUG (SEQ ID NO: 601)
		hg-hASGR1-8-U1 CUGCUCUCCC (SEQ ID NO: 645)
		hg-hASGR1-8-U2 UGCUCUCCCU (SEQ ID NO: 646)
		hg-hASGR1-8-U3

		CUGCUGCUUG (SEQ ID NO: 647)
mg- hASGR1-9	AUCCCAAAGUGGGUGCCCCA (SEQ ID NO: 571)	hg-hASGR1-9-U1 UCGCCUCCUCCUGCUCUCCC (SEQ ID NO: 602)
		hg-hASGR1-9-U2 CGCCUCCUCCUGCUCUCCCU (SEQ ID NO: 603)
		hg-hASGR1-9-U3 CCUCAGCCUCCUGCUGCUUG (SEQ ID NO: 604)
		hg-hASGR1-9-U1 CUGCUCUCCC (SEQ ID NO: 648)
		hg-hASGR1-9-U2 UGCUCUCCCU (SEQ ID NO: 649)
		hg-hASGR1-9-U3 CUGCUGCUUG (SEQ ID NO: 650)
mg- hASGR1-10	CCCAGCUGCAGGAGGAGCUG (SEQ ID NO: 572)	hg-hASGR1-10-U1 GGGAGUGGUGGGUGCAGUGG (SEQ ID NO: 605)
		hg-hASGR1-10-U2 AGUGGUGGGUGCAGUGGUGG (SEQ ID NO: 606)
		hg-hASGR1-10-U1 GGUGCAGUGG (SEQ ID NO: 651)
		hg-hASGR1-10-U2 GCAGUGGUGG (SEQ ID NO: 652)
mg- hASGR1-11	CCAGCUGCAGGAGGAGCUGC (SEQ ID NO: 573)	hg-hASGR1-11-U1 GGGAGUGGUGGGUGCAGUGG (SEQ ID NO: 607)
		hg-hASGR1-11-U2 AGUGGUGGGUGCAGUGGUGG (SEQ ID NO: 608)
		hg-hASGR1-11-U1 GGUGCAGUGG (SEQ ID NO: 653)
		hg-hASGR1-11-U2 GCAGUGGUGG (SEQ ID NO: 654)
mg- hASGR1-12	CAGCUGCAGGAGGAGCUGCG (SEQ ID NO: 574)	hg-hASGR1-12-U1 GGGAGUGGUGGGUGCAGUGG (SEQ ID NO: 609)
		hg-hASGR1-12-U2 AGUGGUGGGUGCAGUGGUGG (SEQ ID NO: 610)

		hg-hASGR1-12-U1 GGUGCAGUGG (SEQ ID NO: 655)
		hg-hASGR1-12-U2 GCAGUGGUGG (SEQ ID NO: 656)
mg- hASGR1-13	AGCACCCAGGGUGAGGGCGC (SEQ ID NO: 575)	hg-hASGR1-13-U1 CAGCAACUUCACAGCGAGCA (SEQ ID NO: 611)
		hg-hASGR1-13-U2 CAACUUCACAGCGAGCACGG (SEQ ID NO: 612)
		hg-hASGR1-13-U1 ACAGCGAGCA (SEQ ID NO: 657)
		hg-hASGR1-13-U2 GCGAGCACGG (SEQ ID NO: 658)
mg- hASGR1-14	GCACCCAGGGUGAGGGCGCU (SEQ ID NO: 576)	hg-hASGR1-14-U1 CAGCAACUUCACAGCGAGCA (SEQ ID NO: 613)
		hg-hASGR1-14-U2 CAACUUCACAGCGAGCACGG (SEQ ID NO: 614)
		hg-hASGR1-14-U1 ACAGCGAGCA (SEQ ID NO: 659)
		hg-hASGR1-14-U2 GCGAGCACGG (SEQ ID NO: 660)
mg- hASGR1-15	CACCCAGGGUGAGGGCGCUG (SEQ ID NO: 577)	hg-hASGR1-15-U1 CAGCAACUUCACAGCGAGCA (SEQ ID NO: 615)
		hg-hASGR1-15-U2 CAACUUCACAGCGAGCACGG (SEQ ID NO: 616)
		hg-hASGR1-15-U1 ACAGCGAGCA (SEQ ID NO: 661)
		hg-hASGR1-15-U2 GCGAGCACGG (SEQ ID NO: 662)
mg- hASGR1-16	CAGCAGAAGGACCUGAGUGA (SEQ ID NO: 578)	hg-hASGR1-16-U1 GCUGAGCGAGCCUCUCCCGC (SEQ ID NO: 617)
		hg-hASGR1-16-U2 GAGCGAGCCUCUCCCGCAGG (SEQ ID NO: 618)
		hg-hASGR1-16-U3 UCUCCCGCAGGAGGCAAUGU (SEQ ID NO: 619)

		hg-hASGR1-16-U1 CCUCUCCCGC (SEQ ID NO: 663)
		hg-hASGR1-16-U2 CUCCCGCAGG (SEQ ID NO: 664)
		hg-hASGR1-16-U3 GAGGCAAUGU (SEQ ID NO: 665)
mg- hASGR1-17	AUCUGGGGAGACCGGGCGGA (SEQ ID NO: 579)	hg-hASGR1-17-U1 CAGACACGAACUGCUUCACG (SEQ ID NO: 620)
		hg-hASGR1-17-U2 UCUGACAGCUCAGGCUCCGC (SEQ ID NO: 621)
		hg-hASGR1-17-U3 GCGCCGCCAUCUGACAGCUC (SEQ ID NO: 622)
		hg-hASGR1-17-U1 CUGCUUCACG (SEQ ID NO: 666)
		hg-hASGR1-17-U2 CAGGCUCCGC (SEQ ID NO: 667)
		hg-hASGR1-17-U3 CUGACAGCUC (SEQ ID NO: 668)
mg- hASGR1-18	AGUGAUCUGGGGAGACCGGG (SEQ ID NO: 580)	hg-hASGR1-18-U1 CAGACACGAACUGCUUCACG (SEQ ID NO: 623)
		hg-hASGR1-18-U2 UCUGACAGCUCAGGCUCCGC (SEQ ID NO: 624)
		hg-hASGR1-18-U3 GCGCCGCCAUCUGACAGCUC (SEQ ID NO: 625)
		hg-hASGR1-18-U1 CUGCUUCACG (SEQ ID NO: 669)
		hg-hASGR1-18-U2 CAGGCUCCGC (SEQ ID NO: 670)
		hg-hASGR1-18-U3 CUGACAGCUC (SEQ ID NO: 671)
mg- hASGR1-20	AGCAGUUCGUGUCUGACCUG (SEQ ID NO: 581)	hg-hASGR1-20-U1 UCCUCCCGCUCUCCCGCC (SEQ ID NO: 626)
		hg-hASGR1-20-U1 CCCCUCCGCC (SEQ ID NO: 672)

mg-hASGR1-23	GGCGCUCCAGGGCAAUGGUA (SEQ ID NO: 582)	hg-hASGR1-23-U1 AGCAGUUCGUGUCUGACCUG (SEQ ID NO: 627)
		hg-hASGR1-23-U1 GUCUGACCUG (SEQ ID NO: 673)
mg-hASGR1-24	GCUCCAGGGCAAUGGUAAGG (SEQ ID NO: 583)	hg-hASGR1-24-U1 AGCAGUUCGUGUCUGACCUG (SEQ ID NO: 628)
		hg-hASGR1-24-U1 GUCUGACCUG (SEQ ID NO: 674)
mg-hASGR1-28	CACCCAGUUGACCGGGCAGC (SEQ ID NO: 584)	hg-hASGR1-28-U1 GGCGUCAGCCCAGGCCUCC (SEQ ID NO: 629)
		hg-hASGR1-28-U2 GUAGUUGUCGGCGUCAGCCC (SEQ ID NO: 630)
		hg-hASGR1-28-U1 CAGGCCUCC (SEQ ID NO: 675)
		hg-hASGR1-28-U2 GCGUCAGCCC (SEQ ID NO: 676)
mg-mASGR1-1	UUAUCAAGAUUCCAGCACCC (SEQ ID NO: 677)	hg-mASGR1-1-U1 AGCUCUAAAGGCUCUAAAUU (SEQ ID NO: 685)
		hg-mASGR1-1-U2 GCUCUAAAUUUGGCUGUCCU (SEQ ID NO: 686)
		hg-mASGR1-1-U3 AAAUUUGGCUGUCCUAGGUC (SEQ ID NO: 687)
		hg-mASGR1-1-U1 GCUCUAAAUU (SEQ ID NO: 701)
		hg-mASGR1-1-U2 UGGCUGUCCU (SEQ ID NO: 702)
		hg-mASGR1-1-U3 GUCCUAGGUC (SEQ ID NO: 703)
mg-mASGR1-2	AUCAACUCCGGAGAGGUGAG (SEQ ID NO: 678)	hg-mASGR1-2-U1 AUCCAGUGCCAUCAUGACAA (SEQ ID NO: 688)
		hg-mASGR1-2-U2 UUAUCAAGAUUCCAGCACCC (SEQ ID NO: 689)
		hg-mASGR1-2-U1 AUCAUGACAA (SEQ ID NO: 704)

		hg-mASGR1-2-U2 UUCCAGCACC (SEQ ID NO: 705)
mg- mASGR1-3	CACCUCUCCGGAGUUGAUGA (SEQ ID NO: 679)	hg-mASGR1-3-U1 ACUGAUGUUCUCCUCCAGAG (SEQ ID NO: 690)
		hg-mASGR1-3-U2 CCACUGAUGUUCUCCUCCAG (SEQ ID NO: 691)
		hg-mASGR1-3-U1 UCCUCCAGAG (SEQ ID NO: 706)
		hg-mASGR1-3-U2 UCUCCUCCAG (SEQ ID NO: 707)
mg- mASGR1-4	CUCUUGCAGCGACUCUGCUC (SEQ ID NO: 680)	hg-mASGR1-4-U1 CUCUUGAUACGCUCUCUUGC (SEQ ID NO: 692)
		hg-mASGR1-4-U2 UCUUGAUACGCUCUCUUGCA (SEQ ID NO: 693)
		hg-mASGR1-4-U1 GCUCUCUUGC (SEQ ID NO: 708)
		hg-mASGR1-4-U2 CUCUCUUGCA (SEQ ID NO: 709)
mg- mASGR1-5	CAUCCCAAAGUGGGUGGCCA (SEQ ID NO: 681)	hg-mASGR1-5-U1 GAGCCUCAGCAUUCUGUUGC (SEQ ID NO: 694)
		hg-mASGR1-5-U1 AUUCUGUUGC (SEQ ID NO: 710)
mg- mASGR1-6	AGCCUGAGGUGAGGGAAUGC (SEQ ID NO: 682)	hg-mASGR1-6-U1 CAUACUCCACCCAGUUGAUG (SEQ ID NO: 695)
		hg-mASGR1-6-U2 UUCAUACUCCACCCAGUUGA (SEQ ID NO: 696)
		hg-mASGR1-6-U1 CCAGUUGAUG (SEQ ID NO: 711)
		hg-mASGR1-6-U2 ACCCAGUUGA (SEQ ID NO: 712)
mg- mASGR1-7	CACCCAGUUGAUGGGGCAGC (SEQ ID NO: 683)	hg-mASGR1-7-U1 AGUCCAAGGCCUCACAGAGC (SEQ ID NO: 697)
		hg-mASGR1-7-U2 UACUUGUCAGCUUCAGUCCA (SEQ ID NO: 698)

		hg-mASGR1-7-U1 CUCACAGAGC (SEQ ID NO: 713)
		hg-mASGR1-7-U2 CUUCAGUCCA (SEQ ID NO: 714)
mg-mASGR1-8	AGUCCAAGGCCUCACAGAGC (SEQ ID NO: 684)	hg-mASGR1-8-U1 CCAGAUGGGCAUUUCCAGC (SEQ ID NO: 699)
		hg-mASGR1-8-U2 GGAGGUCACCACCAGAU (SEQ ID NO: 700)
		hg-mASGR1-8-U1 AUUUUCCAGC (SEQ ID NO: 715)
		hg-mASGR1-8-U2 ACCACCAGAU (SEQ ID NO: 716)

[00441] Table 7D the mgRNA spacer and the hgRNA spacer binding to *LPA* gene

mgRNA	Sequence	hgRNA
mg-hLPA-1	UGAGCAAAGCCAUGUGGUCC (SEQ ID NO: 717)	hg-hLPA-1-U1 CUAUUCAGCUUGAUUUCUUC (SEQ ID NO: 751)
		hg-hLPA-1-U2 GUUCUAAGAACUAUUCAGCU (SEQ ID NO: 752)
		hg-hLPA-1-U3 UUCUGUUCUAAGAACUAUUC (SEQ ID NO: 753)
		hg-hLPA-1-U4 UCACAUUUUUUCUGUUCUA (SEQ ID NO: 754)
		hg-hLPA-1-U5 AAUGACUUCACAUUUUUUUC (SEQ ID NO: 755)
		hg-hLPA-1-U1 UGAUUUCUUC (SEQ ID NO: 838)
		hg-hLPA-1-U2 CUAUUCAGCU (SEQ ID NO: 839)
		hg-hLPA-1-U3 AGAACUAUUC (SEQ ID NO: 840)
		hg-hLPA-1-U4 UUCUGUUCUA (SEQ ID NO: 841)

		hg-hLPA-1-U5 CAUUUUUUUC (SEQ ID NO: 842)
mg-hLPA-2	GUGGUCCAGGAUUGCUACCA (SEQ ID NO: 718)	hg-hLPA-2-U1 GUUUUAAUUUUAGCAGCACC (SEQ ID NO: 756)
		hg-hLPA-2-U2 UCUUCUGUUUUAAUUUUAGC (SEQ ID NO: 757)
		hg-hLPA-2-U3 CUAUUCAGCUUGAUUUCUUC (SEQ ID NO: 758)
		hg-hLPA-2-U4 GUUCUAAGAACUAUUCAGCU (SEQ ID NO: 759)
		hg-hLPA-2-U5 UUCUGUUCUAAGAACUAUUC (SEQ ID NO: 760)
		hg-hLPA-2-U1 UAGCAGCACC (SEQ ID NO: 843)
		hg-hLPA-2-U2 UAAUUUUAGC (SEQ ID NO: 844)
		hg-hLPA-2-U3 UGAUUUCUUC (SEQ ID NO: 845)
		hg-hLPA-2-U4 CUAUUCAGCU (SEQ ID NO: 846)
		hg-hLPA-2-U5 AGAACUAUUC (SEQ ID NO: 847)
mg-hLPA-3	UGGACAGAGUUAUCGAGGCA (SEQ ID NO: 719)	hg-hLPA-3-U1 GAGCAAAGCCAUGUGGUCCA (SEQ ID NO: 761)
		hg-hLPA-3-U2 UGAGCAAAGCCAUGUGGUCC (SEQ ID NO: 762)
		hg-hLPA-3-U3 AGCACCUGAGCAAAGCCAUG (SEQ ID NO: 763)
		hg-hLPA-3-U4 GCAGCACCUGAGCAAAGCCA (SEQ ID NO: 764)
		hg-hLPA-3-U5 UUUUAGCAGCACCUGAGCAA (SEQ ID NO: 765)
		hg-hLPA-3-U1 AUGUGGUCCA (SEQ ID NO: 848)

		hg-hLPA-3-U2 CAUGUGGUCC (SEQ ID NO: 849)
		hg-hLPA-3-U3 CAAAGCCAUG (SEQ ID NO: 850)
		hg-hLPA-3-U4 AGCAAAGCCA (SEQ ID NO: 851)
		hg-hLPA-3-U5 ACCUGAGCAA (SEQ ID NO: 852)
mg-hLPA-4	CUGCCAAGCUUGGUCAUCUA (SEQ ID NO: 720)	hg-hLPA-4-U1 CGAGGCACGUACUCCACCAC (SEQ ID NO: 766)
		hg-hLPA-4-U2 UGGACAGAGUUAUCGAGGCA (SEQ ID NO: 767)
		hg-hLPA-4-U3 GGUGAUGGACAGAGUUAUCG (SEQ ID NO: 768)
		hg-hLPA-4-U4 GCUACCAUGGUGAUGGACAG (SEQ ID NO: 769)
		hg-hLPA-4-U1 ACUCCACCAC (SEQ ID NO: 853)
		hg-hLPA-4-U2 UAUCGAGGCA (SEQ ID NO: 854)
		hg-hLPA-4-U3 AGAGUUAUCG (SEQ ID NO: 855)
		hg-hLPA-4-U4 UGAUGGACAG (SEQ ID NO: 856)
mg-hLPA-5	CAUCAACAUAUAGGACCAC (SEQ ID NO: 721)	hg-hLPA-5-U1 CAGGAAGGACCUGCCAAGCU (SEQ ID NO: 770)
		hg-hLPA-5-U2 GUCACAGGAAGGACCUGCCA (SEQ ID NO: 771)
		hg-hLPA-5-U3 CCACUGUCACAGGAAGGACC (SEQ ID NO: 772)
		hg-hLPA-5-U4 ACUCCACCACUGUCACAGGA (SEQ ID NO: 773)
		hg-hLPA-5-U1 CUGCCAAGCU (SEQ ID NO: 857)

		hg-hLPA-5-U2 GGACCUGCCA (SEQ ID NO: 858)
		hg-hLPA-5-U3 AGGAAGGACC (SEQ ID NO: 859)
		hg-hLPA-5-U4 UGUCACAGGA (SEQ ID NO: 860)
mg-hLPA-6	GGUGAUGGACAGAGUUAUCG (SEQ ID NO: 722)	hg-hLPA-6-U1 UGAGCAAAGCCAUGUGGUCC (SEQ ID NO: 774)
		hg-hLPA-6-U2 AGCACCUGAGCAAAGCCAUG (SEQ ID NO: 775)
		hg-hLPA-6-U1 CAUGUGGUCC (SEQ ID NO: 861)
		hg-hLPA-6-U2 CAAAGCCAUG (SEQ ID NO: 862)
mg-hLPA-7	ACGCAAUGCUCAGACGCAGA (SEQ ID NO: 723)	hg-hLPA-7-U1 GAGGGAUCCCGUGUCAGGU (SEQ ID NO: 776)
		hg-hLPA-7-U2 AUACGAGGGAUCCCGUGUC (SEQ ID NO: 777)
		hg-hLPA-7-U3 UAUUGUUAUACGAGGGAUCC (SEQ ID NO: 778)
		hg-hLPA-7-U1 GGUGUCAGGU (SEQ ID NO: 863)
		hg-hLPA-7-U2 UCCCGUGUC (SEQ ID NO: 864)
		hg-hLPA-7-U3 CGAGGGAUCC (SEQ ID NO: 865)
mg-hLPA-8	CGAACAAGGUAAGGAGUCUG (SEQ ID NO: 724)	hg-hLPA-8-U1 CGCGCCUCCGACUGUUACCC (SEQ ID NO: 779)
		hg-hLPA-8-U1 ACUGUUACCC (SEQ ID NO: 866)
mg-hLPA-9	CAGUACUCCCACCUGACACC (SEQ ID NO: 725)	hg-hLPA-9-U1 GGUACAGUCGGAGGCGCGA (SEQ ID NO: 780)
		hg-hLPA-9-U2 GGAACCGGGGUAACAGUCGG (SEQ ID NO: 781)

		hg-hLPA-9-U3 CUUGGAACCGGGGUAACAGU (SEQ ID NO: 782)
		hg-hLPA-9-U1 GGAGGCGCGA (SEQ ID NO: 867)
		hg-hLPA-9-U2 UACAGUCGG (SEQ ID NO: 868)
		hg-hLPA-9-U3 GGGUAACAGU (SEQ ID NO: 869)
mg-hLPA-10	UCUGAACAAGGUAAGGAGCC (SEQ ID NO: 726)	hg-hLPA-10-U1 CAACUAAUACCCCGAUUCCA (SEQ ID NO: 783)
		hg-hLPA-10-U2 CGCGCCUCCAACUAAUACCC (SEQ ID NO: 784)
		hg-hLPA-10-U3 CGCAGAAGGGACUGCCGUCG (SEQ ID NO: 785)
		hg-hLPA-10-U1 CCCGAUUCCA (SEQ ID NO: 870)
		hg-hLPA-10-U2 ACUAAUACCC (SEQ ID NO: 871)
		hg-hLPA-10-U3 ACUGCCGUCG (SEQ ID NO: 872)
mg-hLPA-11	ACACAAUGCUCAGACGCAGA (SEQ ID NO: 727)	hg-hLPA-11-U1 GAGGGAUCCAGUGUCAGGU (SEQ ID NO: 786)
		hg-hLPA-11-U2 AUACGAGGGAUCCAGUGUC (SEQ ID NO: 787)
		hg-hLPA-11-U3 AGCCCCUAAUUGUUAUACGA (SEQ ID NO: 788)
		hg-hLPA-11-U1 AGUGUCAGGU (SEQ ID NO: 873)
		hg-hLPA-11-U2 UCCAGUGUC (SEQ ID NO: 874)
		hg-hLPA-11-U3 UGUUAUACGA (SEQ ID NO: 875)
mg-hLPA-12	UGAACAAGGUAAGGAGCCUG (SEQ ID NO: 728)	hg-hLPA-12-U1 CACAAGCUCAGACGCAGAA (SEQ ID NO: 789)

		hg-hLPA-12-U1 AGACGCAGAA (SEQ ID NO: 876)
mg-hLPA-13	CAGUACUCCCACCUGACACU (SEQ ID NO: 729)	hg-hLPA-13-U1 GGUAAUAGUUGGAGGCGCGA (SEQ ID NO: 790)
		hg-hLPA-13-U2 GGAAUCGGGGUAAUAGUUGG (SEQ ID NO: 791)
		hg-hLPA-13-U3 CUUGGAAUCGGGGUAAUAGU (SEQ ID NO: 792)
		hg-hLPA-13-U1 GGAGGCGCGA (SEQ ID NO: 877)
		hg-hLPA-13-U2 UAAUAGUUGG (SEQ ID NO: 878)
		hg-hLPA-13-U3 GGGUAAUAGU (SEQ ID NO: 879)
mg-hLPA-14	UGAGCAAAGGCCUGGGGUGC (SEQ ID NO: 730)	hg-hLPA-14-U1 UUCACAUGUUUGUCUCUUCU (SEQ ID NO: 793)
		hg-hLPA-14-U1 UGUCUCUUCU (SEQ ID NO: 880)
mg-hLPA-15	CUGCCGAAAUCCAGAUCCUG (SEQ ID NO: 731)	hg-hLPA-15-U1 UAUUCUUUUGGAAUUUCCAG (SEQ ID NO: 794)
		hg-hLPA-15-U2 UUUUGUGAUGUGUAUUCUUU (SEQ ID NO: 795)
		hg-hLPA-15-U1 GAAUUUCCAG (SEQ ID NO: 881)
		hg-hLPA-15-U2 UGUAUUCUUU (SEQ ID NO: 882)
mg-hLPA-16	CACGAUGCUCAGAUGCAGAA (SEQ ID NO: 732)	hg-hLPA-16-U1 AACAGAUCCCAGUGUCAGGU (SEQ ID NO: 796)
		hg-hLPA-16-U2 AUACAACAGAUCCCAGUGUC (SEQ ID NO: 797)
		hg-hLPA-16-U3 CAGAUCCUGUGGCAGCCCCU (SEQ ID NO: 798)
		hg-hLPA-16-U1 AGUGUCAGGU (SEQ ID NO: 883)

		hg-hLPA-16-U2 UCCCAGUGUC (SEQ ID NO: 884)
		hg-hLPA-16-U3 GGCAGCCCCU (SEQ ID NO: 885)
mg-hLPA-17	UAACACCAAGGGGCUGCCAC (SEQ ID NO: 733)	hg-hLPA-17-U1 CUGCAUCUGAGCAUCGUGUC (SEQ ID NO: 799)
		hg-hLPA-17-U1 GCAUCGUGUC (SEQ ID NO: 886)
mg-hLPA-18	CAGUACUCCCACCUGACACU (SEQ ID NO: 734)	hg-hLPA-18-U1 AAUAACAUUCGGAGGGACGA (SEQ ID NO: 800)
		hg-hLPA-18-U2 GAGCCAGAAUAACAUUCGGA (SEQ ID NO: 801)
		hg-hLPA-18-U3 CUUGGAGCCAGAAUAACAUU (SEQ ID NO: 802)
		hg-hLPA-18-U1 GGAGGGACGA (SEQ ID NO: 887)
		hg-hLPA-18-U2 AACAUUCGGA (SEQ ID NO: 888)
		hg-hLPA-18-U3 GAAUAACAUU (SEQ ID NO: 889)
mg-hLPA-19	CAGUACUCCCACCUGACACU (SEQ ID NO: 735)	hg-hLPA-19-U1 GGACACUUGAUUCUGUCACC (SEQ ID NO: 803)
		hg-hLPA-19-U2 GGACCACCGUGAGAGUUGCA (SEQ ID NO: 804)
		hg-hLPA-19-U1 UUCUGUCACC (SEQ ID NO: 890)
		hg-hLPA-19-U2 GAGAGUUGCA (SEQ ID NO: 891)
mg-hLPA-20	AUGCCAGUGUGGUGUCAUAG (SEQ ID NO: 736)	hg-hLPA-20-U1 AACUCAAGGUUGUACCCAUI (SEQ ID NO: 805)
		hg-hLPA-20-U2 CUGUCUUUGAAGAAAACUCA (SEQ ID NO: 806)
		hg-hLPA-20-U1 UGUACCCAUI

		(SEQ ID NO: 892)
		hg-hLPA-20-U2 AGAAAACUCA (SEQ ID NO: 893)
mg-hLPA-21	GGAGCAAAGCCCCACAGUCC (SEQ ID NO: 737)	hg-hLPA-21-U1 UUUCUCAUGCUUCUGUGUUC (SEQ ID NO: 807)
		hg-hLPA-21-U1 UUCUGUGUUC (SEQ ID NO: 894)
mg-hLPA-22	ACAGUCCAGGACUGCUACCA (SEQ ID NO: 738)	hg-hLPA-22-U1 UCUUUGAAUUUCAGCACCAA (SEQ ID NO: 808)
		hg-hLPA-22-U1 UCAGCACCAA (SEQ ID NO: 895)
mg-hLPA-23	AUGCCAGUGUGGUGUCAUAG (SEQ ID NO: 739)	hg-hLPA-23-U1 ACUCAAAGACAUACCCAUUU (SEQ ID NO: 809)
		hg-hLPA-23-U2 AGUGGGUGGCUGUUUCUCUU (SEQ ID NO: 810)
		hg-hLPA-23-U1 AUACCCAUUU (SEQ ID NO: 896)
		hg-hLPA-23-U2 UGUUUCUCUU (SEQ ID NO: 897)
mg-hLPA-24	CCUGACGCAAUGUCCAGUGA (SEQ ID NO: 740)	hg-hLPA-24-U1 CAUGGAUCCCAGUGUCAGAU (SEQ ID NO: 811)
		hg-hLPA-24-U2 UCGCCCUGGUGUUUAUACCA (SEQ ID NO: 812)
		hg-hLPA-24-U3 CAGAUGCUGAGAUUCGCCC (SEQ ID NO: 813)
		hg-hLPA-24-U1 AGUGUCAGAU (SEQ ID NO: 898)
		hg-hLPA-24-U2 UGUUAUACCA (SEQ ID NO: 899)
		hg-hLPA-24-U3 GAUUCGCCC (SEQ ID NO: 900)
mg-hLPA-25	UGAACAAGGUAAGAAAUUUG (SEQ ID NO: 741)	hg-hLPA-25-U1 CACAACUCCCACAGUGGCCC (SEQ ID NO: 814)
		hg-hLPA-25-U2 UGUCCUCACAACUCCCACAG

		(SEQ ID NO: 815)
		hg-hLPA-25-U1 ACAGUGGCC (SEQ ID NO: 901)
		hg-hLPA-25-U2 ACUCCACAG (SEQ ID NO: 902)
mg-hLPA-26	ACGCGAUGCUCAGACACAGA (SEQ ID NO: 742)	hg-hLPA-26-U1 CAUGGACCCCAGCAUCAGGU (SEQ ID NO: 816)
		hg-hLPA-26-U2 UUACCAUGGACCCCAGCAUC (SEQ ID NO: 817)
		hg-hLPA-26-U3 CAGAUGCCGAUACAGGCCCU (SEQ ID NO: 818)
		hg-hLPA-26-U1 AGCAUCAGGU (SEQ ID NO: 903)
		hg-hLPA-26-U2 CCCCAGCAUC (SEQ ID NO: 904)
		hg-hLPA-26-U3 UACAGGCCCU (SEQ ID NO: 905)
mg-hLPA-27	UCAUCCAGGUUCCAAGCCUA (SEQ ID NO: 743)	hg-hLPA-27-U1 CUCAGACACAGAAGGGACUG (SEQ ID NO: 819)
		hg-hLPA-27-U2 CGCGAUGCUCAGACACAGAA (SEQ ID NO: 820)
		hg-hLPA-27-U1 GAAGGGACUG (SEQ ID NO: 906)
		hg-hLPA-27-U2 AGACACAGAA (SEQ ID NO: 907)
mg-hLPA-28	AUGCCAGGAAUGGGCUGCCC (SEQ ID NO: 744)	hg-hLPA-28-U1 GAAAGGAUACCGGGCAAGA (SEQ ID NO: 821)
		hg-hLPA-28-U2 GGGAAUGGGAAAGGAUACCG (SEQ ID NO: 822)
		hg-hLPA-28-U3 CAGACUGUAUGUUUGGAAU (SEQ ID NO: 823)
		hg-hLPA-28-U1 CGGGGCAAGA (SEQ ID NO: 908)
		hg-hLPA-28-U2 AAGGAUACCG

		(SEQ ID NO: 909)
		hg-hLPA-28-U3 GUUUGGGAAU (SEQ ID NO: 910)
mg-hLPA-29	CCUGCCCAUUUAUUUGUCCC (SEQ ID NO: 745)	hg-hLPA-29-U1 AAAAAGAGUCCAAAUCAAG (SEQ ID NO: 824)
		hg-hLPA-29-U2 UGAAAAGAUUUGUCAGCAAA (SEQ ID NO: 825)
		hg-hLPA-29-U1 CAAAUCAAG (SEQ ID NO: 911)
		hg-hLPA-29-U2 UGUCAGCAAA (SEQ ID NO: 912)
mg-hLPA-30	GGCAAGUCAGUCUCAGAACA (SEQ ID NO: 746)	hg-hLPA-30-U1 AAGCAUUGUAGGGGGUGUG (SEQ ID NO: 826)
		hg-hLPA-30-U2 GUCCUGGAAGCAUUGUAGGG (SEQ ID NO: 827)
		hg-hLPA-30-U3 GUGGAGCCGAAGAAAUGUCC (SEQ ID NO: 828)
		hg-hLPA-30-U1 GGGGGGUGUG (SEQ ID NO: 913)
		hg-hLPA-30-U2 CAUUGUAGGG (SEQ ID NO: 914)
		hg-hLPA-30-U3 AGAAAUGUCC (SEQ ID NO: 915)
mg-hLPA-31	CUUGCCAGGGCCAGGAAUGU (SEQ ID NO: 747)	hg-hLPA-31-U1 GGACAGUAUAGAUGGUUUCU (SEQ ID NO: 829)
		hg-hLPA-31-U2 ACAUGGAAGGACAGUAUAGA (SEQ ID NO: 830)
		hg-hLPA-31-U3 UUUUGUGGGGCUUACAUGGA (SEQ ID NO: 831)
		hg-hLPA-31-U1 GAUGGUUUCU (SEQ ID NO: 916)
		hg-hLPA-31-U2 ACAGUAUAGA (SEQ ID NO: 917)
		hg-hLPA-31-U3 CUUACAUGGA

		(SEQ ID NO: 918)
mg-hLPA-32	CCAGGGCCAGGAAUGUGGGU (SEQ ID NO: 748)	hg-hLPA-32-U1 GGACAGUAUAGAUGGUUUCU (SEQ ID NO: 832)
		hg-hLPA-32-U2 ACAUGGAAGGACAGUAUAGA (SEQ ID NO: 833)
		hg-hLPA-32-U1 GAUGGUUUCU (SEQ ID NO: 919)
		hg-hLPA-32-U2 ACAGUAUAGA (SEQ ID NO: 920)
mg-hLPA-33	UUCAGGAAAUAGAAGUGUCU (SEQ ID NO: 749)	hg-hLPA-33-U1 UCAUCCUACAAGGUCAUCCU (SEQ ID NO: 834)
		hg-hLPA-33-U1 AGGUCAUCCU (SEQ ID NO: 921)
mg-hLPA-34	UUUACAAGGAGUCACUUCU (SEQ ID NO: 750)	hg-hLPA-34-U1 GGGUGACAGUGGAGGGCCUC (SEQ ID NO: 835)
		hg-hLPA-34-U2 CUGUUUAGGGUGACAGUGGA (SEQ ID NO: 836)
		hg-hLPA-34-U3 ACCUCUGUUUAGGGUGACAG (SEQ ID NO: 837)
		hg-hLPA-34-U1 (SEQ ID NO: 922)
		hg-hLPA-34-U2 (SEQ ID NO: 923)
		hg-hLPA-34-U3 (SEQ ID NO: 924)

[00442] Table 7E the mgRNA spacer and the hgRNA spacer binding to *AGT* gene

mgRNA	Sequence	hgRNA
mg-hAGT-1	CAGCCCAGGCCAGGAGGCAG (SEQ ID NO: 925)	hg-hAGT-1-U1 GGAAGGGGUGUAUGUACACC (SEQ ID NO: 962)
		hg-hAGT-1-U2 UUGUGGAUGACGAGGUGGAA (SEQ ID NO: 963)
		hg-hAGT-1-U3 UACUCUCAUUGGAUGACG (SEQ ID NO: 964)
		hg-hAGT-1-U1 UAUGUACACC

		(SEQ ID NO: 1034)
		hg-hAGT-1-U2 CGAGGUGGAA (SEQ ID NO: 1035)
		hg-hAGT-1-U3 GUGGAUGACG (SEQ ID NO: 1036)
mg-hAGT-2	GAGCAGCUGGCAAAGGCCAA (SEQ ID NO: 926)	hg-hAGT-2-U1 UGGCCUGGCUGCAGGUGACC (SEQ ID NO: 965)
		hg-hAGT-2-U2 UACAUACACCCCUUCCACCU (SEQ ID NO: 966)
		hg-hAGT-2-U1 GCAGGUGACC (SEQ ID NO: 1037)
		hg-hAGT-2-U2 CCUUCCACCU (SEQ ID NO: 1038)
mg-hAGT-3	AUUCAGGCCAAGACAUCCCC (SEQ ID NO: 927)	hg-hAGT-3-U1 UACCUGUGAGCAGCUGGCAA (SEQ ID NO: 967)
		hg-hAGT-3-U2 AGCUGGCCAAAGGCCAAUGCC (SEQ ID NO: 968)
		hg-hAGT-3-U1 CAGCUGGCAA (SEQ ID NO: 1039)
		hg-hAGT-3-U2 GGCCAAUGCC (SEQ ID NO: 1040)
mg-hAGT-4	UCAGGCCAAGACAUCCCCUG (SEQ ID NO: 928)	hg-hAGT-4-U1 UACCUGUGAGCAGCUGGCAA (SEQ ID NO: 969)
		hg-hAGT-4-U2 AGCUGGCCAAAGGCCAAUGCC (SEQ ID NO: 970)
		hg-hAGT-4-U1 CAGCUGGCAA (SEQ ID NO: 1041)
		hg-hAGT-4-U2 GGCCAAUGCC (SEQ ID NO: 1042)
mg-hAGT-5	CUACAGGACCAGCUGGUGCU (SEQ ID NO: 929)	hg-hAGT-5-U1 AAAGACCCACCUUCAUACC (SEQ ID NO: 971)
		hg-hAGT-5-U2 CUUCAUACCUGCUCCAAUUC (SEQ ID NO: 972)
		hg-hAGT-5-U1 CCUUCAUACC

		(SEQ ID NO: 1043)
		hg-hAGT-5-U2 GCUCCAAUUC (SEQ ID NO: 1044)
mg-hAGT-6	CAGGACCAGCUGGUGCUAGU (SEQ ID NO: 930)	hg-hAGT-6-U1 AAAGACCCCAACCUUCAUACC (SEQ ID NO: 973)
		hg-hAGT-6-U2 CUUCAUACCUGCUCCAAUUC (SEQ ID NO: 974)
		hg-hAGT-6-U1 CCUUCAUACC (SEQ ID NO: 1045)
		hg-hAGT-6-U2 GCUCCAAUUC (SEQ ID NO: 1046)
mg-hAGT-7	GCCCCAUAGCUCACUGUGCA (SEQ ID NO: 931)	hg-hAGT-7-U1 CAAAGACAGCCGUUGGGGAG (SEQ ID NO: 975)
		hg-hAGT-7-U2 GGGUGCCAAAGACAGCCGUU (SEQ ID NO: 976)
		hg-hAGT-7-U3 UCCCAGAUAGAGAGAGGCCA (SEQ ID NO: 977)
		hg-hAGT-7-U1 CGUUGGGGAG (SEQ ID NO: 1047)
		hg-hAGT-7-U2 GACAGCCGUU (SEQ ID NO: 1048)
		hg-hAGT-7-U3 AGAGAGGCCA (SEQ ID NO: 1049)
mg-hAGT-8	CCACGCCCCAUAGCUCACUG (SEQ ID NO: 932)	hg-hAGT-8-U1 CAAAGACAGCCGUUGGGGAG (SEQ ID NO: 978)
		hg-hAGT-8-U2 GGGUGCCAAAGACAGCCGUU (SEQ ID NO: 979)
		hg-hAGT-8-U3 UCCCAGAUAGAGAGAGGCCA (SEQ ID NO: 980)
		hg-hAGT-8-U1 CGUUGGGGAG (SEQ ID NO: 1050)
		hg-hAGT-8-U2 GACAGCCGUU (SEQ ID NO: 1051)
		hg-hAGT-8-U3 AGAGAGGCCA

		(SEQ ID NO: 1052)
mg-hAGT-9	AGGCUACAGGCAAUCCUGGG (SEQ ID NO: 933)	hg-hAGT-9-U1 ACCCUGGCCUCUCUCAUCU (SEQ ID NO: 981)
		hg-hAGT-9-U1 CUCUCAUCU (SEQ ID NO: 1053)
mg-hAGT-10	UUCCAAGGAACACCCAGGAU (SEQ ID NO: 934)	hg-hAGT-10-U1 GGACCUUGUGCGCAUCCAGC (SEQ ID NO: 982)
		hg-hAGT-10-U2 GUACAGCCUGCAGGGCAGAC (SEQ ID NO: 983)
		hg-hAGT-10-U3 CAGGCCUGUACAGCCUGCA (SEQ ID NO: 984)
		hg-hAGT-10-U1 CGCAUCCAGC (SEQ ID NO: 1054)
		hg-hAGT-10-U2 CAGGGCAGAC (SEQ ID NO: 1055)
		hg-hAGT-10-U3 ACAGCCUGCA (SEQ ID NO: 1056)
		hg-hAGT-11-U1 GGACCUUGUGCGCAUCCAGC (SEQ ID NO: 985)
mg-hAGT-11	UGUCCUCCAAGGAACACCC (SEQ ID NO: 935)	hg-hAGT-11-U2 GUACAGCCUGCAGGGCAGAC (SEQ ID NO: 986)
		hg-hAGT-11-U3 CAGGCCUGUACAGCCUGCA (SEQ ID NO: 987)
		hg-hAGT-11-U1 CGCAUCCAGC (SEQ ID NO: 1057)
		hg-hAGT-11-U2 CAGGGCAGAC (SEQ ID NO: 1058)
		hg-hAGT-11-U3 ACAGCCUGCA (SEQ ID NO: 1059)
		hg-hAGT-12-U1 AGGACAAGAACUGCACCUC (SEQ ID NO: 988)
mg-hAGT-12	CCUGCAGGCUGUACAGGGCC (SEQ ID NO: 936)	hg-hAGT-12-U2 CAAGAACUGCACCUCGGC (SEQ ID NO: 989)
		hg-hAGT-12-U1 CUGCACCUC

		(SEQ ID NO: 1060)
		hg-hAGT-12-U2 ACCUCCCGGC (SEQ ID NO: 1061)
mg-hAGT-13	GGCUGUACAGGGCCUGCUAG (SEQ ID NO: 937)	hg-hAGT-13-U1 AGGACAAGAACUGCACCUC (SEQ ID NO: 990)
		hg-hAGT-13-U2 CAAGAACUGCACCUCGCGC (SEQ ID NO: 991)
		hg-hAGT-13-U1 CUGCACCUC (SEQ ID NO: 1062)
		hg-hAGT-13-U2 ACCUCCCGGC (SEQ ID NO: 1063)
mg-hAGT-14	CCAGGGCAGGGCUGAUAGCC (SEQ ID NO: 938)	hg-hAGT-14-U1 CUCCCGGCUGGAUGCGCACA (SEQ ID NO: 992)
		hg-hAGT-14-U2 CAAGGUCCUGUCUGCCUGC (SEQ ID NO: 993)
		hg-hAGT-14-U1 GAUGCGCACA (SEQ ID NO: 1064)
		hg-hAGT-14-U2 UCUGCCUGC (SEQ ID NO: 1065)
mg-hAGT-15	UAGCCAGGCCCAGCUGCUGC (SEQ ID NO: 939)	hg-hAGT-15-U1 CAAGGUCCUGUCUGCCUGC (SEQ ID NO: 994)
		hg-hAGT-15-U2 UCUGCCUGCAGGCUGUACA (SEQ ID NO: 995)
		hg-hAGT-15-U1 UCUGCCUGC (SEQ ID NO: 1066)
		hg-hAGT-15-U2 AGGCUGUACA (SEQ ID NO: 1067)
mg-hAGT-16	GGCCCAGCUGCUGCUGUCCA (SEQ ID NO: 940)	hg-hAGT-16-U1 CAAGGUCCUGUCUGCCUGC (SEQ ID NO: 996)
		hg-hAGT-16-U2 UCUGCCUGCAGGCUGUACA (SEQ ID NO: 997)
		hg-hAGT-16-U1 UCUGCCUGC (SEQ ID NO: 1068)
		hg-hAGT-16-U2 AGGCUGUACA

		(SEQ ID NO: 1069)
mg-hAGT-17	CCAGCUGCUGCUGUCCACGG (SEQ ID NO: 941)	hg-hAGT-17-U1 CAAGGUCCUGUCUGCCCUGC (SEQ ID NO: 998)
		hg-hAGT-17-U2 UCUGCCCUGCAGGCUGUACA (SEQ ID NO: 999)
		hg-hAGT-17-U1 UCUGCCCUGC (SEQ ID NO: 1070)
		hg-hAGT-17-U2 AGGCUGUACA (SEQ ID NO: 1071)
mg-hAGT-18	CUGAAGCAGCCGUUUGUGCA (SEQ ID NO: 942)	hg-hAGT-18-U1 GGCCCAGCUGCUGCUGUCCA (SEQ ID NO: 1000)
		hg-hAGT-18-U2 CUGCUGCUGUCCACGGUGGU (SEQ ID NO: 1001)
		hg-hAGT-18-U1 CUGCUGUCCA (SEQ ID NO: 1072)
		hg-hAGT-18-U2 CCACGGUGGU (SEQ ID NO: 1073)
mg-hAGT-19	UCAUGCAGGCUGUGACAGGA (SEQ ID NO: 943)	hg-hAGT-19-U1 UGUGGUCCUCCACGCUCUC (SEQ ID NO: 1002)
		hg-hAGT-19-U2 CUCUCUGGACUUCACAGAAC (SEQ ID NO: 1003)
		hg-hAGT-19-U1 CCACGCUCUC (SEQ ID NO: 1074)
		hg-hAGT-19-U2 UUCACAGAAC (SEQ ID NO: 1075)
mg-hAGT-20	UCUUCCAUCCUGUCACAGCC (SEQ ID NO: 944)	hg-hAGT-20-U1 AGCCAGGGUGCUGUCCACAC (SEQ ID NO: 1004)
		hg-hAGT-20-U2 GACGUAGGUGUUGAAAGCCA (SEQ ID NO: 1005)
		hg-hAGT-20-U1 CUGUCCACAC (SEQ ID NO: 1076)
		hg-hAGT-20-U2 UUGAAAGCCA (SEQ ID NO: 1077)
	CUUACCUUGGAAGUGGACGU (SEQ ID NO: 945)	hg-hAGT-21-U1 ACAUUGGAUACUAAGUCCUA

mg-hAGT-21		(SEQ ID NO: 1006)
		hg-hAGT-21-U2 GGCUGAUCUCAGCUACACAU (SEQ ID NO: 1007)
		hg-hAGT-21-U1 CUAAGUCCUA (SEQ ID NO: 1078)
		hg-hAGT-21-U2 AGCUACACAU (SEQ ID NO: 1079)
mg-hAGT-22	AUCUUCCCUGAAAUCCAGAC (SEQ ID NO: 946)	hg-hAGT-22-U1 CACCCAGAACUCCUGGGGCU (SEQ ID NO: 1008)
		hg-hAGT-22-U2 GUUGUCCACCCAGAACUCCU (SEQ ID NO: 1009)
		hg-hAGT-22-U1 UCCUGGGGCU (SEQ ID NO: 1080)
		hg-hAGT-22-U2 CAGAACUCCU (SEQ ID NO: 1081)
mg-hAGT-23	CGAGCCCCAGGAGUUCUGGG (SEQ ID NO: 947)	hg-hAGT-23-U1 UUCCCUCCUGUCUCCUGUC (SEQ ID NO: 1010)
		hg-hAGT-23-U2 UGUCUCCUGUCUGGAUUUCA (SEQ ID NO: 1011)
		hg-hAGT-23-U1 GUCUCCUGUC (SEQ ID NO: 1082)
		hg-hAGT-23-U2 CUGGAUUUCA (SEQ ID NO: 1083)
mg-hAGT-24	CACCCAGAACUCCUGGGGCU (SEQ ID NO: 948)	hg-hAGT-24-U1 GUGCCCAUGCCAGAGAGCAU (SEQ ID NO: 1012)
		hg-hAGT-24-U1 CAGAGAGCAU (SEQ ID NO: 1084)
mg-hAGT-25	CCAGCACUGGAGUGACAUCC (SEQ ID NO: 949)	hg-hAGT-25-U1 CGAGCCCCAGGAGUUCUGGG (SEQ ID NO: 1013)
		hg-hAGT-25-U1 GAGUUCUGGG (SEQ ID NO: 1085)
mg-hAGT-26	CAUCCAGGACAACUUCUCGG (SEQ ID NO: 950)	hg-hAGT-26-U1 GUGUCUGUUCCCAUGCUCUC (SEQ ID NO: 1014)
		hg-hAGT-26-U2 GUUCCCAUGCUCUCUGGCAU

		(SEQ ID NO: 1015)
		hg-hAGT-26-U1 CCAUGCUCUC (SEQ ID NO: 1086)
		hg-hAGT-26-U2 UCUCUGGCAU (SEQ ID NO: 1087)
mg-hAGT-27	CUCAAGUGCCCUUCACUGAG (SEQ ID NO: 951)	hg-hAGT-27-U1 GUUCCCAUGCUCUCUGGCAU (SEQ ID NO: 1016)
		hg-hAGT-27-U2 GCAUGGGCACCUUCCAGCAC (SEQ ID NO: 1017)
		hg-hAGT-27-U1 UCUCUGGCAU (SEQ ID NO: 1088)
		hg-hAGT-27-U2 CUUCCAGCAC (SEQ ID NO: 1089)
mg-hAGT-28	AUCCAGCCUCACUAUGCCUC (SEQ ID NO: 952)	hg-hAGT-28-U1 UGACAUCCAGGACAACUUCU (SEQ ID NO: 1018)
		hg-hAGT-28-U2 CAACUUCUCGGUGACUCAAG (SEQ ID NO: 1019)
		hg-hAGT-28-U1 GACAACUUCU (SEQ ID NO: 1090)
		hg-hAGT-28-U2 GUGACUCAAG (SEQ ID NO: 1091)
mg-hAGT-29	UCCAGCAAAACUCCCUCAAC (SEQ ID NO: 953)	hg-hAGT-29-U1 GCCUCACUAUGCCUCUGACC (SEQ ID NO: 1020)
		hg-hAGT-29-U1 GCCUCUGACC (SEQ ID NO: 1092)
mg-hAGT-30	UCCAGUUGAGGGAGUUUUGC (SEQ ID NO: 954)	hg-hAGT-30-U1 CCCACAUUCCAGGGGAGACC (SEQ ID NO: 1021)
		hg-hAGT-30-U2 CAGUGUGGCUCCACAUUCC (SEQ ID NO: 1022)
		hg-hAGT-30-U1 AGGGGAGACC (SEQ ID NO: 1093)
		hg-hAGT-30-U2 CCCACAUUCC (SEQ ID NO: 1094)
	AUGCCCCAACUGGUGCUGCA (SEQ ID NO: 955)	hg-hAGT-31-U1 UAAACUGUGCAUCAUCUCCCC

mg-hAGT-31		(SEQ ID NO: 1023)
		hg-hAGT-31-U1 UCAUCUCCCC (SEQ ID NO: 1095)
mg-hAGT-32	GCAAGGAUCUUAUGACCUGC (SEQ ID NO: 956)	hg-hAGT-32-U1 UAAACUGUGCAUCAUCUCCCC (SEQ ID NO: 1024)
		hg-hAGT-32-U1 UCAUCUCCCC (SEQ ID NO: 1096)
mg-hAGT-33	CCUGCAGGACCUGCUCGCCC (SEQ ID NO: 957)	hg-hAGT-33-U1 UAAACUGUGCAUCAUCUCCCC (SEQ ID NO: 1025)
		hg-hAGT-33-U2 CCACCUGACCAUGCCCCAAC (SEQ ID NO: 1026)
		hg-hAGT-33-U1 UCAUCUCCCC (SEQ ID NO: 1097)
		hg-hAGT-33-U2 AUGCCCCAAC (SEQ ID NO: 1098)
mg-hAGT-34	CUCGCCCAGGCUGAGCUGCC (SEQ ID NO: 958)	hg-hAGT-34-U1 CCACCUGACCAUGCCCCAAC (SEQ ID NO: 1027)
		hg-hAGT-34-U2 AUGCCCCAACUGGUGCUGCA (SEQ ID NO: 1028)
		hg-hAGT-34-U1 AUGCCCCAAC (SEQ ID NO: 1099)
		hg-hAGT-34-U2 UGGUGCUGCA (SEQ ID NO: 1100)
mg-hAGT-35	UGCAAAAAUUGAGCAAUGAC (SEQ ID NO: 959)	hg-hAGT-35-U1 CCUGCAGGACCUGCUCGCCC (SEQ ID NO: 1029)
		hg-hAGT-35-U2 CUCGCCCAGGCUGAGCUGCC (SEQ ID NO: 1030)
		hg-hAGT-35-U1 CUGCUCGCCC (SEQ ID NO: 1101)
		hg-hAGT-35-U2 CUGAGCUGCC (SEQ ID NO: 1102)
mg-hAGT-36	CCAACAGCUUAACAAGCCUG (SEQ ID NO: 960)	hg-hAGT-36-U1 CAUUUUUUUUGAGCUUGAAG (SEQ ID NO: 1031)
		hg-hAGT-36-U1

		GAGCUUGAAG (SEQ ID NO: 1103)
mg-hAGT-37	UGAUCAAAGCGCCACUGCCC (SEQ ID NO: 961)	hg-hAGT-37-U1 GCUUAACAAGCCUGAGGUCU (SEQ ID NO: 1032)
		hg-hAGT-37-U2 UAACAAGCCUGAGGUCUUGG (SEQ ID NO: 1033)
		hg-hAGT-37-U1 CCUGAGGUCU (SEQ ID NO: 1104)
		hg-hAGT-37-U2 GAGGUCUUGG (SEQ ID NO: 1105)

[00443] Table 7F the mgRNA spacer and the hgRNA spacer binding to *APOC3* gene

mgRNA	Sequence	hgRNA
mg-hAPOC3-1	AAGCUCCUGAGGAAAGAGCA (SEQ ID NO: 1249)	hg-hAPOC3-1-U1 CUGCAUGAAGCUGAGAAGGG (SEQ ID NO: 1252)
		hg-hAPOC3-1-U2 ACCCUGCAUGAAGCUGAGAA (SEQ ID NO: 1253)
		hg-hAPOC3-1-U3 AACCCUGCAUGAAGCUGAGA (SEQ ID NO: 1254)
		hg-hAPOC3-1-U1 CUGAGAAGGG (SEQ ID NO: 1259)
		hg-hAPOC3-1-U2 AAGCUGAGAA (SEQ ID NO: 1260)
		hg-hAPOC3-1-U3 GAAGCUGAGA (SEQ ID NO: 1261)
mg-hAPOC3-2	GGUGCUCCAGUAGUCUUUCA (SEQ ID NO: 1250)	hg-hAPOC3-2-U1 CUGAAGUUGGUCUGACCUCA (SEQ ID NO: 1255)
		hg-hAPOC3-2-U2 CAGGCAGCCACGGCUGAAGU (SEQ ID NO: 1256)
		hg-hAPOC3-2-U1 UCUGACCUCA (SEQ ID NO: 1262)
		hg-hAPOC3-2-U2 CGGCUGAAGU (SEQ ID NO: 1263)
	CCAGCCCCUAAAUCAGUCAG	hg-hAPOC3-3-U1

mg-hAPOC3-3	(SEQ ID NO: 1251)	GGUGCUCCAGUAGUCUUUCA (SEQ ID NO: 1257)
		hg-hAPOC3-3-U2 CUCAGAGAACUUGUCCUUA (SEQ ID NO: 1258)
		hg-hAPOC3-3-U1 UAGUCUUUCA (SEQ ID NO: 1264)
		hg-hAPOC3-3-U2 UUGUCCUUA (SEQ ID NO: 1265)

[00444] Table 8A the mgRNA and the hgRNA binding to *PCSK9* gene

mgRNA	Sequence	hgRNA
mg-PCSK9-Mouse-end modified	mC*mA*mG*GUUCCAUGGGAUG CUCUGUUUGAGAGCUAGGGCCC UGAAGAAGGGCCCUAGCAAGU UCAAUAAGGCUAGUCCGUUA UCAACUUGAAAAAGUGGCACC GAGUCGG*mU*mG*mC (SEQ ID NO: 1109)	hg-PCSK9-Mouse-end modified ma*mc*mC*AGGGGAGGUUUGA GAGCUAGGCCAACAUAGAGGAU CACCCAUGUCUGCAGGGCCUA GCAAGUUCAAAUAAGGCUAGU CCGUUAUCAACUUGAAAAAGU GGCACCGAGUCGG*mU*mG*mC (SEQ ID NO: 1108)
		hg-PCSK9-Mouse-moderately modified mA*mC*mC*AGGGGAGGUUUG AGAGCUAGGCCAACAUAGAGGA UCACCCAUGUCUGCAGGGCCU AGCAAGUUCAAAUAAGGCUAG UCCGUUAUCAmAmCmUmUmG mAmAmAmAmAmGmUmGmGmC mAmCmCmGmAmGmUmCmGmG *mU*mG*mC (SEQ ID NO: 1118)
		hg-PCSK9-Mouse-highly modified mA*mC*mC*AGGGGAGGUUUG AGAmGmCmUmAmGmGmCmCm AACAUAGAGGAUCACCCAUGUm CmUmGmCmAmGmGmGmCmCm UmAmGmCAAGUUCAAAUAAGG CUAGUCCGUUAUCAmAmCmUm UmGmAmAmAmAmAmGmUmGm GmCmAmCmCmGmAmGmUmCm GmG*mU*mG*mC (SEQ ID NO: 1120)
		hg-PCSK9-Mouse-end modified-103 mA*mC*mC*AGGGGAGGUUUG AGAGCUAGACAUGAGGAUCAC CCAUGUCUAGCAAGUUCAAA AAGGCUAGUCCGUUAUCAACU

		UGAAAAAGUGGCACCGAGUCG G*mU*mG*mC (SEQ ID NO: 1122) hg-PCSK9-Mouse-end modified-107 mA*mC*mC*AGGGGAGGUUUG AGAGCUAGGCACAUGAGGAUC ACCCAUGUGCCUAGCAAGUUC AAAUAAAGGCUAGUCCGUUAUC AACUUGAAAAAGUGGCACCGA GUCGG*mU*mG*mC (SEQ ID NO: 1123)
mg-PCSK9- Mouse- 2xboxB-end modified	mC*mA*mG*GUUCCAUGGGAUG CUCUGUUUGAGAGCUAGGGCCC UGAAGAAGGGCCCUAGCAAGU UCAAUAAGGCUAGUCCGUUA UCAACUUGGGCCCUGAAGAAG GGCCCAAGUGGCACCGAGUCGG *mU*mG*mC (SEQ ID NO: 1110)	hg-PCSK9-Mouse-end modified ma*mc*mC*AGGGGAGGUUUGA GAGCUAGGCCAACAUAGAGGAU CACCCAUGUCUGCAGGGCCUA GCAAGUUCAAAUAAGGCUAGU CCGUUAUCAACUUGAAAAAGU GGCACCGAGUCGG*mU*mG*mC (SEQ ID NO: 1108) hg-PCSK9-Mouse-moderately modified mA*mC*mC*AGGGGAGGUUUG AGAGCUAGGCCAACAUAGAGGA UCACCCAUGUCUGCAGGGCCU AGCAAGUUCAAAUAAGGCUAG UCCGUUAUCAmAmCmUmUmG mAmAmAmAmAmGmUmGmGmC mAmCmCmGmAmGmUmCmGmG *mU*mG*mC (SEQ ID NO: 1118) hg-PCSK9-Mouse-highly modified mA*mC*mC*AGGGGAGGUUUG AGAmGmCmUmAmGmGmCmCm AACAUGAGGAUCACCCAUGUm CmUmGmCmAmGmGmGmCmCm UmAmGmCAAGUUCAAAUAAGG CUAGUCCGUUAUCAmAmCmUm UmGmAmAmAmAmAmGmUmGm GmCmAmCmCmGmAmGmUmCm GmG*mU*mG*mC (SEQ ID NO: 1120) hg-PCSK9-Mouse-end modified-103 mA*mC*mC*AGGGGAGGUUUG AGAGCUAGACAUGAGGAUCAC CCAUGUCUAGCAAGUUCAAAU AAGGCUAGUCCGUUAUCAACU UGAAAAAGUGGCACCGAGUCG G*mU*mG*mC (SEQ ID NO: 1122) hg-PCSK9-Mouse-end modified-107 mA*mC*mC*AGGGGAGGUUUG AGAGCUAGGCACAUGAGGAUC ACCCAUGUGCCUAGCAAGUUC

		AAAUAAGGCUAGUCCGUUAUC AACUUGAAAAAGUGGCACCGA GUCGG*mU*mG*mC (SEQ ID NO: 1123)
mg-PCSK9- Mouse- moderately modified	mC*mA*mG*GUUCCAUGGGAUG CUCUGUUUGAGAGCUAGGGCCC UGAAGAAGGGCCCUAGCAAGU UCAAUAAGGCUAGUCCGUUA UCAmAmCmUmUmGmAmAmAmA mAmGmUmGmGmCmAmCmCmG mAmGmUmCmGmG*mU*mG*mC (SEQ ID NO: 1119)	hg-PCSK9-Mouse-end modified ma*mc*mC*AGGGGAGGUUUGA GAGCUAGGCCAACAUAGAGGAU CACCCAUGUCUGCAGGGCCUA GCAAGUUCAAAUAAGGCUAGU CCGUUAUCAACUUGAAAAAGU GGCACCGAGUCGG*mU*mG*mC (SEQ ID NO: 1108)
		hg-PCSK9-Mouse-moderately modified mA*mC*mC*AGGGGAGGUUUG AGAGCUAGGCCAACAUAGAGGA UCACCCAUGUCUGCAGGGCCU AGCAAGUUCAAAUAAGGCUAG UCCGUUAUCAmAmCmUmUmG mAmAmAmAmAmGmUmGmGmC mAmCmCmGmAmGmUmCmGmG *mU*mG*mC (SEQ ID NO: 1118)
		hg-PCSK9-Mouse-highly modified mA*mC*mC*AGGGGAGGUUUG AGAmGmCmUmAmGmGmCmCm AACAUAGAGGAUCACCCAUGUm CmUmGmCmAmGmGmGmCmCm UmAmGmCAAGUUCAAUAAGG CUAGUCCGUUAUCAmAmCmUm UmGmAmAmAmAmAmGmUmGm GmCmAmCmCmGmAmGmUmCm GmG*mU*mG*mC (SEQ ID NO: 1120)
		hg-PCSK9-Mouse-end modified-103 mA*mC*mC*AGGGGAGGUUUG AGAGCUAGACAUGAGGAUCAC CCAUGUCUAGCAAGUUCAAAU AAGGCUAGUCCGUUAUCAACU UGAAAAAGUGGCACCGAGUCG G*mU*mG*mC (SEQ ID NO: 1122)
mg-PCSK9- Mouse-	mC*mA*mG*GUUCCAUGGGAUG CUCUGUUUGAGAmGmCmUmAm	hg-PCSK9-Mouse-end modified-107 mA*mC*mC*AGGGGAGGUUUG AGAGCUAGGCACAUGAGGAUC ACCCAUGUGCCUAGCAAGUUC AAAUAAGGCUAGUCCGUUAUC AACUUGAAAAAGUGGCACCGA GUCGG*mU*mG*mC (SEQ ID NO: 1123)
		hg-PCSK9-Mouse-end modified ma*mc*mC*AGGGGAGGUUUGA GAGCUAGGCCAACAUAGAGGAU

highly modified	GGGCCCUGAAGAAGGGCCmCmUmAmGmCAAGUUCAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmG*mU*mG*mC (SEQ ID NO: 1121)	CACCCAUGUCUGCAGGGCCUAGCAAGUUCAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGG*mU*mG*mC (SEQ ID NO: 1108)
		hg-PCSK9-Mouse-moderately modified mA*mC*mC*AGGGGAGGUUUGAGAGCUAGGCCAACAUAGAGGAUCACCAUGUCUGCAGGGCCUAGCAAGUUCAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmG*mU*mG*mC (SEQ ID NO: 1118)
		hg-PCSK9-Mouse-highly modified mA*mC*mC*AGGGGAGGUUUGAGAmGmCmUmAmGmGmCmCmAACAUGAGGAUCACCAUGUmCmUmGmCmAmGmGmCmCmUmAmGmCAAGUUCAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmG*mU*mG*mC (SEQ ID NO: 1120)
		hg-PCSK9-Mouse-end modified-103 mA*mC*mC*AGGGGAGGUUUGAGAGCUAGACAUGAGGAUCACCAUGUCUAGCAAGUUCAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGG*mU*mG*mC (SEQ ID NO: 1122)
		hg-PCSK9-Mouse-end modified-107 mA*mC*mC*AGGGGAGGUUUGAGAGCUAGGCCAUGAGGAUACACCAUGUGCCUAGCAAGUUCAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCCGG*mU*mG*mC (SEQ ID NO: 1123)
mg-PCSK9-Human-end modified	mC*mA*mG*GUUCCACGGGAUGCUCUGUUUGAGAGCUAGGGCCCUGAAGAAGGGCCCUAGCAAGUUCAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGG*mU*mG*mC (SEQ ID NO: 1125)	hg-PCSK9-Human-end modified mU*mU*mC*AUCCGCCGUUUGAGAGCUAGGCCAACAUAGAGGAUCACCAUGUCUGCAGGGCCUAGCAAGUUCAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCCGG*mU*mG*mC (SEQ ID NO: 1124)

mg-PCSK9-Monkey-end modified	mC*mA*mG*GUUCCAUGGGAUG CUCUGUUUGAGAGCUAGGGCCC UGAAGAAGGGCCCUAGCAAGU UCAAAUAAGGCUAGUCCGUUA UCAACUUGAAAAAGUGGCACC GAGUCGG*mU*mG*mC (SEQ ID NO: 1127)	hg-PCSK9-Monkey-end modified mU*mU*mC*AUCCGCCGUUU GAGAGCUAGGCCAACAUAGA GGAUCACCCAUGUCUGCAG GGCCUAGCAAGUUCAAAUA AGGCUAGUCCGUUAUCAAC UUGAAAAAGUGGCACCGAG UCGG*mU*mG*mC (SEQ ID NO: 1126)
m: 2'-O-methyl *: phosphorothioate linkage		

[00445] Table 8B the mgRNA and the hgRNA binding to *ANGPTL3* gene

mgRNA	Sequence	hgRNA
mg-ANGPTL3-Mouse-end modified	mA*mC*mU*ACAAGUUA AAAAC GAGGGUUUGAGAGCUAGGGCC CUGAAGAAGGGCCCUAGCAAG UUCAAAUAAGGCUAGUCCGUU AUCAACUUGAAAAAGUGGCAC CGAGUCGG*mU*mG*mC (SEQ ID NO: 1132)	hg-ANGPTL3-Mouse-end modified mG*mA*mA*GAGGAAAGUUU GAGAGCUAGGCCAACAUAGA GGAUCACCCAUGUCUGCAG GGCCUAGCAAGUUCAAAUA AGGCUAGUCCGUUAUCAAC UUGAAAAAGUGGCACCGAG UCGG*mU*mG*mC (SEQ ID NO: 1131)
mg-ANGPTL3-Human-end modified	mA*mC*mU*ACAAGUCA AAAAU GAAGGUUUGAGAGCUAGGGCC CUGAAGAAGGGCCCUAGCAAG UUCAAAUAAGGCUAGUCCGUU AUCAACUUGAAAAAGUGGCAC CGAGUCGG*mU*mG*mC (SEQ ID NO: 1134)	hg-ANGPTL3-Human-end modified mG*mA*mA*GAAGAAAGUUU GAGAGCUAGGCCAACAUAGA GGAUCACCCAUGUCUGCAG GGCCUAGCAAGUUCAAAUA AGGCUAGUCCGUUAUCAAC UUGAAAAAGUGGCACCGAG UCGG*mU*mG*mC (SEQ ID NO: 1133)
mg-ANGPTL3-Monkey-end modified	mA*mC*mU*ACAAGUCA AAAAU GAAGGUUUGAGAGCUAGGGCC CUGAAGAAGGGCCCUAGCAAG UUCAAAUAAGGCUAGUCCGUU AUCAACUUGAAAAAGUGGCAC CGAGUCGG*mU*mG*mC (SEQ ID NO: 1136)	hg-ANGPTL3-Monkey-end modified mG*mA*mA*GAAGAAAGUUU GAGAGCUAGGCCAACAUAGA GGAUCACCCAUGUCUGCAG GGCCUAGCAAGUUCAAAUA AGGCUAGUCCGUUAUCAAC UUGAAAAAGUGGCACCGAG UCGG*mU*mG*mC (SEQ ID NO: 1135)

m: 2'-O-methyl

*: phosphorothioate linkage

[00446] Table 8C the mgRNA and the hgRNA binding to *APOC3* gene

mgRNA	Sequence	hgRNA
mg-hAPOC3-1	mA*mA*mG*CUCCUGAGGAAAG AGCAGUUUGAGAmGmCmUmAm GGGCCUGAAGAAGGGCCmCm UmAmGmCAAGUUCAAAUAAGG CUAGUCCGUUAUCAmAmCmUm UmGmAmAmAmAmAmGmUmGm GmCmAmCmCmGmAmGmUmCmG mG*mU*mG*mC (SEQ ID NO: 1266)	hg-APOC3-1: mC*mU*mG*AGAAGGGGUUU GAGAmGmCmUmAmGGCACA UGAGGAUCACCCAUGUGCm CmUmAmGmCAAGUUCAAAU AAGGCUAGUCCGUUAUCAm AmCmUmUmGmAmAmAmAm AmGmUmGmGmCmAmCmCm GmAmGmUmCmGmG*mU*mG *mC (SEQ ID NO: 1267)
mg-hAPOC3-2	mG*mG*mU*GCUCCAGUAGUCU UUCAGUUUGAGAmGmCmUmAm GGGCCUGAAGAAGGGCCmCm UmAmGmCAAGUUCAAAUAAGG CUAGUCCGUUAUCAmAmCmUm UmGmAmAmAmAmAmGmUmGm GmCmAmCmCmGmAmGmUmCmG mG*mU*mG*mC (SEQ ID NO: 1268)	hg-APOC3-2: mU*mC*mU*GACCUCAGUUU GAGAmGmCmUmAmGGCACA UGAGGAUCACCCAUGUGCm CmUmAmGmCAAGUUCAAAU AAGGCUAGUCCGUUAUCAm AmCmUmUmGmAmAmAmAm AmGmUmGmGmCmAmCmCm GmAmGmUmCmGmG*mU*mG *mC (SEQ ID NO: 1269)
mg-hAPOC3-3	mC*mC*mA*GCCCCUAAAUCAG UCAGGUUUGAGAmGmCmUmAm GGGCCUGAAGAAGGGCCmCm UmAmGmCAAGUUCAAAUAAGG CUAGUCCGUUAUCAmAmCmUm UmGmAmAmAmAmAmGmUmGm GmCmAmCmCmGmAmGmUmCmG mG*mU*mG*mC (SEQ ID NO: 1270)	hg-APOC3-3: mU*mU*mG*UCCUUAAGUUU GAGAmGmCmUmAmGGCACA UGAGGAUCACCCAUGUGCm CmUmAmGmCAAGUUCAAAU AAGGCUAGUCCGUUAUCAm AmCmUmUmGmAmAmAmAm AmGmUmGmGmCmAmCmCm GmAmGmUmCmGmG*mU*mG *mC (SEQ ID NO: 1271)
m: 2'-O-methyl *: phosphorothioate linkage		

[00447] In some embodiments, the gene editing system disclosed herein comprises (1) the hgRNA comprising a CRISPR motif, the hgRNA spacer, and a first protein-binding motif, or a DNA polynucleotide encoding the hgRNA, (2) the mgRNA comprising a second CRISPR motif and the mgRNA spacer, or a DNA polynucleotide encoding the mgRNA, (3) a first
5 CRISPR-associated protein (Cas protein), or a polynucleotide encoding the first Cas protein, wherein the first Cas protein binds to the first CRISPR motif, (4) a second Cas protein, or a polynucleotide encoding the second Cas protein, wherein the second Cas protein binds to the second CRISPR motif, and (5) a first fusion protein comprising a nucleobase deaminase or a catalytic domain thereof and a first RNA binding domain, or a polynucleotide encoding the
10 first fusion protein, wherein the nucleobase deaminase or the catalytic domain thereof and the first RNA binding domain are optionally connected by a linker, and wherein the first RNA binding domain binds to the first protein-binding motif, and wherein the first Cas protein and second Cas protein are the same or different.

[00448] In some embodiments, the gene editing system disclosed herein comprises (1) the
15 hgRNA comprising a CRISPR motif, the hgRNA spacer, and a first protein-binding motif, or a DNA polynucleotide encoding the hgRNA, (2) the mgRNA comprising a second CRISPR motif and the mgRNA spacer, or a DNA polynucleotide encoding the mgRNA, (3) a first CRISPR-associated protein (Cas protein), or a polynucleotide encoding the first Cas protein, wherein the first Cas protein binds to the first CRISPR motif, (4) a second Cas protein, or a
20 polynucleotide encoding the second Cas protein, wherein the second Cas protein binds to the second CRISPR motif, (5) a first fusion protein comprising a nucleobase deaminase or a catalytic domain thereof and a first RNA binding domain, or a polynucleotide encoding the first fusion protein, wherein the nucleobase deaminase or the catalytic domain thereof and the first RNA binding domain are optionally connected by a linker, and wherein the first RNA
25 binding domain binds to the first protein-binding motif, and (6) a protease, or a polynucleotide encoding the protease, (7) a nucleobase deaminase inhibitor domain, wherein the first Cas protein and second Cas protein are the same or different, wherein the nucleobase deaminase inhibitor domain is connected to the nucleobase deaminase or the catalytic domain thereof in the first fusion protein optionally by a linker, and wherein there is a cleavage site
30 for the protease between the nucleobase deaminase inhibitor domain and the nucleobase deaminase or the catalytic domain thereof.

[00449] In some embodiments, the gene editing system disclosed herein comprises (1) the hgRNA comprising a CRISPR motif, the hgRNA spacer, and a first protein-binding motif, or a DNA polynucleotide encoding the hgRNA, (2) the mgRNA comprising a second CRISPR
35 motif and the mgRNA spacer, or a DNA polynucleotide encoding the mgRNA, (3) a first CRISPR-associated protein (Cas protein), or a polynucleotide encoding the first Cas protein, wherein the first Cas protein binds to the first CRISPR motif, (4) a second Cas protein, or a polynucleotide encoding the second Cas protein, wherein the second Cas protein binds to the

second CRISPR motif, (5) a first fusion protein comprising a nucleobase deaminase or a catalytic domain thereof and a first RNA binding domain, or a polynucleotide encoding the first fusion protein, wherein the nucleobase deaminase or the catalytic domain thereof and the first RNA binding domain are optionally connected by a linker, and wherein the first RNA
5 binding domain binds to the first protein-binding motif, (6) a protease, or a polynucleotide encoding the protease, (7) a nucleobase deaminase inhibitor domain, and (8) a second fusion protein comprising the protease and a second RNA binding domain, or a polynucleotide encoding the second fusion protein, wherein the first Cas protein and second Cas protein are the same or different, wherein the nucleobase deaminase inhibitor domain is connected to the
10 nucleobase deaminase or the catalytic domain thereof in the first fusion protein optionally by a linker, and wherein there is a cleavage site for the protease between the nucleobase deaminase inhibitor domain and the nucleobase deaminase or the catalytic domain thereof, wherein the protease and the second RNA binding domain are optionally connected by a linker, wherein the mgRNA further comprises a second protein-binding motif, and wherein
15 the second RNA binding domain binds to the second protein-binding motif.

[00450] In some embodiments, the protease is split into a first protease fragment and a second protease fragment, wherein the first or second protease fragment alone is not able to cleave the cleavage site.

[00451] In some embodiments, the gene editing system disclosed herein comprises (1) the
20 hgRNA comprising a CRISPR motif, the hgRNA spacer, and a first protein-binding motif, or a DNA polynucleotide encoding the hgRNA, (2) the mgRNA comprising a second CRISPR motif and the mgRNA spacer, or a DNA polynucleotide encoding the mgRNA, (3) a first CRISPR-associated protein (Cas protein), or a polynucleotide encoding the first Cas protein, wherein the first Cas protein binds to the first CRISPR motif, (4) a second Cas protein, or a
25 polynucleotide encoding the second Cas protein, wherein the second Cas protein binds to the second CRISPR motif, (5) a first fusion protein comprising a nucleobase deaminase or a catalytic domain thereof and a first RNA binding domain, or a polynucleotide encoding the first fusion protein, wherein the nucleobase deaminase or the catalytic domain thereof and the first RNA binding domain are optionally connected by a linker, and wherein the first RNA
30 binding domain binds to the first protein-binding motif, (6) a protease, or a polynucleotide encoding the protease, (7) a nucleobase deaminase inhibitor domain, (8) a second fusion protein comprising the first protease fragment and a second RNA binding domain, or a polynucleotide encoding the second fusion protein, wherein the first protease fragment and the second RNA binding domain are optionally connected by a linker, and (9) a third fusion
35 protein comprising the second protease fragment and a third RNA binding domain, or a polynucleotide encoding the third fusion protein, wherein the second protease fragment and the third RNA binding domain are optionally connected by a linker, wherein the first Cas protein and second Cas protein are the same or different, wherein the nucleobase deaminase

inhibitor domain is connected to the nucleobase deaminase or the catalytic domain thereof in the first fusion protein optionally by a linker, and wherein there is a cleavage site for the protease between the nucleobase deaminase inhibitor domain and the nucleobase deaminase or the catalytic domain thereof, wherein the mgRNA further comprises a second protein-binding motif and a third protein-binding motif, wherein the second RNA binding domain binds to the second protein-binding motif, and wherein the third RNA binding domain binds to the third protein-binding motif.

[00452] In some embodiments, the gene editing system disclosed herein comprises (1) the hgRNA comprising a CRISPR motif, the hgRNA spacer, and a first protein-binding motif, or a DNA polynucleotide encoding the hgRNA, (2) the mgRNA comprising a second CRISPR motif and the mgRNA spacer, or a DNA polynucleotide encoding the mgRNA, (3) a first CRISPR-associated protein (Cas protein), or a polynucleotide encoding the first Cas protein, wherein the first Cas protein binds to the first CRISPR motif, (4) a second Cas protein, or a polynucleotide encoding the second Cas protein, wherein the second Cas protein binds to the second CRISPR motif, (5) a first fusion protein comprising a nucleobase deaminase or a catalytic domain thereof and a first RNA binding domain, or a polynucleotide encoding the first fusion protein, wherein the nucleobase deaminase or the catalytic domain thereof and the first RNA binding domain are optionally connected by a linker, and wherein the first RNA binding domain binds to the first protein-binding motif, (6) a protease, or a polynucleotide encoding the protease, (7) a nucleobase deaminase inhibitor domain, (8) a second fusion protein comprising the first protease fragment and a second RNA binding domain, or a polynucleotide encoding the second fusion protein, wherein the first protease fragment and the second RNA binding domain are optionally connected by a linker, and (9) a third fusion protein comprising the second protease fragment and a third RNA binding domain, or a polynucleotide encoding the third fusion protein, wherein the second protease fragment and the third RNA binding domain are optionally connected by a linker, wherein the first Cas protein and second Cas protein are the same or different, wherein the nucleobase deaminase inhibitor domain is connected to the nucleobase deaminase or the catalytic domain thereof in the first fusion protein optionally by a linker, and wherein there is a cleavage site for the protease between the nucleobase deaminase inhibitor domain and the nucleobase deaminase or the catalytic domain thereof, wherein the mgRNA further comprises a second protein-binding motif and a third protein-binding motif, wherein the second RNA binding domain binds to the second protein-binding motif, wherein the third RNA binding domain binds to the third protein-binding motif, and wherein the second and third RNA binding domains are the same or different, and the second and third protein-binding motifs are the same or different.

[00453] In some embodiments, the gene editing system disclosed herein comprises (1) the hgRNA comprising a CRISPR motif, the hgRNA spacer, and a first protein-binding motif, or

a DNA polynucleotide encoding the hgRNA, (2) the mgRNA comprising a second CRISPR motif and the mgRNA spacer, or a DNA polynucleotide encoding the mgRNA, (3) a first CRISPR-associated protein (Cas protein), or a polynucleotide encoding the first Cas protein, wherein the first Cas protein binds to the first CRISPR motif, (4) a second Cas protein, or a polynucleotide encoding the second Cas protein, wherein the second Cas protein binds to the second CRISPR motif, (5) a first fusion protein comprising a nucleobase deaminase or a catalytic domain thereof and a first RNA binding domain, or a polynucleotide encoding the first fusion protein, wherein the nucleobase deaminase or the catalytic domain thereof and the first RNA binding domain are optionally connected by a linker, and wherein the first RNA binding domain binds to the first protein-binding motif, (6) a protease, or a polynucleotide encoding the protease, (7) a nucleobase deaminase inhibitor domain, and (8) a second fusion protein comprising the first protease fragment and a second RNA binding domain, or a polynucleotide encoding the second fusion protein, wherein the first Cas protein and second Cas protein are the same or different, wherein the nucleobase deaminase inhibitor domain is connected to the nucleobase deaminase or the catalytic domain thereof in the first fusion protein optionally by a linker, and wherein there is a cleavage site for the protease between the nucleobase deaminase inhibitor domain and the nucleobase deaminase or the catalytic domain thereof, wherein the first protease fragment and the second RNA binding domain are optionally connected by a linker, wherein the mgRNA further comprises a second protein-binding motif, and wherein the second RNA binding domain binds to the second protein-binding motif..

[00454] A “protease” refers to an enzyme that catalyzes proteolysis. A “cleavage site for a protease” refers to a short peptide that the protease recognizes, and within which creates a proteolytic cleavage. Non-limiting examples of proteases include TEV protease, TuMV protease, PPV protease, PVY protease, ZIKV protease, and WNV protease. The protein sequences of example proteases and their corresponding cleavage sites are provided in Table 9.

[00455] Table 9 Exemplary proteases and their cleavage sites

Name	Sequence	SEQ ID NO
TEV protease	MGESLFKGPRDYNPISSTICHLTNESDGHTTSLYGIGFGPFITNKHLEFRNNGTL LVQSLHGVFKVKNTTTLQQLIDGRDMIIIRMPKDFPPFPQKLKFREPQREERIC LVTTNFQTKSMSSMVSDTCTFPSSDGIFWKHWIQTQDQCGSPLVSTRDGFIV GIHSASNFTNTNNYFTSVPKNFMELLTNQEAQQWVSGWRLNADSVLWGGHKV FMVKPEEPFQPVKEATQLMN	SEQ ID NO: 195

TEV protease N- terminal domain	MGESLFKGPRDYNPISSTICHLTNESDGHSTSLYGIGFGPFITNKHLFRRNNGTL LVQSLHGVFKVKNTTTLQQHLIDGRDMIIRMPKDFPPFPQKLKFREPQREERIC LVTTNFQT	SEQ ID NO: 196
TEV protease C- terminal domain	MKSMSSMVSDTSCTFPSSDGIFWKHWIQTGDGQCGSPLVSTRDGFIVGIHSASN FTNTNNYFTSVPKNFMELLTNQEAQQWVSGWRLNADSVLWGGHKVFMVKPE EPFQPVKEATQ	SEQ ID NO: 197
TEV protease cleavage site	ENLYFQS	SEQ ID NO: 198
TuMV protease	MASSNSMFRGLRDYNPISNNICHLTNVSDGASNSLYGVGFGPLILTNRHLFERN NGELVIKSRHGEFVIKNTTQLHLLPIPDRLDLLIRLPKDVPPFPQKLGFRRQPEKGE RICMVGSNFQTKSITSIVSETSTIMPVENSQFWKHWISTKDGQCGSPMVSTKDG KILGLHSLANFQNSINYFAAFPDDFAEKYLHTIEAHEWVKHWKYNTSAISWGSL NIQASQPSGLFKVSKLISDLDTAVYAQ	SEQ ID NO: 199
TuMV protease cleavage site	GGCSHQ	SEQ ID NO: 200
PPV protease	MASSKSLFRGLRDYNPIASSICQLNNSGARQSEMFGFGGLIVTNQHFLKRN DGELTIRSHHGEFVVKDTKTLKLLPCKGRDIVIIRLPKDFPPFPRLQFRTPTTED RVCLIGSNFQTKSISSTMSETSATYPVDNSHFWKHWISTKDGHCGLPIVSTRDGS ILGLHSLANSTNTQNFYAAFPDNFETTYLSNQDNDNWIKQWRYNPDEVCWGSL QLKRDIPQSPFTICKLLTDLDGEFVYTQ	SEQ ID NO: 201
PPV protease cleavage site	QVVVHQSK	SEQ ID NO: 202
PVY protease	MASAKSLMRGLRDFNPQAQTVCRLLKVSVEYGASEMYGFGFGAYIVANHHLFRS YNGSMEVQSMHGTFRVKNLHSLSVLPKGRDIIKMPKDFPVFPQKLHFRAPT QNERICLVGTNFQEKYASSIITETSTTYNIPGSTFWKHWIETDNGHCGLPVVSTA DGCIVGIHSLANNAHTTNYSAFDEDFESKYLRTNEHNEWVKSWSVYNPDTVL WGPLKLDSTPKGLFKTTKLVDLIDHDVVVEQ	SEQ ID NO: 203
PVY protease cleavage site	YDVRHQSR	SEQ ID NO: 204

ZIKV protease	MASDMYIERAGDITWEKDAEVTGNSPRLDVALDESGDFSLVEEDGPPMREGGG GSGGGGSGALWDVPAPKEVKKGETTDGVYRVMTRLLGSTQVGVGVMQEGV FHTMWHVTKGAALRSGEGRDPYWGDVKQDLVSYCGPWKLDAAWDGLSEV QLLAVPPGERARNIQTLPGIFKTKDGDIGAVALDYPAGTSGSPILDKCGRVIGLY GNGVVIKNGSYVSAITQGKREEETPVECFE	SEQ ID NO: 205
ZIKV protease cleavage site	KERKRRGA	SEQ ID NO: 206
WNV protease	MASSTDMWIERTADISWESDAEITGSSSERVDVRLDDDGNFQLMNDPGAPWKG GGGSGGGGGVLWDTPSPKEYKKGDTTGTGVYRIMTRGLLGSYQAGAGVMVEG VFHTLWHTTKGAALMSGEGRLDPYWGSVKEDRLCYGGPWKLQHKWNGQDE VQMIVVEPGKNVKNVQTKPGVFKTPEGEIGAVTLDFPTGTSGSPIVDKNGDVIG LYGNGVIMPNGSYISAIVQGERMDEPIPAGFEPEML	SEQ ID NO: 207
WNV protease cleavage site	KQKKRGGK	SEQ ID NO: 208

[00456] For any protein of the present disclosure, biological equivalents thereof are also provided. In some embodiments, the biological equivalents have at least about 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% sequence identity with the reference protein. Preferably, the biological equivalents retained the desired activity of the reference protein. In some embodiments, the biological equivalents are derived by including one, two, three, four, five or more amino acid additions, deletions, substitutions, or the combinations thereof. In some embodiments, the substitution is a conservative amino acid substitution.

[00457] In some embodiments of the gene editing systems described herein, the guide RNA (the main guide RNA and/or the helper guide RNA) is a dual-RNA structure formed by a ligand-bound CRISPR RNA (crRNA) and a trans-activating crRNA (tracrRNA). In some embodiments, the crRNA comprises a spacer sequence and is capable of forming a base-pair structure with the tracrRNA, and wherein the base-pair structure binds to a Cas protein. In some embodiments, the crRNA further comprises a linker sequence which comprises a protein-binding motif.

[00458] For the purpose of the present disclosure, when the guide RNA is a dual-RNA structure of crRNA and tracrRNA, the “CRISPR motif” refers to the base-pair structure formed between the crRNA and the tracrRNA.

[00459] In some embodiments, the gene editing system is a LigoRNA-based gene editing system, as described in PCT/CN2023/096482, which is incorporated herein by reference in its

entirety. In the LigoRNA-based gene editing system, at least one guide RNA is a LigoRNA. A LigoRNA system comprises a dual-RNA structure, which can be used as a guide RNA in CRISPR-based gene editing systems. The dual-RNA structure can be formed by a ligand-bound CRISPR RNA (crRNA) and a trans-activating crRNA (tracrRNA). For example, the LigoRNA system comprises an hgRNA set of a hcrRNA and a tracrRNA, and an mgRNA set of mcrRNA and a tracrRNA. Preferably, all of these RNA molecules are not longer than 100 nucleotides.

[00460] Since the LigoRNA system is formed by two short RNAs, it helps to solve the problem of synthesizing long single guide RNAs in previous gene editing systems.

Chemically synthesized RNAs over 100 nt demonstrated much lower yield and purity, resulting in challenges for large-scale production and cost control.

[00461] Original types of crRNA and tracrRNA are capable of guiding nCas9-mediated DNA location. The crRNAs and the tracrRNAs in the LigoRNA system are further modified. In some embodiments, an MS2 or boxB hairpin is fused to crRNA in multiple different sites.

In some embodiments, at least one nucleotide in the crRNAs and the tracrRNAs is modified, such as by a 2'-O-methyl modification and/or 3'-phosphorothioate modification.

[00462] In some embodiments, the crRNA comprises a spacer sequence and a linker sequence, wherein the linker sequence comprises at least one protein-binding motif, wherein the protein-binding motif is an RNA aptamer motif. In some embodiments, the protein binding motif is selected from MS2, PP7, boxB, SfMu hairpin motif, telomerase Ku, and Sm7 binding motif, or a variant thereof. Aptamers are single-stranded oligonucleotides that fold into defined architectures and selectively bind to a specific target, including proteins, peptides, carbohydrates, small molecules, toxins, and even live cells.

[00463] In some embodiments, the crRNA is capable of forming a base-pair structure with a trans-activating crRNA (tracrRNA).

[00464] In some embodiments, the crRNA comprises at least one nucleotide with modification. In some embodiments, the modification is selected from 2'-O-alkyl, 2'-substituted alkoxy, 2'-substituted alkyl, 2'-halo, 3'-phosphorothioate, bridged nucleic acid (BNA), and locked nucleic acid (LNA). In some embodiments, the at least one nucleotide with modification is any one of the first three nucleotides from 3'-end of the engineered crRNA.

[00465] In some embodiments, the tracrRNA comprises at least one nucleotide with modification. In some embodiments, the modification is selected from 2'-O-alkyl, 2'-substituted alkoxy, 2'-substituted alkyl, 2'-halo, 3'-phosphorothioate, bridged nucleic acid (BNA), and locked nucleic acid (LNA). In some embodiments, the at least one nucleotide

with modification is any one of the first three nucleotides from 3'-end of the engineered tracrRNA.

[00466] In some embodiments, the crRNA and/or tracrRNA comprises at least one nucleotide with modification. In some embodiments, the modification is selected from 2'-O-alkyl (such as 2'-O-methyl), 2'-substituted alkoxy, 2'-substituted alkyl, 2'-halo (such as 2'-fluoro), 3'-phosphorothioate, bridged nucleic acid (BNA), and locked nucleic acid (LNA). In some embodiments, the crRNA and/or tracrRNA comprises nucleotides comprising 2'-O-methyl and 3'-phosphorothioate. In some embodiments, the first three nucleotides from the 5'-end of the crRNA and/or tracrRNA are modified with 2'-O-methyl and 3'-phosphorothioate. In some embodiments, the first three nucleotides from the 3'-end of the crRNA and/or tracrRNA are modified with 2'-O-methyl, and the second to fourth nucleotides from the 3'-end of the crRNA and/or tracrRNA are modified with 3'-phosphorothioate. In some embodiments, the first three nucleotides from the 5'-end of the crRNA and/or tracrRNA are modified with 2'-O-methyl and 3'-phosphorothioate, and the first three nucleotides from the 3'-end of the crRNA and/or tracrRNA are modified with 2'-O-methyl, and the second to fourth nucleotides from the 3'-end of the crRNA and/or tracrRNA are modified with 3'-phosphorothioate.

[00467] In some embodiments, the present disclosure provides a tBE system comprising two LigoRNA structures: an mcrRNA-tracrRNA base-paired structure and an hcrRNA-tracrRNA base-paired structure. In some embodiments, the mcrRNA contains a boxB hairpin to generate an R-loop region for intended base editing and the hcrRNA contains an MS2 hairpin to recruit a nucleotide deaminase (e.g., an APOBEC linked to a nucleobase deaminase inhibitor (e.g., a cytosine deaminase inhibitor (dCDI)) domain through a cleavage site such as a TEV protease cleavage site. For example, to cleave off the dCDI domain at the on-target sites, an N22p-fused TEVc is recruited by the boxB-containing mcrRNA, working as the key in tBE system with free TEVn. In some embodiments, mcrRNA and hcrRNA form a base-paired structure with the same tracrRNA to locate a target DNA, and the dCDI domain is cleaved off at the target site to induce efficient base editing.

[00468] In some embodiments of the gene editing system described herein, the gene editing system comprises:

- a. an hcrRNA comprising a first spacer sequence and a first linker sequence, wherein the first linker sequence comprises a first protein-binding motif,
- b. an mcrRNA comprising a second spacer sequence and a second linker sequence, wherein the second linker sequence comprises a second protein-binding motif,

- c. a first tracrRNA which is capable of forming a first base-pair structure with the hcrRNA,
- d. a second tracrRNA which is capable of forming a second base-pair structure with the mcrRNA,
- 5 e. a first CRISPR-associated protein (Cas protein), or a polynucleotide encoding the first Cas protein, wherein the first Cas protein binds to the first base-pair structure,
- f. a second Cas protein, or a polynucleotide encoding the second Cas protein, wherein the second Cas protein binds to the second base pair structure,
- 10 g. a first fusion protein comprising a nucleobase deaminase or a catalytic domain thereof and a first RNA binding domain, or a polynucleotide encoding the first fusion protein, wherein the nucleobase deaminase or the catalytic domain thereof and the first RNA binding domain are optionally connected by a linker, and wherein the first RNA binding domain binds to the first protein-
- 15 binding motif,

wherein the first Cas protein and the second Cas protein are the same or different, and the first tracrRNA and the second tracrRNA are the same or different.

[00469] In some embodiments of the gene editing system described herein, the gene editing system further comprises

- 20 a. a protease, or a polynucleotide encoding the protease, and
- b. a nucleobase deaminase inhibitor domain,

wherein the nucleobase deaminase inhibitor domain is connected to the nucleobase deaminase or the catalytic domain thereof in the first fusion protein optionally by a linker, and wherein there is a cleavage site for the protease

25 between the nucleobase deaminase inhibitor domain and the nucleobase deaminase or the catalytic domain thereof.

[00470] In some embodiments of the gene editing system described herein, the gene editing system comprises

- 30 a. an hcrRNA comprising a first spacer sequence and a first linker sequence, wherein the first linker sequence comprises a first protein-binding motif,
- b. an mcrRNA comprising a second spacer sequence and a second linker sequence, wherein the second linker sequence comprises a second protein-binding motif,

- c. a first tracrRNA which is capable of forming a first base-pair structure with the hcrRNA,
- d. a second tracrRNA which is capable of forming a second base-pair structure with the mcrRNA,
- 5 e. a first CRISPR-associated protein (Cas protein), or a polynucleotide encoding the first Cas protein, wherein the first Cas protein binds to the first base-pair structure,
- f. a second Cas protein, or a polynucleotide encoding the second Cas protein, wherein the second Cas protein binds to the second base pair structure,
- 10 g. a first fusion protein comprising a nucleobase deaminase or a catalytic domain thereof and a first RNA binding domain, or a polynucleotide encoding the first fusion protein, wherein the nucleobase deaminase or the catalytic domain thereof and the first RNA binding domain are optionally connected by a linker, and wherein the first RNA binding domain binds to the first protein-binding motif,
- 15 h. a protease, or a polynucleotide encoding the protease,
- i. a nucleobase deaminase inhibitor domain, and
- j. a second fusion protein comprising the protease and a second RNA binding domain, or a polynucleotide encoding the second fusion protein,
- 20 wherein the first Cas protein and the second Cas protein are the same or different, and the first tracrRNA and the second tracrRNA are the same or different, wherein the nucleobase deaminase inhibitor domain is connected to the nucleobase deaminase or the catalytic domain thereof in the first fusion protein optionally by a linker, and wherein there is a cleavage site for the protease
- 25 between the nucleobase deaminase inhibitor domain and the nucleobase deaminase or the catalytic domain thereof, wherein the protease and the second RNA binding domain are optionally connected by a linker, and wherein the second RNA binding domain binds to the second protein-binding motif.
- 30

[00471] In some embodiments of the gene editing system described herein, the protease is split into a first protease fragment and a second protease fragment, wherein the first and/or second protease fragment alone is not able to cleave the cleavage site.

[00472] In some embodiments of the gene editing system described herein, wherein the
35 gene editing system comprises

- 5
- a. an hcrRNA comprising a first spacer sequence and a first linker sequence, wherein the first linker sequence comprises a first protein-binding motif,
- b. an mcrRNA comprising a second spacer sequence and a second linker sequence, wherein the second linker sequence comprises a second protein-binding motif,
- c. a first tracrRNA which is capable of forming a first base-pair structure with the hcrRNA,
- d. a second tracrRNA which is capable of forming a second base-pair structure with the mcrRNA,
- 10 e. a first CRISPR-associated protein (Cas protein), or a polynucleotide encoding the first Cas protein, wherein the first Cas protein binds to the first base-pair structure,
- f. a second Cas protein, or a polynucleotide encoding the second Cas protein, wherein the second Cas protein binds to the second base pair structure,
- 15 g. a first fusion protein comprising a nucleobase deaminase or a catalytic domain thereof and a first RNA binding domain, or a polynucleotide encoding the first fusion protein, wherein the nucleobase deaminase or the catalytic domain thereof and the first RNA binding domain are optionally connected by a linker, and wherein the first RNA binding domain binds to the first protein-binding motif,
- 20 h. a protease, or a polynucleotide encoding the protease, wherein the protease is split into a first protease fragment and a second protease fragment, wherein the first and/or second protease fragment alone is not able to cleave the cleavage site,
- 25 i. a nucleobase deaminase inhibitor domain,
- j. a second fusion protein comprising the first protease fragment and a second RNA binding domain, or a polynucleotide encoding the second fusion protein, wherein the first protease fragment and the second RNA binding domain are optionally connected by a linker, and
- 30 k. a third fusion protein comprising the second protease fragment and a third RNA binding domain, or a polynucleotide encoding the third fusion protein, wherein the second protease fragment and the third RNA binding domain are optionally connected by a linker,

35 wherein the first Cas protein and the second Cas protein are the same or different, and the first tracrRNA and the second tracrRNA are the same or different,

wherein the nucleobase deaminase inhibitor domain is connected to the nucleobase deaminase or the catalytic domain thereof in the first fusion protein optionally by a linker, and wherein there is a cleavage site for the protease between the nucleobase deaminase inhibitor domain and the nucleobase deaminase or the catalytic domain thereof,

wherein the mcrRNA further comprises a third protein-binding motif, wherein the second RNA binding domain binds to the second protein-binding motif, and

wherein the third RNA binding domain binds to the third protein-binding motif.

[00473] In some embodiments of the gene editing system described herein, the gene editing system comprises

- a. an hcrRNA comprising a first spacer sequence and a first linker sequence, wherein the first linker sequence comprises a first protein-binding motif,
- b. an mcrRNA comprising a second spacer sequence and a second linker sequence, wherein the second linker sequence comprises a second protein-binding motif,
- c. a first tracrRNA which is capable of forming a first base-pair structure with the hcrRNA,
- d. a second tracrRNA which is capable of forming a second base-pair structure with the mcrRNA,
- e. a first CRISPR-associated protein (Cas protein), or a polynucleotide encoding the first Cas protein, wherein the first Cas protein binds to the first base-pair structure,
- f. a second Cas protein, or a polynucleotide encoding the second Cas protein, wherein the second Cas protein binds to the second base pair structure,
- g. a first fusion protein comprising a nucleobase deaminase or a catalytic domain thereof and a first RNA binding domain, or a polynucleotide encoding the first fusion protein, wherein the nucleobase deaminase or the catalytic domain thereof and the first RNA binding domain are optionally connected by a linker, and wherein the first RNA binding domain binds to the first protein-binding motif,
- h. a protease, or a polynucleotide encoding the protease, wherein the protease is split into a first protease fragment and a second protease fragment, wherein the first and/or second protease fragment alone is not able to cleave the cleavage site,
- i. a nucleobase deaminase inhibitor domain,

- j. a second fusion protein comprising the first protease fragment and a second RNA binding domain, or a polynucleotide encoding the second fusion protein, wherein the first protease fragment and the second RNA binding domain are optionally connected by a linker, and
 - 5 k. a third fusion protein comprising the second protease fragment and a third RNA binding domain, or a polynucleotide encoding the third fusion protein, wherein the second protease fragment and the third RNA binding domain are optionally connected by a linker,
- wherein the first Cas protein and the second Cas protein are the same or different, and
- 10 the first tracrRNA and the second tracrRNA are the same or different, wherein the nucleobase deaminase inhibitor domain is connected to the nucleobase deaminase or the catalytic domain thereof in the first fusion protein optionally by a linker, and wherein there is a cleavage site for the protease between the nucleobase deaminase inhibitor domain and the nucleobase deaminase or the catalytic domain
- 15 thereof,
- wherein the mcrRNA further comprises a third protein-binding motif, wherein the second RNA binding domain binds to the second protein-binding motif, wherein the third RNA binding domain binds to the third protein-binding motif, and wherein the second and the third RNA binding domains are the same or different, and
- 20 the second and the third protein-binding motifs are the same or different.

[00474] In some embodiments of the gene editing system described herein, the gene editing system comprises

- a. an hcrRNA comprising a first spacer sequence and a first linker sequence, wherein the first linker sequence comprises a first protein-binding motif,
- 25 b. an mcrRNA comprising a second spacer sequence and a second linker sequence, wherein the second linker sequence comprises a second protein-binding motif,
- c. a first tracrRNA which is capable of forming a first base-pair structure with the hcrRNA,
- 30 d. a second tracrRNA which is capable of forming a second base-pair structure with the mcrRNA,
- e. a first CRISPR-associated protein (Cas protein), or a polynucleotide encoding the first Cas protein, wherein the first Cas protein binds to the first base-pair structure,
- 35 f. a second Cas protein, or a polynucleotide encoding the second Cas protein, wherein the second Cas protein binds to the second base pair structure,

- g. a first fusion protein comprising a nucleobase deaminase or a catalytic domain thereof and a first RNA binding domain, or a polynucleotide encoding the first fusion protein, wherein the nucleobase deaminase or the catalytic domain thereof and the first RNA binding domain are optionally connected by a linker, and wherein the first RNA binding domain binds to the first protein-binding motif,
- h. a protease, or a polynucleotide encoding the protease, wherein the protease is split into a first protease fragment and a second protease fragment, wherein the first and/or second protease fragment alone is not able to cleave the cleavage site,
- i. a nucleobase deaminase inhibitor domain,
- j. a second fusion protein comprising the first protease fragment and a second RNA binding domain, or a polynucleotide encoding the second fusion protein,
- wherein the first Cas protein and the second Cas protein are the same or different, and the first tracrRNA and the second tracrRNA are the same or different, wherein the nucleobase deaminase inhibitor domain is connected to the nucleobase deaminase or the catalytic domain thereof in the first fusion protein optionally by a linker, and wherein there is a cleavage site for the protease between the nucleobase deaminase inhibitor domain and the nucleobase deaminase or the catalytic domain thereof, wherein the first protease fragment and the second RNA binding domain are optionally connected by a linker, and

[00475] wherein the second RNA binding domain binds to the second protein-binding motif. In some embodiments, the LigoRNA-based gene editing system comprises a main crRNA (mcrRNA), a helper crRNA (hcrRNA), and a tracrRNA respectively.

- [00476] In some embodiments of the gene editing system described herein, the mgRNA and/or the hgRNA comprises a dual-RNA structure.

[00477] In some embodiments, the dual-RNA structure is formed by a CRISPR RNA (crRNA) and a trans-activating crRNA (tracrRNA), wherein the crRNA comprises the spacer.

- [00478] In some embodiments of the gene editing system described herein, the mgRNA comprises a mcrRNA and a first tracrRNA, and the mcrRNA comprises the mgRNA spacer, wherein the hgRNA comprises a hcrRNA and a second tracrRNA, and the hcrRNA comprises the hgRNA spacer, and wherein the first tracrRNA and the second tracrRNA are same or different.

- [00479] In some embodiments, the tracrRNA has a sequence of SEQ ID NO: 1117 and 1242.

- [00480] In some embodiments, the mcrRNA and/or the hcrRNA are capable of binding to the *PCSK9* gene. In some embodiments, the mcrRNA and the hcrRNA SEQ ID NO: 1112 and SEQ ID NO: 1111, respectively; or SEQ ID NO: 1114 and SEQ ID NO: 1113, respectively; or SEQ ID NO: 1116 and SEQ ID NO: 1115, respectively.
- 5 [00481] In some embodiments, the mcrRNA and/or the hcrRNA are capable of binding to the *ANGPTL3* gene. In some embodiments, the mcrRNA and the hcrRNA are SEQ ID NO: 1138 and SEQ ID NO: 1137, respectively; or SEQ ID NO: 1140 and SEQ ID NO: 1139, respectively; or SEQ ID NO: 1142 and SEQ ID NO: 1141, respectively.
- [00482] The sequences of the exemplary mcrRNA and hcrRNA are illustrated in Table
- 10 10A and 10B.

Table 10A the mcrRNA and the hcrRNA binding to *PCSK9* gene

	mcrRNA	hcrRNA	tracrRNA
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1	mcr-PCSK9-Mouse mC*mA*mG*GUUCC AUGGGAUGCUCUG UUUGAGAGCUAUG CUGUUUUUGGGGCC UGAAGAAGGGCCC* mU*mU*mU (SEQ ID NO: 1112)	hcr-PCSK9-Mouse mU*mU*mC*CUCUGU CGUUUGAGAGCUAU GCUGUUUUGGGCCA ACAUGAGGAUCACCC AUGUCUGCAGGGCC* mU*mU*mU (SEQ ID NO: 1111)	tracrRNA mG*mG*mA*ACCAUUCAA AACAGCAUAGCAAGUUCA AAUAAGGCUAGUCCGUUA UCAACUUGAAAAAGUGGC ACCGAGUCGGUGCUUUU* mU*mU*mU (SEQ ID NO: 1117)
2	mcr-PCSK9-Human mC*mA*mG*GUUCC ACGGAUGCUCUG UUUGAGAGCUAUG CUGUUUUUGGGGCC UGAAGAAGGGCCC* mU*mU*mU (SEQ ID NO: 1114)	hcr-PCSK9-Human mU*mU*mC*AUCGCG CGUUUGAGAGCUAU GCUGUUUUGGGCCA ACAUGAGGAUCACCC AUGUCUGCAGGGCC* mU*mU*mU (SEQ ID NO: 1113)	tracrRNA mG*mG*mA*ACCAUUCAA AACAGCAUAGCAAGUUCA AAUAAGGCUAGUCCGUUA UCAACUUGAAAAAGUGGC ACCGAGUCGGUGCUUUU* mU*mU*mU (SEQ ID NO: 1117)
3	mcr-PCSK9-Monkey mC*mA*mG*GUUCC AUGGGAUGCUCUG UUUGAGAGCUAUG CUGUUUUUGGGGCC UGAAGAAGGGCCC* mU*mU*mU (SEQ ID NO: 1116)	hcr-PCSK9-Monkey mU*mU*mC*AUCGCG CGUUUGAGAGCUAU GCUGUUUUGGGCCA ACAUGAGGAUCACCC AUGUCUGCAGGGCC* mU*mU*mU (SEQ ID NO: 1115)	tracrRNA mG*mG*mA*ACCAUUCAA AACAGCAUAGCAAGUUCA AAUAAGGCUAGUCCGUUA UCAACUUGAAAAAGUGGC ACCGAGUCGGUGCUUUU* mU*mU*mU (SEQ ID NO: 1117)
m: 2'-O-methyl *: phosphorothioate linkage			

Table 10B the mcrRNA and the hcrRNA binding to *ANGPTL3* gene

	mcrRNA	hcrRNA	tracrRNA
1	mcr-ANGPTL3-Mouse mA*mC*mU*ACAAG UUAAAAACGAGGG UUUGAGAGCUAUG CUGUUUUUGGGGCC UGAAGAAGGGCCC* mU*mU*mU (SEQ ID NO: 1138)	hcr-ANGPTL3-Mouse mG*mA*mA*GAGGAA AGUUUGAGAGCUAU GCUGUUUUGGGCCA ACAUGAGGAUCACCC AUGUCUGCAGGGCC* mU*mU*mU (SEQ ID NO: 1137)	tracrRNA mG*mG*mA*ACCAUUCAA AACAGCAUAGCAAGUUCA AAUAAGGCUAGUCCGUUA UCAACUUGAAAAAGUGGC ACCGAGUCGGUGCUUUU* mU*mU*mU (SEQ ID NO: 1117)
2	mcr-ANGPTL3-Human mA*mC*mU*ACAAG UCAAAAAUGAAGG UUUGAGAGCUAUG	hcr-ANGPTL3-Human mG*mA*mA*GAAGAA AGUUUGAGAGCUAU GCUGUUUUGGGCCA	tracrRNA mG*mG*mA*ACCAUUCAA AACAGCAUAGCAAGUUCA AAUAAGGCUAGUCCGUUA

	CUGUUUUGGGGCCC UGAAGAAGGGCCC* mU*mU*mU (SEQ ID NO: 1140)	ACAUGAGGAUCACCC AUGUCUGCAGGGCC* mU*mU*mU (SEQ ID NO: 1139)	UCAACUUGAAAAAGUGGC ACCGAGUCGGUGCUUUU* mU*mU*mU (SEQ ID NO: 1117)
3	mcr-ANGPTL3-Monkey mA*mC*mU*ACAAG UCAAAAAUGAAGG UUUGAGAGCUAUG CUGUUUUGGGGCCC UGAAGAAGGGCCC* mU*mU*mU (SEQ ID NO: 1142)	hcr-ANGPTL3-Monkey mG*mA*mA*GAAGAA AGUUUGAGAGCUAU GCUGUUUUGGGCCA ACAUGAGGAUCACCC AUGUCUGCAGGGCC* mU*mU*mU (SEQ ID NO: 1141)	tracrRNA mG*mG*mA*ACCAUUCAA AACAGCAUAGCAAGUUCA AAUAAGGCUAGUCCGUUA UCAACUUGAAAAAGUGGC ACCGAGUCGGUGCUUUU* mU*mU*mU (SEQ ID NO: 1117)
	m: 2'-O-methyl *: phosphorothioate linkage		

Polynucleotides

[00483] In another aspect, the present disclosure provides a polynucleotide encoding the hgRNA and/or the mgRNA disclosed herein.

- 5 [00484] In another aspect, the present disclosure provides a polynucleotide encoding all components except the first and the second Cas protein in the gene editing system disclosed herein.

[00485] In another aspect, the present disclosure provides a polynucleotide encoding all components in the gene editing system disclosed herein.

- 10 [00486] In another aspect, the present disclosure provides a kit comprising a polynucleotide encoding all components except the first and the second Cas protein in the gene editing system disclosed herein, and a polynucleotide encoding the first and/or second Cas protein in the gene editing system disclosed herein. In some embodiments, the first and the second Cas proteins are the same Cas protein.

- 15 [00487] The polynucleotides disclosed herein can be obtained by methods known in the art. For example, the polynucleotide can be obtained from cloned DNA (e.g., from a DNA library), by chemical synthesis, by cDNA cloning, or by the cloning of genomic DNA or fragments thereof, purified from the desired cell. When the polynucleotides are produced by recombinant means, any method known to those skilled in the art for identification of nucleic acids that encode desired genes can be used. Any method available in the art can be used to
20 obtain a full length (i.e., encompassing the entire coding region) cDNA or genomic DNA encoding a desired protein, such as from a cell or tissue source. Modified or variant

polynucleotides can be engineered from a wildtype polynucleotide using standard recombinant DNA methods. Polynucleotides can be cloned or isolated using any available methods known in the art for cloning and isolating nucleic acid molecules. Such methods include PCR amplification of nucleic acids and screening of libraries, including nucleic acid hybridization screening, antibody-based screening, and activity-based screening.

[00488] Methods for amplification of polynucleotides can be used to isolate polynucleotides encoding a desired protein, including for example, polymerase chain reaction (PCR) methods. PCR can be carried out using any known methods or procedures in the art. Exemplary methods include use of a Perkin-Elmer Cetus thermal cycler and Taq polymerase (Gene Amp). A nucleic acid containing gene of interest can be used as a source material from which a desired polypeptide-encoding nucleic acid molecule can be amplified. For example, DNA and mRNA preparations, cell extracts, tissue extracts from an appropriate source (e.g. testis, prostate, breast), fluid samples (e.g. blood, serum, saliva), samples from healthy and/or diseased subjects can be used in amplification methods. The source can be from any eukaryotic species including, but not limited to, vertebrate, mammalian, human, porcine, bovine, feline, avian, equine, canine, and other primate sources. Nucleic acid libraries also can be used as a source material. Primers can be designed to amplify a desired polynucleotide. For example, primers can be designed based on expressed sequences from which a desired polynucleotide is generated. Primers can be designed based on back-translation of a polypeptide amino acid sequence. If desired, degenerate primers can be used for amplification. Oligonucleotide primers that hybridize to sequences at the 3' and 5' termini of the desired sequence can be used as primers to amplify by PCR from a nucleic acid sample. Primers can be used to amplify the entire full-length polynucleotide, or a truncated sequence thereof. Nucleic acid molecules generated by amplification can be sequenced and confirmed to encode a desired polypeptide.

Vectors

[00489] In another aspect, the present disclosure provides a vector comprising the polynucleotide encoding the hgRNA and/or the mgRNA disclosed herein.

[00490] In another aspect, the present disclosure provides a vector comprising the polynucleotide encoding all components except the first and the second Cas protein in the gene editing system disclosed herein.

[00491] In another aspect, the present disclosure provides a vector comprising the polynucleotide encoding all components in the gene editing system disclosed herein.

[00492] In some embodiments, the vector is a plasmid, lipid nanoparticles (LNPs) or a viral vector.

[00493] In some embodiments, the vector is a polycistronic vector.

[00494] In some embodiments, the vector is an Adeno-Associated Virus (AAV) vector.

[00495] In another aspect, the present disclosure provides a kit comprising the vector disclosed above, and a vector comprising the polynucleotide encoding the first and/or second Cas protein in the gene editing system disclosed herein.

5 [00496] Any methods known in the art for the insertion of DNA fragments into a vector can be used to construct expression vectors comprising a polynucleotide disclosed herein. These methods can include *in vitro* recombinant DNA and synthetic techniques and *in vivo* (genetic) recombination. The polynucleotide disclosed herein can be operably linked to control sequences in the expression vector(s) to ensure protein expression. Such control
10 sequences may include, but are not limited to, leader or signal sequences, promoters (e.g., naturally associated or heterologous promoters), ribosomal binding sites, enhancer or activator elements, translational start and termination sequences, and transcription start and termination sequences, and are chosen to be compatible with the host cell chosen to express the proteins. Constitutive or inducible promoters as known in the art are also contemplated.
15 The promoters may be either naturally occurring promoters, hybrid promoters that combine elements of more than one promoter, or synthetic promoters. An expression construct may be present in a cell on an episome, such as a plasmid, or the expression construct may be inserted in a chromosome such as in a gene locus. In some embodiment, the expression vector includes a selectable marker gene to allow the selection of transformed host cells. In
20 some embodiments, the vector is an expression vector comprising a nucleotide sequence encoding a variant polypeptide operably linked to at least one regulatory control sequence. Regulatory control sequence for use herein include promoters, enhancers, and other expression control elements. In some embodiments, the expression vector is designed for the choice of the host cell to be transformed, the particular variant polypeptide desired to be
25 expressed, the vector's copy number, the ability to control that copy number, and/or the expression of any other protein encoded by the vector, such as antibiotic markers.

[00497] The vector can include, but is not limited to, viral vectors, LNPs, and plasmid DNA. Viral vectors can include, but are not limited to, adenoviral vectors, lentiviral vectors, retroviral vectors, and adeno-associated viral vectors. Commonly, expression vectors contain
30 selection markers such as ampicillin-resistance, hygromycin-resistance, tetracycline resistance, kanamycin resistance, or neomycin resistance to permit detection of those cells transformed with the desired DNA sequences. Suitable vectors, promoter, and enhancer elements are known in the art; many are commercially available for generating subject recombinant constructs. In some embodiments, the vector is a polycistronic vector. In some
35 embodiments, the vector is a bicistronic vector or a tricistronic vector. Bicistronic or polycistronic expression vectors may include (1) multiple promoters fused to each of the open reading frames; (2) insertion of splicing signals between genes; (3) fusion of genes

whose expressions are driven by a single promoter; and (4) insertion of proteolytic cleavage sites between genes (self-cleavage peptide) or insertion of internal ribosomal entry sites (IRESs) between genes.

[00498] Lipid Nanoparticles (LNPs)

5 [00499] LNPs are lipid-based nanoparticles that serve as carriers to enhance the delivery of therapeutic payloads, such as mRNA, siRNA, or other nucleic acids. LNPs are typically composed of lipids, which can include cationic lipids, neutral lipids, and sometimes polyethylene glycol (PEG). Cationic lipids interact with negatively charged nucleic acids, forming complexes that protect the payload and facilitate cellular uptake. The process of
10 forming LNPs involves the combination of lipids and the payload (e.g., mRNA or siRNA) in an aqueous solution. This mixture undergoes self-assembly, resulting in the formation of nanoscale lipid particles. LNPs provide stability to the encapsulated cargo, protecting it from enzymatic degradation and other unfavorable conditions in the extracellular environment. This stability is crucial for preserving the integrity of the therapeutic payload during
15 transportation to the target cells. LNPs facilitate cellular uptake through endocytosis. Once the LNPs are internalized by the target cells, they typically undergo endosomal escape to release their cargo into the cytoplasm. This step is essential for the therapeutic payload to exert its function.

[00500] LNP could serve as carriers to deliver tBE system, for example a tBE system targeting the *PCSK9* and/or the *APOC3* gene, to the target cells or tissues with mRNA and sgRNA, comprising mRNA sequence of tBE-V5-mA3 mRNA and nCas9 mRNA, respectively, as represented by

GGGGGACAGAUCCGCGGAGACGCAUCCACGCUGUUUUGACCUCCAUAAGAAG
ACACCGGGACCGAUCCAGCCUCCGCGGCCGGAACGGUGCAUUGGAACGCGGA
25 UUUUUUUGGCAAGAGUGACUACCGUCCUUGACACGGCCACCAUGGCCUCUA
ACUUCACCCAGUUUGUGCUGGUGGACAAUGGAGGAACCGGCGAUGUGACAGU
GGCACCAUCCAACUUUGCCAAUGGCAUCGCCGAGUGGAUCAGCUCCAACUCUA
GGAGCCAGGCCUACAAGGUGACCUGCAGCGUGCGGCAGUCUAGCGCCCAGAAU
AGAAAGUACACAAUCAAGGUGGAGGUGCCAAAGGGAGCAUGGCGCAGCUAUC
30 UGAACAUGGAGCUGACCAUCCCCAUUCGCCACAAAUCCGACUGUGAGCUG
AUCGUGAAGGCCAUGCAGGGCCUGCUGAAGGAUGGCAACCCCAUCCUUCUGC
CAUCGCCGCCAAUAGCGGCAUCUACUCUGGAGGAUCUAGCGGAGGCAGCUCUG
GCAGCGAGACACCAGGAACAAGCGAGUCAGCAACACCAGAGAGCAGUGGCGGC
AGCAGCGGCGGCAGCAGCGGCGGAUCCAAGCGGCCCGCCGCCACCAAGAAGGC
35 CGGCCAGGCCAAGAAGAAGAUGACCAACCUGUCUGACAUAUCGAGAAGG
AGACAGGCAAGCAGCUGGUCAUCCAGGAGAGCAUCCUGAUGCUGCCCGAAGAA
GUCGAAGAAGUGAUCGGAAACAAGCCUGAGAGCGAUUCCUGGUCCAUACCGC

CUACGACGAGAGUACCGACGAAAAUGUGAUGCUGCUGACAUCCGACGCCCCAG
AGUAUAAGCCCUGGGCUCUGGUCAUCCAGGAUUCCAACGGAGAGAAACAAAUC
AAAAUGCUGUCUGGAGGCAGCAUGGGACCAUUUUGCCUGGGCUGUUCACCG
GAAGUGCUAUAGCCCCAUCAGAAACCGAUCAGCCAGGAGACAUAAGUUUC
5 ACUUCAAGAAUCUGGGCUACGCCAAGGGCCGGAAGGAUACCUUCCUGUGCUAU
GAGGUGACAAGAAAGGACUGUGAUAGCCCCGUGUCCUGCACCACGGCGUGUU
UAAGAACAAGGACAAUAUCCACGCCGAGAUCUGUUUUCUGUACUGGUUCCACG
AUAAGGUGCUGAAGGUGCUGUCCCCCAGGGAGGAGUUAAGAUCACCUGGUA
UAUGUCUUGGAGCCCUUGCUUCGAGUGUGCCGAGCAGAUCCUGCGCUUUCUGG
10 CCACACACCACAACCUGAGCCUGGACAUCUUUAGCUCCCGGCGUACAACGUG
CAGGAUCCUGAGACACAGCAGAAUCUGUGCAGACUGGUGCAGGAGGGAGCAC
AGGUGGCAGCAAUGGACCUGUAUGAGUUCAAGAAGUGUUGGAAGAAGUUUGU
GGAUAACGGCGGCCGAGAUUCCGGCCGUGGAAGAGACUGCUGACCAACUCC
GGUACCAGGACAGCAAGCUGCAGGAGAUCUGCGCCCUUGCUAUAUUCUCCGUG
15 CCAUCUAGCGAGAAUCUGUACUUCAGAGCAUGUCCUCUAGCACCCUGUCUAA
UAUCUGCCUGACCAAGGGCCUGCCCAGACAAGGUUCUGGGUGGAGGGCCGGA
GAAUGGACCCUCUGAGCGAGGAGGAGUUUACUCCAGUUCUAUAACCAGAG
GGUGAAGCACCCUGUGCUACUAUCACCGCAUGAAGCCUUAACUGUGCUAUCAGC
UGGAGCAGUUAUAUGGACAGGCACCACUGAAGGGAUGCCUGCUGUCCGAGAA
20 GGGCAAGCAGCACGCCGAGAUCCUGUUUCUGGAUAAGAUCAGAUCUAUGGAG
CUGAGCCAGGUGACCAUCACAUGUUACCUGACAUGGUCCCCAUGCCCAAACUG
UGCAUGGCAGCUGGCAGCCUUAAGAGGGACCGCCAGAUUCUGAUCCUGCACA
UCUACACCUCUAGGCUGUAUUUACUGGAAGCGCCCUUCCAGAAGGGCCUG
UGCUCUCCUGUGGCAGUCUGGCAUCCUGGUGGACGUGAUGGAUCUGCCCCAGUU
25 UACCGACUGUUGGACAAACUUCGUGAAUCCUAAGCGGCCAUUUUGGCCUUGGA
AGGGCCUGGAGAUCAUCAGCAGGCGCACACAGCGGAGACUGAGGCGCAUCAAG
GAGUCCUGGGGCCUGCAGGACCUGGUGAACGAUUUUGGCAAUCUGCAGCUGG
GACCCCUAUGAGCAAGCGGCCCGCCGCCACCAAGAAGGCCGGCCAGGCCAAG
AAGAAGAAGGCUACUAACUUCAGCCUGCUGAAGCAGGCUGGGGACGUGGAGG
30 AGAACCCUGGACCUAUGGGCAACGCCAGAACAAGACGGCGGGAGCGCAGAGCC
GAGAAGCAGGCCCAAUGGAAAGCCGCUAAUUCGGCGGGAGCAGUGGCGGAUC
CAGUGGGUCCGAAACCCUGGCACAAGCGAAAGCGCUACCCUUGAGUCCAGCG
GAGGGUCCUCAGGGGAUUCAUGAAAAGCAUGUCUAGCAUGGUGUCUGACAC
AAGCUGUACCUUCCCCUCCUCUGAUGGCAUCUUUUGGAAGCACUGGAUUCAGA
35 CAAAGGACGGCCAGUGUGGCUCCCCUCUGGUGUCUACCAGGGAUGGCUUCAUC
GUGGGCAUCCACAGCGCCUCCAACUUCACAAACACCAACAACUACUUUACAUC
CGUGCCUAAGAACUUCAUGGAGCUGCUGACCAAUCAGGAGGCACAGCAGUGGG
UGUCUGGAUGGCGCCUGAACGCCGAUAGCGUGCUGUGGGGCGGCCACAAGGUG
UUUAUGGUGAAGCCAGAGGAGCCCUUCCAGCCUGUGAAGGAGGCCACCCAGAA

GCGGCCCCGCCGCCACCAAGAAGGCCGGCCAGGCCAAGAAGAAGAAGGAGGGCA
GAGGAAGUCUGCUAACAUGCGGUGACGUCGAGGAGAAUCCUGGCCCAAUGGG
CGAGUCCCCUGUUUAAGGGCCCCACGGGACUACAACCCCAUCAGCUCCACAAUCU
GCCACCUGACCAAUAGAGAGCGAUGGCCACACCACAUCCUGUAUGGCAUCGGC
5 UUCGGCCCCUUCAUCAUCACAAACAAGCACCUGUUUCGGAGAAACAAUGGCAC
CCUGCUGGUGCAGUCUCUGCACGGCGUGUUAAGGUGAAGAAUACCACAACCC
UGCAGCAGCACCUGAUCGACGGAAGGGAUAUGAUAUCAUCAGAAUGCCUAA
GGACUUCCCCCUUUUCCACAGAAGCUGAAGUUUCGGGAGCCACAGAGGGAGG
AGAGGAUCUGCCUGGUGACAACCAACUCCAGACACUCGAGAAGCGGCCCGCC
10 GCCACCAAGAAGGCCGGCCAGGCCAAGAAGAAGAAGUAAUGAGCUCCGGGUGG
CAUCCUGUGACCCCUCCCCAGUGCCUCUCCUGGCCUGGAAGUUGCCACUCC
AGUGCCACCAGCCUUGUCCUAAUAAAAUUAAGUUGCAUCAAGCUGCGGCCGC
AA
AA (SEQ
15 ID NOs: 1106) and
GGGGGACAGAUCCUGGAGACGCCAUCCACGCUGUUUUGACCUCCAUAAGAAG
ACACCGGGACCGAUCCAGCCUCCGCGGCCGGGAACGGUGCAUUGGAACGCGGA
UCCCCCGUGCCAAGAGUGACUCACCGUCCUUGACACGGCCACCAUGGCCCCUG
CCGCCAAGCGGGUCAAGCUCGACGGUAUCCACGGAGUCCCAGCAGCUAUGGAC
20 AAGAAGUACAGCAUCGGCCUGGCCAUCCGGCACCAACAGCGUGGGCUGGGCCGU
GAUCACCGACGAGUACAAGGUGCCAGCAAGAAGUUAAGGUGCUGGGCAACA
CCGACCGGCACAGCAUCAAGAAGAACCUGAUCGGCGCCCUGCUGUUCGACAGC
GGCGAGACCGCCGAGGCCACCCGGCUGAAGCGGACCGCCCGCGGCGGUACAC
CCGGCGGAAGAACCGGAUCUGCUACCUGCAGGAGAUCUUCAGCAACGAGAUGG
25 CCAAGGUGGACGACAGCUUCUCCACCGGCUGGAGGAGAGCUUCCUGGUGGAG
GAGGACAAGAAGCAGACGCGGCACCCCAUCUUCGGCAACAUCGUGGACGAGGU
GGCCUACCACGAGAAGUACCCACCAUCUACCACCUGCGGAAGAAGCUGGUGG
ACAGCACCGACAAGGCCGACCUGCGGCUGAUCUACCUGGCCUGGCCACAUG
AUCAAGUUCGGGGGCCACUCCUGAUCGAGGGCGACCUGAACCCCGACAACAG
30 CGACGUGGACAAGCUGUUAUCCAGCUGGUGCAGACCUACAACCAGCUGUUCG
AGGAGAACCCCAUCAACGCCAGCGGCGUGGACGCCAAGGCCAUCCUGAGCGCC
CGGCUGAGCAAGAGCCGGCGGCUGGAGAACCUGAUCGCCAGCUGCCCGGCGA
GAAGAAGAACGGCCUGUUCGGCAACCUGAUCGCCUGAGCCUGGGCCUGACCC
CCAACUUAAGAGCAACUUCGACCUGGCCGAGGACGCCAAGCUGCAGCUGAGC
35 AAGGACACCUACGACGACGACCUGGACAACCUGCUGGCCCAGAUCGGCGACCA
GUACGCCGACCUGUCCUGGCCGCCAAGAACCUGAGCGACGCCAUCCUGCUGA
GCGACAUCCUGCGGGUGAACACCGAGAUACCAAGGCCCCCUGAGCGCCAGC
AUGAUAAGCGGUACGACGAGCACCACCAGGACCUGACCCUGCUGAAGGCCCU
GGUGCGGCAGCAGCUGCCCGAGAAGUACAAGGAGAUCUUCUUCGACCAGAGCA

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5 GAGGACUUCUACCCCUUCCUGAAGGACAACCGGGAGAAGAUCGAGAAGAUCU
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10 ACGAGUACUUCACCGUGUACAACGAGCUGACCAAGGUGAAGUACGUGACCGGAG
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15 ACAAGGACUUCUGGACAACGAGGAGAACGAGGACAUCUGGAGGACAUCGU
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 AA
 AA (SEQ ID
 25 NO: 1107).

[00501] LNP could serve as carriers to deliver tBE system, for example a tBE system
 targeting the *PCSK9* gene, to the target cells or tissues with mRNA and sgRNA, comprising
 mRNA sequence of tBE-V1-mA3 mRNA and nCas9 mRNA, respectively, as represented by
 AGGACTTGTTCTTTTTGCAGAAGCTCAGAATAAACGCTCAACTTTGGCCACCATG
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 35 GTGAAGGCCATGCAGGGCCTGCTGAAGGATGGCAACCCCATCCCTTCTGCCATC
 GCCGCCAATAGCGGCATCTACTCTGGAGGATCTAGCGGAGGCAGCTCTGGCAGC
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 30 UGCCACCAGCCUUGUCCUAAUAAAAUUAAGUUGCAUCAAGCUGCGGCCGCAA
 AA
 AA (SEQ ID
 NO: 1107).

[00502] LNP could serve as carriers to deliver tBE system, for example a tBE system
 35 targeting the *PCSK9* gene, to the target cells or tissues with mRNA and sgRNA, comprising
 mRNA sequence of tBE-V1-mA3-2A-nCas9 mRNA, as represented by
 AGGACTTGTCTTTTTGCAGAAGCTCAGAATAAACGCTCAACTTTGGCCACCATG
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CAGTGGCACCATCCAACCTTTGCCAATGGCATCGCCGAGTGGATCAGCTCCAACCTC
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 AATGAGGGCTGCCCTCCCACCTCCGCTGGGAGGAACCTGAACCTGGGAACCATG
 AAGCTGGAAGCACTGCTGTGTCCGCTTTCATGAACACAGCCTGGGACCAGGGCA
 30 TATTAAAGGCTTTTGGCAGCAAAGTGTCAGTGTTGGCAGCGGCCGCAAAAAAAA
 AA
 AA (SEQ ID NO: 1279).

[00503] Polycistronic Vector

[00504] A polycistronic vector is used to co-express multiple genes in the same cell. Two
 35 strategies are most commonly used to construct a multicistronic vector. First, an Internal
 Ribosome Entry Site (IRES) element is typically used for bi-cistronic vectors. The IRES
 element, acting as another ribosome recruitment site, allows initiation of translation from an
 internal region of the mRNA. Thus, two proteins are translated from one mRNA. IRES

elements are quite large (usually 500-600 bp) (Pelletier et al., 1988; Jang et al., 1988). The engineered CD47 proteins disclosed herein have a smaller size compared to the wild-type full-length human CD47, and thus could be used with IRES element in a multicistronic vectors having limited packaging capacity.

5 [00505] AAV vectors

[00506] The Adeno-Associated Virus (AAV) is a small, non-enveloped virus with a single-stranded DNA genome. The AAV genome is flanked by inverted terminal repeats (ITRs), which serve as recognition sites for replication and packaging. The AAV capsid, composed of three proteins (VP1, VP2, and VP3), encapsulates the genetic material and
10 facilitates the virus's entry into host cells.

[00507] AAV vectors are commonly produced through a plasmid-based transfection system. The plasmids typically include the gene of interest, the AAV rep and cap genes, and the AAV ITRs. Cells are transfected with these plasmids, and the AAV vectors are generated through helper virus-free systems or helper virus-based systems, depending on the desired
15 application.

[00508] After AAV vector production, purification is crucial to obtain high-quality vectors for gene therapy. Common purification methods include ultracentrifugation, chromatography, and precipitation techniques to isolate AAV particles from cellular debris. In vivo administration involves direct injection of AAV vectors into the target tissue or systemic
20 delivery. Ex vivo approaches involve isolating target cells, transducing them with AAV vectors in vitro, and then transplanting the modified cells back into the patient.

Cells

[00509] In another aspect, the present disclosure provides a cell comprising the gene
25 editing system disclosed herein.

[00510] In another aspect, the present disclosure provides a cell comprising the polynucleotide disclosed herein. In some embodiments, the cell further comprises a polynucleotide encoding the first and/or second Cas protein in the gene editing system disclosed herein.

30 [00511] In another aspect, the present disclosure provides a cell comprising the vector disclosed herein. In some embodiments, the cell further comprises a vector comprising a polynucleotide encoding the first and/or second Cas protein in the gene editing system disclosed herein.

[00512] In another aspect, the present disclosure provides a cell comprising the kit disclosed herein.

[00513] In some embodiments, the cell is a stem cell.

5 [00514] In some embodiments, the cell is a pluripotent stem cell. Pluripotent stem cells are cells that have the capacity to self-renew by dividing and to develop into the three primary germ cell layers of the early embryo and therefore into all cells of the adult body, but not extra-embryonic tissues such as the placenta. Embryonic stem cells and induced pluripotent stem cells are pluripotent stem cells.

10 [00515] In some embodiments, the cell is an embryonic stem cell (ESC). Embryonic stem cells are pluripotent stem cells derived from the inner cell mass of a blastocyst, an early-stage pre-implantation embryo.

[00516] In some embodiments, the cell is an induced pluripotent stem cell (iPSC). iPSCs are derived from adult somatic cells that have been genetically reprogrammed back into an embryonic-like pluripotent state that enables the development of an unlimited source of any
15 type of cell needed for therapeutic purposes.

[00517] "Pluripotent stem cells" as used herein have the potential to differentiate into any of the three germ layers: endoderm (*e.g.*, the stomach lining, gastrointestinal tract, lungs, etc.), mesoderm (*e.g.*, muscle, bone, blood, urogenital tissue, etc.) or ectoderm (*e.g.*, epidermal tissues and nervous system tissues). The term "pluripotent stem cells," as used
20 herein, also encompasses induced pluripotent stem cells (iPSCs or iPS cells), or a type of pluripotent stem cell derived from a non-pluripotent cell. In some embodiments, a pluripotent stem cell is produced or generated from a cell that is not a pluripotent cell. In other words, pluripotent stem cells can be direct or indirect progeny of a non-pluripotent cell. Examples of parent cells include somatic cells that have been reprogrammed to induce a pluripotent,
25 undifferentiated phenotype by various means. Such "iPS" or "iPSC" cells can be created by inducing the expression of certain regulatory genes or by the exogenous application of certain proteins. Methods for the induction of iPS cells are known in the art and are further described below. (See, *e.g.*, Zhou et al., *Stem Cells* 27 (11): 2667-74 (2009); Huangfu et al., *Nature Biotechnol.* 26 (7): 795 (2008); Woltjen et al., *Nature* 458 (7239): 766-770 (2009); and Zhou
30 et al., *Cell Stem Cell* 8:381-384 (2009); each of which is incorporated by reference herein in their entirety.) As used herein, "hiPSCs" are human induced pluripotent stem cells. In some embodiments, "pluripotent stem cells," as used herein, also encompasses mesenchymal stem cells (MSCs), and/or embryonic stem cells (ESCs).

[00518] In some embodiments, the cell is an endothelial cell. Endothelial cells form the
35 endothelium, which is a single layer that line the interior surface of blood vessels and lymphatic vessels, providing an anticoagulant barrier between the vessel wall and blood. In

addition to its role as a selective permeability barrier, the endothelial cell is a unique multifunctional cell with critical basal and inducible metabolic and synthetic functions. The endothelial cell reacts with physical and chemical stimuli within the circulation and regulates hemostasis, vasomotor tone, and immune and inflammatory responses. In addition, the
5 endothelial cell is pivotal in angiogenesis and vasculogenesis. (Sumpio et al., *Cells in focus: endothelial cell*, Int. J. Biochem Cell Biol., 2002.)

[00519] Somatic cell

[00520] Somatic cells are the cells in the body other than sperm and egg cells (which are called germ cells). In mammals, somatic cells make up all the internal organs, skin, bones,
10 blood and connective tissue, while mammalian germ cells give rise to spermatozoa and ova which fuse during fertilization to produce a cell called a zygote, which divides and differentiates into the cells of an embryo. Somatic cells engage in mitotic divisions, facilitating tissue repair, growth, and overall physiological homeostasis. Within this category, various specialized cells perform distinctive functions integral to the organism's vitality.
15 Exemplary somatic cells encompass a wide array of specialized cell types, each with unique functions within the organism, for example, neurons, cardiomyocytes, adipocytes, osteocytes, epithelial cells, myocytes, chondrocytes, fibroblasts, erythrocytes, leukocytes, hepatocytes, etc.

[00521] Hepatocyte

20 [00522] A hepatocyte, as described herein, represents a specialized somatic cell exhibiting distinctive characteristics, prominently localized within the hepatic tissue of an organism. This unique cell type is recognized for its intricate morphology and multifaceted functionality, encompassing pivotal roles in metabolic processes, detoxification mechanisms, and the synthesis of crucial proteins contributing to overall physiological equilibrium. The
25 hepatocyte's significance extends beyond hepatic functions, as emerging research suggests potential implications in the context of cardiovascular diseases.

[00523] Recent studies have elucidated a dynamic interplay between hepatocytes and cardiovascular health. Hepatocytes have been identified as key contributors to lipid metabolism, impacting circulating lipid levels and influencing atherosclerosis development.
30 Additionally, hepatocytes play a central role in the production of certain proteins which may have downstream effects on cardiovascular function.

[00524] In some embodiments, the cell is a primary cell. Primary cells are isolated directly from human or animal tissue using enzymatic or mechanical methods. Once isolated, they are placed in an artificial environment in plastic or glass containers supported with specialized
35 medium containing essential nutrients and growth factors to support proliferation. Primary cells could be of two types: adherent or suspension. Adherent cells require attachment for

growth and are said to be anchorage-dependent cells. Adherent cells are usually derived from tissues of organs. Suspension cells do not require attachment for growth and are said to be anchorage-independent cells. Most suspension cells are isolated from the blood system, but some tissue-derived cells can also be used in suspension, such as hepatocytes or intestinal
5 cells. Although primary cells usually have a limited lifespan, they offer a number of advantages compared to cell lines. Primary cell culture enables researchers to study donors and not just cells. Several factors such as age, medical history, race, and sex can be considered when building an experimental model. With a growing trend towards personalized medicine, such donor variability and tissue complexity can be achieved with use of primary
10 cells, but are difficult to replicate with cell lines that are more systematic and uniform in nature and do not capture the true diversity of a living tissue.

[00525] In some embodiments, the cell is a differentiated cell. Differentiated cells are cells that have undergone differentiation. They are mature cells that perform a specialized function. Some examples of differentiated cells are epithelial cells, skin fibroblasts,
15 endothelial cells lining the blood vessels, smooth muscle cells, liver cells, nerve cells, human cardiac muscle cells, etc. Generally, these cells have a unique morphology, metabolic activity, membrane potential, and responsiveness to signals facilitating their function in a body tissue or organ.

Composition

20 [00526] In another aspect, the present disclosure provides a composition comprising the gene editing system disclosed herein.

[00527] In another aspect, the present disclosure provides a composition comprising the cell disclosed herein.

[00528] As used herein, the term “composition” includes, but is not limited to, a
25 pharmaceutical composition. A “pharmaceutical composition” refers to an active pharmaceutical agent formulated in pharmaceutically acceptable or physiologically acceptable solutions for administration to a cell or an animal, either alone, or in combination with one or more other modalities of therapy. It will also be understood that, if desired, the compositions of the invention may be administered in combination with other agents, such as,
30 e.g., cytokines, growth factors, hormones, small molecules, chemotherapeutics, pro-drugs, drugs, antibodies, or other various pharmaceutically active agents. There is virtually no limit to other components that may also be included in the compositions, provided that the additional agents do not adversely affect the ability of the composition to deliver the intended therapy. The phrase “pharmaceutically acceptable” is used herein to refer to those
35 compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and

animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00529] The compositions may also comprise a pharmaceutically acceptable carrier, diluent, or excipient. As used herein “pharmaceutically acceptable carrier, diluent, or excipient” includes, without limitation, any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, surfactant, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals. Exemplary pharmaceutically acceptable carriers include, but are not limited to, to sugars, such as lactose, glucose, and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and cellulose acetate; tragacanth; malt; gelatin; talc; cocoa butter; waxes; animal and vegetable fats; paraffins; silicones; bentonites; silicic acid; zinc oxide; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil, and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol, and polyethylene glycol; esters, such as ethyl oleate, and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; and any other compatible substances employed in pharmaceutical formulations.

[00530] The liquid pharmaceutical compositions, whether they be solutions, suspensions or other like form, may include one or more of the following: sterile diluents such as water for injection, saline solution, preferably physiological saline; Ringers solution; isotonic sodium chloride; fixed oils such as synthetic mono or diglycerides which may serve as the solvent or suspending medium; polyethylene glycols; glycerin; propylene glycol or other solvents; antibacterial agents, such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents, such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates, or phosphates; and agents for the adjustment of tonicity, such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampoules, disposable syringes, or multiple dose vials made of glass or plastic. An injectable pharmaceutical composition is preferably sterile.

[00531] The composition may be suitably developed for intravenous, intratumoral, oral, rectal, vaginal, parenteral, topical, pulmonary, intranasal, buccal, ophthalmic, or another route of administration.

Methods of treatment

[00532] In another aspect, the present disclosure provides a method for disrupting *PCSK9*, *ANGPTL3*, *ASGR1*, *LPA*, *AGT*, or *APOC3* gene in a cell, comprising introducing into the cell the gene editing system disclosed herein. As used herein, “disrupt” or “disruption” of a gene

refers to gene knock-down or gene knock-out. In a gene knock-down, the expression of the gene is reduced via methods such as genetic modification and treatment as disclosed herein. In a gene knock-out, a gene is made inoperative, partially or completely, via methods such as genetic modification.

5 [00533] In some embodiments, the *PCSK9* gene is disrupted by adding stop codons using the gene editing system disclosed herein. In some embodiments, the gene editing system disclosed herein is used to induce C-to-T base editing in the codons of CAA (Gln), CAG (Gln) or CGA (Arg) in *PCSK9* genes to create TAA, TAG or TGA stop codon. In some
10 embodiments, the gene editing system disclosed herein is used to induce G-to-A (C-to-T on the opposite strand) base editing in the codons of TGG (Trp) in *PCSK9* genes to create a TAA, TAG or TGA stop codon.

[00534] In some embodiments, the *PCSK9* gene is disrupted by destroying splicing site in it using the gene editing system disclosed herein. In some embodiments, the gene editing
15 system disclosed herein is used to induce G-to-A (C-to-T on the opposite strand) base editing in 5' GU or 3' AG splice site to destroy the GU-AG canonical splicing pattern.

[00535] In some embodiments, the *ANGPTL3* gene is disrupted by adding stop codons using the gene editing system disclosed herein. In some embodiments, the gene editing system disclosed herein is used to induce C-to-T base editing in the codons of CAA (Gln), CAG (Gln) or CGA (Arg) in *ANGPTL3* genes to create TAA, TAG or TGA stop codon. In
20 some embodiments, the gene editing system disclosed herein is used to induce G-to-A (C-to-T on the opposite strand) base editing in the codons of TGG (Trp) in *ANGPTL3* genes to create a TAA, TAG or TGA stop codon.

[00536] In some embodiments, the *ANGPTL3* gene is disrupted by destroying splicing site in it using the gene editing system disclosed herein. In some embodiments, the gene editing
25 system disclosed herein is used to induce G-to-A (C-to-T on the opposite strand) base editing in 5' GU or 3' AG splice site to destroy the GU-AG canonical splicing pattern.

[00537] In some embodiments, the *ASGR1* gene is disrupted by adding stop codons using the gene editing system disclosed herein. In some embodiments, the gene editing system disclosed herein is used to induce C-to-T base editing in the codons of CAA (Gln), CAG (Gln) or CGA (Arg) in *ASGR1* genes to create TAA, TAG or TGA stop codon. In some
30 embodiments, the gene editing system disclosed herein is used to induce G-to-A (C-to-T on the opposite strand) base editing in the codons of TGG (Trp) in *ASGR1* genes to create a TAA, TAG or TGA stop codon.

[00538] In some embodiments, the *ASGR1* gene is disrupted by destroying splicing site in
35 it using the gene editing system disclosed herein. In some embodiments, the gene editing

system disclosed herein is used to induce G-to-A (C-to-T on the opposite strand) base editing in 5' GU or 3' AG splice site to destroy the GU-AG canonical splicing pattern.

[00539] In some embodiments, the *LPA* gene is disrupted by adding stop codons using the gene editing system disclosed herein. In some embodiments, the gene editing system disclosed herein is used to induce C-to-T base editing in the codons of CAA (Gln), CAG (Gln) or CGA (Arg) in *LPA* genes to create TAA, TAG or TGA stop codon. In some embodiments, the gene editing system disclosed herein is used to induce G-to-A (C-to-T on the opposite strand) base editing in the codons of TGG (Trp) in *LPA* genes to create a TAA, TAG or TGA stop codon.

[00540] In some embodiments, the *LPA* gene is disrupted by destroying splicing site in it using the gene editing system disclosed herein. In some embodiments, the gene editing system disclosed herein is used to induce G-to-A (C-to-T on the opposite strand) base editing in 5' GU or 3' AG splice site to destroy the GU-AG canonical splicing pattern.

[00541] In some embodiments, the *AGT* gene is disrupted by adding stop codons using the gene editing system disclosed herein. In some embodiments, the gene editing system disclosed herein is used to induce C-to-T base editing in the codons of CAA (Gln), CAG (Gln) or CGA (Arg) in *AGT* genes to create TAA, TAG or TGA stop codon. In some embodiments, the gene editing system disclosed herein is used to induce G-to-A (C-to-T on the opposite strand) base editing in the codons of TGG (Trp) in *AGT* genes to create a TAA, TAG or TGA stop codon.

[00542] In some embodiments, the *AGT* gene is disrupted by destroying splicing site in it using the gene editing system disclosed herein. In some embodiments, the gene editing system disclosed herein is used to induce G-to-A (C-to-T on the opposite strand) base editing in 5' GU or 3' AG splice site to destroy the GU-AG canonical splicing pattern.

[00543] In some embodiments, the *APOC3* gene is disrupted by adding stop codons using the gene editing system disclosed herein. In some embodiments, the gene editing system disclosed herein is used to induce C-to-T base editing in the codons of CAA (Gln), CAG (Gln) or CGA (Arg) in *AGT* genes to create TAA, TAG or TGA stop codon. In some embodiments, the gene editing system disclosed herein is used to induce G-to-A (C-to-T on the opposite strand) base editing in the codons of TGG (Trp) in *APOC3* genes to create a TAA, TAG or TGA stop codon.

[00544] In some embodiments, the *APOC3* gene is disrupted by destroying splicing site in it using the gene editing system disclosed herein. In some embodiments, the gene editing system disclosed herein is used to induce G-to-A (C-to-T on the opposite strand) base editing in 5' GU or 3' AG splice site to destroy the GU-AG canonical splicing pattern.

[00545] In another aspect, the present disclosure provides a method for regulating Low-Density Lipoprotein cholesterol (LDL-C) metabolism in a subject, comprising introducing the cell the gene editing system disclosed herein. In some embodiments, the gene editing system targets the *PCSK9* gene, the *ANGPTL3* gene, the *ASGR1* gene or the *APOC3* gene.

5 [00546] In another aspect, the present disclosure provides a method for lowering Low-Density Lipoprotein cholesterol (LDL-C) level in a subject, comprising introducing the cell the gene editing system disclosed herein.

[00547] In another aspect, the present disclosure provides a method for regulating triglyceride-rich remnant particles metabolism in a subject, comprising introducing the cell
10 the gene editing system disclosed herein. In some embodiment, the gene editing system targets the *ANGPTL3* or the *APOC3* gene.

[00548] In another aspect, the present disclosure provides a method for regulating lipoprotein(a) (Lp(a)) metabolism in a subject, comprising introducing the cell the gene editing system disclosed herein. In some embodiment, the gene editing system targets the
15 *LPA* gene.

[00549] In another aspect, the present disclosure provides a method for lowering the level of triglyceride-rich remnant particles in a subject, comprising introducing the cell the gene editing system disclosed herein.

[00550] In another aspect, the present disclosure provides a method for lowering the level
20 of lipoprotein(a) (Lp(a)) particles in a subject, comprising introducing the cell the gene editing system disclosed herein.

[00551] In another aspect, the present disclosure provides a method for regulating blood pressure in a subject, comprising introducing the cell the gene editing system disclosed herein. In some embodiment, the gene editing system targets the *AGT* gene.

25 [00552] In another aspect, the present disclosure provides a method for reducing the expression of angiotensinogen in a subject, comprising introducing the cell the gene editing system disclosed herein. In some embodiment, the gene editing system targets the *AGT* gene.

[00553] In another aspect, the present disclosure provides a method for reducing the level of angiotensinogen in a subject, comprising introducing the cell the gene editing system
30 disclosed herein.

[00554] In another aspect, the present disclosure provides a method for disruption or regulation the expression of two or more genes selected from *PCSK9*, *ANGPTL3*, *ASGR1*, *LPA*, *AGT*, and *APOC3* gene in a cell, comprising introducing into the cell two or more gene editing systems,

wherein when the two or more genes include the *PCSK9* gene, the two or more gene editing systems include any of the gene editing systems targeting the *PCSK9* gene as disclosed herein,

5 wherein when the two or more genes include the *ANGPTL3* gene, the two or more gene editing systems include any of the gene editing systems targeting the *ANGPTL3* gene as disclosed herein,

wherein when the two or more genes include the *ASGR1* gene, the two or more gene editing systems include any of the gene editing systems targeting the *ASGR1* gene as disclosed herein,

10 wherein when the two or more genes include the *LPA* gene, the two or more gene editing systems include any of the gene editing systems targeting the *LPA* gene as disclosed herein,

wherein when the two or more genes include the *AGT* gene, the two or more gene editing systems include any of the gene editing systems targeting the *AGT* gene as disclosed herein,

15 wherein when the two or more genes include the *APOC3* gene, the two or more gene editing systems include any of the gene editing systems targeting the *APOC3* gene as disclosed herein.

[00555] In some embodiments, the two or more genes include 2, 3, 4, 5, or 6 genes
20 selected from *PCSK9*, *ANGPTL3*, *ASGR1*, *LPA*, *AGT*, and *APOC3* gene. For example, in some embodiments, the two or more genes are *PCSK9* gene and *ANGPTL3* gene.

[00556] In some embodiments, the cell is a stem cell.

[00557] In some embodiments, the cell is a pluripotent stem cell.

[00558] In some embodiments, the cell is an embryonic stem cell (ESC).

25 [00559] In some embodiments, the cell is an induced pluripotent stem cell (iPSC).

[00560] In some embodiments, the cell is the cell is a somatic cell.

[00561] In some embodiments, the cell is the cell is a hepatocyte.

[00562] In some embodiments, the cell is a primary cell.

[00563] In some embodiments, the cell is a differentiated cell.

30 [00564] In another aspect, the present disclosure provides a method for treating hypercholesterolemia in a subject, comprising introducing the cell the gene editing system disclosed herein.

[00565] In some embodiments, the present disclosure provides use of a gene editing system, a cell, or a composition as disclosed herein for the manufacture of a medicament for treating hypercholesterolemia.

5 [00566] In some embodiments, the present disclosure provides a gene editing system, a cell, or a composition as disclosed herein for use in treating hypercholesterolemia.

[00567] In another aspect, the present disclosure provides a method for treating hypertension in a subject, comprising introducing the cell the gene editing system disclosed herein.

10 [00568] In some embodiments, the present disclosure provides use of a gene editing system, a cell, or a composition as disclosed herein for the manufacture of a medicament for treating hypertension.

[00569] In some embodiments, the present disclosure provides a gene editing system, a cell, or a composition as disclosed herein for use in treating hypertension.

15 [00570] In another aspect, the present disclosure provides a method for treating cardiovascular disease (CVD) in a subject, comprising introducing the cell the gene editing system disclosed herein.

20 [00571] In some embodiments, cardiovascular disease (CVD) can be selected from, but not limited to, atherosclerosis, congestive heart failure, peripheral vascular disease, cerebrovascular disease, rheumatic heart disease, arrhythmia, hypertension, and coronary artery disease.

[00572] In some embodiments, the present disclosure provides use of a gene editing system, a cell, or a composition as disclosed herein for the manufacture of a medicament for treating cardiovascular disease (CVD).

25 [00573] In some embodiments, the present disclosure provides a gene editing system, a cell, or a composition as disclosed herein for use in treating cardiovascular disease (CVD).

[00574] In another aspect, the present disclosure provides a method for treating atherosclerosis, congestive heart failure, peripheral vascular disease, cerebrovascular disease, rheumatic heart disease, arrhythmia, hypertension, or coronary artery disease in a subject, comprising introducing the cell the gene editing system disclosed herein.

30 [00575] In some embodiments, the various protein components and the gRNAs of a gene editing system disclosed herein may be introduced into a subject or a cell via one or more vectors expressing the protein components and gRNAs.

[00576] In some embodiments, the gRNAs and the protein components of a gene editing system disclosed herein can be delivered into a cell in a form of ribonucleoprotein (RNP) via electroporation.

[00577] While the disclosure has been particularly shown and described with reference to
5 specific embodiments, it should be understood by those having skill in the art that various changes in form and detail may be made therein without departing from the spirit and scope of the present disclosure as disclosed herein.

EXAMPLES

[00578] Plasmid construction

[00579] Primer sets were designed according to the protocol in Wang, Lijie, et al.,
Eliminating base-editor-induced genome-wide and transcriptome-wide off-target mutations,
Nature Cell Biology 23.5 (2021): 552-563. Primer sets (hg_FOR and mg_REV) were used to
amplify the fragment hg-hPCSK9-GU1-U1-MS2-U6-mg-hPCSK9-GU1 using the template
pUC57-sgRNA-MS2-U6 (Addgene plasmid # 171694). In the fragment name, “hg-hPCSK9-
15 GU1-U1” refers to the hgRNA number, “MS2” refers to the operator in the hgRNA scaffold,
and “U6” refers to the gRNA promoter, and “mg-hPCSK9-GU1” refers to the mgRNA
number.

[00580] The primer hg_FOR has a structure of: ATGCGTCTCAACCG (SEQ ID NO:
1280) +hg spacer sequence+GTTTGAGAGCTAGGCCAACATGA (SEQ ID NO: 1281).

[00581] The primer mg_REV has a structure of: ATGCGTCTCGAAAC (SEQ ID NO:
1282)+mg spacer reverse-complementing sequence+CGGTGTTTCGTCCTTCCACAAG
(SEQ ID NO: 1283).

[00582] The fragment hg- hPCSK9-GU1-U1-MS2-U6-mg-hPCSK9-GU1 was then ligated
into BsmBI-linearized U6-ccbB-boxB-tBE-V5 (Addgene plasmid # 171693) to generate the
25 vector ptBE-V5 with target hgRNA and mgRNA.

[00583] Other combinations with different on-target hgRNA and mgRNA were
constructed using the same strategy, respectively.

[00584] Cell culture and Lipofectamine transfection

[00585] 293FT, HepG2, Hepa1-6 or COS-1 cells were maintained in DMEM + 10% FBS
30 and regularly tested to exclude mycoplasma contamination. For base editing with a gene
editing system, cells were seeded in a 24-well plate at a density of 1×10^5 per well and
transfected with 250 μ l serum-free Opti-MEM containing 2.5 μ l LIPOFECTAMINE LTX, 1
 μ l LIPOFECTAMINE plus, 0.5 μ g tBE-V5 expression vector, 0.5 μ g pEFS-nSpCas9 or
pEFS-nSpCas9-SpG expression vector. After 24 h, puromycin was added to the medium at a

final concentration of 4 $\mu\text{g ml}^{-1}$. After another 48 h, the genomic DNA was extracted from the cells using QuickExtractT DNA Extraction Solution for subsequent sequencing analysis. Target genomic sequences were PCR-amplified using high-fidelity DNA polymerase PrimeSTAR HS with primer sets flanking the examined sgRNA target sites.

5 [00586] gRNA, mRNA preparation and electroporation

[00587] Chemically modified gRNA (2'-O-methyl 3' phosphorothioate modifications in the first and last three nucleotides) was synthesized from GenScript. mRNAs encoding the tBE system were transcribed *in vitro*. HepG2, Hepa1-6 or COS-1 cells were electroporated with the end-modified gRNA and the mRNAs described above. Electroporation was
10 performed using Lonza 4D Nucleofector by using officially recommended program (e.g., EH-100). For 20- μl Nucleocuvette Strips, 0.2 million cells were resuspended in 20 μl SF Cell Line 4D-Nucleofector buffer and about 160 pmol RNA complex were added. The editing frequencies of target sequence were measured with cells cultured in medium 120 hours after electroporation.

15 [00588] Base substitution frequency at each target sites was calculated by EditR analysis. See <http://baseeditr.com/>.

[00589] Western blot and ELISA analysis

[00590] Total proteins were extracted using a RIPA buffer with 1mM PMSF and proteinase inhibitor cocktail. The protein concentration was measured using a BCA protein
20 assay kit. Equal amounts of proteins (5 μg) were separated by SDS-PAGE using 4–12% SurePage Mini-PROTEAN Gels and then transferred onto Nitrocellulose membrane. Membranes were blocked using 5% skim milk in Tris-buffered saline, containing 0.1% (v/v) Tween-20 (TBST), for 1 h, and incubated with primary antibodies overnight at 4 °C, followed by incubation with anti-rabbit IgG or anti-mouse IgG conjugated with horseradish
25 peroxidase. GAPDH was used as an internal control. The probed protein was visualized using Amersham Image 680. Some protein levels were determined using ELISA kit according to the manufacturer's protocol. The luminescence signal was collected by spectraMax M5e microplate reader.

[00591] Animal studies

30 [00592] Mice were given free access to food and water, and were maintained under a 12 h–12 h light–dark cycle with controlled temperature (20–25 °C) and humidity (50 $\pm$ 10%). LNP vector was delivered to at least four female C57BL/6 mice (aged 6–8 weeks) intravenously through tail vein injection. Mice were fasted for 5 h before blood was collected before liver perfusion. Two or four weeks after injection, the blood was collected, and the
35 plasma was separated by centrifugation.

[00593] Plasma levels of PCSK9 and LDL-C were measured using the Mouse PCSK9 ELISA Kit, and LDL-C kit, respectively.

[00594] Plasma levels of hApoC3 protein, LDL-C, triglyceride, HDL-C, and cholesterol were measured using the Human ApoC3 ELISA Kit, Mouse triglyceride kit, LDL-C kit,
5 HDL-C kit, cholesterol kit, respectively.

[00595] The genomic DNA from mouse tissues were isolated using the E.Z.N.A. Tissue DNA Kit.

[00596] Base substitution calculation, statistics analysis, and other relevant steps for obtaining the data are essentially the same as disclosed in the “Methods” section of Wang, Lijie, et al., *Eliminating base-editor-induced genome-wide and transcriptome-wide off-target mutations*, Nature Cell Biology 23.5 (2021): 552-563, the content of which is incorporated
10 herein by reference in its entirety.

[00597] Gene editing results obtained from the above experiments are illustrated in Fig. 2-7, 9-11, 12D, 13-19, 21, 23-28, 30-31, 33-52, 57A, and 59. Western blot and ELISA analysis
15 results obtained from the above experiments are illustrated in Fig. 8, 12A-C, 20, 22, 29, 32, 53 and 57B. Animal studies results obtained from the above experiments are illustrated Fig. 54, 56, 58, 60 and 61.

[00598] While the disclosure has been particularly shown and described with reference to specific embodiments, it should be understood by those having skill in the art that various
20 changes in form and detail may be made therein without departing from the spirit and scope of the present disclosure as disclosed herein.

What is claimed is:

1. A gene editing system comprising a main guide RNA (mgRNA) and a helper guide RNA (hgRNA), or at least one DNA polynucleotide encoding the mgRNA and/or the hgRNA,
5 wherein the mgRNA comprises an mgRNA spacer and the hgRNA comprises an hgRNA spacer of about 10 to about 20 nucleotides, wherein the nucleic acid sequence of the mgRNA spacer comprises a sequence selected from SEQ ID NOs: 213-236, 317-328, and 1128;
wherein the mgRNA spacer is capable of binding to a target sequence located in
10 *PCSK9* gene; and
wherein the hgRNA spacer is capable of binding to a site on the *PCSK9* gene that is close to the target sequence of the mgRNA spacer.
2. The gene editing system of claim 1, wherein:
when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 213, the
15 hgRNA spacer comprises a sequence selected from SEQ ID NOs: 237-239, and 277-279;
when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 214, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 240 and 280;
when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 215, the
20 hgRNA spacer comprises a sequence selected from SEQ ID NOs: 241-242, and 281-282;
when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 216, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 243-245, and 283-285;
25 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 217, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 246-247, and 286-287;
when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 218, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 248-250, and 288-
30 290;
when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 219, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 251-253, and 291-293;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 220, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 254 and 294;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 221, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 255-256, and 295-296;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 222, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 257 and 297;

when mgRNA spacer comprises a sequence represented by SEQ ID NO: 223, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 258-259, and 298-299;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 224, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 260 and 300;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 225, the hgRNA spacer comprises a sequence selected from SEQ ID NO: 261 and 301;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 226, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 262 and 302;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 227, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 263 and 303;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 228, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 264 and 304;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 229, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 265 and 305;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 230, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 266 and 306;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 231, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 267 and 307;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 232, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 268 and 308;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 233, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 269 and 309;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 234, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 270 and 310;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 235, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 271-274 and 311-314;

5 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 236, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 275-276 and 315-316;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 317, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 329-331 and 366-368;

10 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 318, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 332-333 and 369-370;

15 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 319, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 334-335 and 371-372;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 320, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 336-337 and 373-374;

20 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 321, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 338-340 and 375-377;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 322, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 341-344 and 378-381;

25 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 323, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 345-349 and 382-386;

30 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 324, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 350-354 and 387-391;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 325, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 355-356 and 392-393;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 326, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 357-359 and 394-396;

5 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 327, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 360-363 and 397-400;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 328, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 364-365 and 401-402; and

10 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 1128, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1129 and 1130.

3. The gene editing system according to claim 1 or 2, wherein:

15 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 218, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 248-250, and 288-290.

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 319, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 334-335, and 371-372.

20 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 1128, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1129 and 1130.

4. The gene editing system according to claim 1 or 2, wherein

when the mgRNA comprises a sequence represented by SEQ ID NO: 1109, the hgRNA comprises a sequence selected from SEQ ID NOs: 1108, 1118, 1120, 1122 and 1123;

25 when the mgRNA comprises a sequence represented by SEQ ID NO: 1110, the hgRNA comprises a sequence selected from SEQ ID NOs: 1108, 1118, 1120, 1122 and 1123;

30 when the mgRNA comprises a sequence represented by SEQ ID NO: 1119, the hgRNA comprises a sequence selected from SEQ ID NOs: 1108, 1118, 1120, 1122 and 1123;

when the mgRNA comprises a sequence represented by SEQ ID NO: 1121, the hgRNA comprises a sequence selected from SEQ ID NOs: 1108, 1118, 1120, 1122 and 1123;

when the mgRNA comprises a sequence represented by SEQ ID NO: 1125, the hgRNA comprises a sequence represented by SEQ ID NOs: 1124; and

when the mgRNA comprises a sequence represented by SEQ ID NO: 1127, the hgRNA comprises a sequence represented by SEQ ID NOs: 1126.

- 5 5. A gene editing system comprising a main guide RNA (mgRNA) and a helper guide RNA (hgRNA), or at least one DNA polynucleotide encoding the mgRNA and/or the hgRNA,

wherein the mgRNA comprises an mgRNA spacer and the hgRNA comprises an hgRNA spacer of about 10 to about 20 nucleotides, wherein the nucleic acid sequence
10 of the mgRNA spacer comprises a sequence selected from SEQ ID NOs: 403-429 and 550-552;

wherein the mgRNA spacer is capable of binding to a target sequence located in *ANGPTL3* gene; and

wherein the hgRNA spacer is capable of binding to a site on the *ANGPTL3* gene that
15 is close to the target sequence of the mgRNA spacer.

6. The gene editing system of claim 5, wherein:

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 403, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 430-432 and 490-492;

20 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 404, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 433-434 and 493-494;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 405, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 435-436 and 495-496;
25

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 406, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 437 and 497;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 407, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 438-440 and 498-500;
30

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 408, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 441-443 and 501-503;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 409, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 444-446 and 504-506;

5 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 410, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 447-449 and 507-509;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 411, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 450-452 and 510-512;

10 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 412, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 453 and 513;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 413, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 454-456 and 514-516;

15 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 414, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 457-458 and 517-518;

20 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 415, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 459-461 and 519-521;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 416, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 462-463 and 522-523;

25 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 417, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 464-465 and 524-525;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 418, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 466-468 and 526-528;

30 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 419, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 469-470 and 529-530;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 420, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 471-472 and 531-532;

5 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 421, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 473 and 533;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 422, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 474-475 and 534-535;

10 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 423, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 476-477 and 538;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 424, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 478 and 538;

15 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 425, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 479-481 and 539-541;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 426, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 482-484 and 542-544;

20 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 427, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 485 and 545;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 428, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 486-487 and 546-547;

25 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 429, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 488-489 and 548-549;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 550, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 553 and 558;

30 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 551, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 554-555 and 559-560; and

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 552, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 556-557 and 561-562.

7. The gene editing system according to claim 5 or 6, wherein:

5 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 406, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 437 and 497;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 551, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 554-555 and 559-560.

10 8. The gene editing system according to claim 5 or 6, wherein:

when the mgRNA comprises a sequence represented by SEQ ID NO: 1132, the hgRNA comprises a sequence represented by SEQ ID NO: 1131;

when the mgRNA comprises a sequence represented by SEQ ID NO: 1134, the hgRNA comprises a sequence represented by SEQ ID NO: 1133; and

15 when the mgRNA comprises a sequence represented by SEQ ID NO: 1136, the hgRNA comprises a sequence represented by SEQ ID NOs: 1135.

9. A gene editing system comprising a main guide RNA (mgRNA) and a helper guide RNA (hgRNA), or at least one DNA polynucleotide encoding the mgRNA and/or the hgRNA,

20 wherein the mgRNA comprises an mgRNA spacer and the hgRNA comprises an hgRNA spacer of about 10 to about 20 nucleotides, wherein the nucleic acid sequence of the mgRNA spacer comprises a sequence selected from SEQ ID NOs: 563-584 and 677-684;

25 wherein the mgRNA spacer is capable of binding to a target sequence located in *ASGR1* gene; and

wherein the hgRNA spacer is capable of binding to a site on the *ASGR1* gene that is close to the target sequence of the mgRNA spacer.

10. The gene editing system of claim 9, wherein:

30 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 563, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 585 and 631;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 564, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 586 and 632;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 565, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 587-588 and 633-634;

5 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 566, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 589-590 and 635-636;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 567, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 591-593 and 637-639;

10 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 568, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 594-596 and 640-642;

15 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 569, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 597-598 and 643-644;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 570, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 599-601 and 645-647;

20 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 571, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 602-604 and 648-650;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 572, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 605-606 and 651-652;

25 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 573, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 607-608 and 653-654;

30 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 574, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 609-610 and 655-656;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 575, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 611-612 and 657-658;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 576, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 613-614 and 659-660;

5 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 577, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 615-616 and 661-662;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 578, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 617-619 and 663-665;

10 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 579, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 620-622 and 666-668;

15 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 580, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 623-625 and 669-671;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 581, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 626 and 672;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 582, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 627 and 673;

20 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 583, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 628 and 674;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 584, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 629-630 and 675-676;

25 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 677, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 685-687 and 701-703;

30 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 678, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 688-689 and 704-705;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 679, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 690-691 and 706-707;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 680, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 692-693 and 708-709;

5 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 681, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 694 and 710;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 682, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 695-696 and 711-712;

10 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 683, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 697-698 and 713-714; and

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 684, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 699-700 and 715-716.

15 11. The gene editing system according to claim 9 or 10, wherein:

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 563, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 585 and 631;

20 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 569, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 597-598 and 643-644;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 570, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 599, and 645.

25 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 584, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 629-630 and 675-676;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 677, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 685-687 and 701-703;

30 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 680, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 692-693 and 708-709;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 681, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 694 and 710; and

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 683, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 697-698 and 713-714.

- 5 12. A gene editing system comprising a main guide RNA (mgRNA) and a helper guide RNA (hgRNA), or at least one DNA polynucleotide encoding the mgRNA and/or the hgRNA,

wherein the mgRNA comprises an mgRNA spacer and the hgRNA comprises an hgRNA spacer of about 10 to about 20 nucleotides, wherein the nucleic acid sequence of the mgRNA spacer comprises a sequence selected from SEQ ID NOs: 717-750;

- 10 wherein the mgRNA spacer is capable of binding to a target sequence located in *LPA* gene; and

wherein the hgRNA spacer is capable of binding to a site on the *LPA* gene that is close to the target sequence of the mgRNA spacer.

13. The gene editing system of claim 12, wherein:

- 15 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 717, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 751-755 and 838-842;

- 20 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 718, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 756-760 and 843-847;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 719, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 761-765 and 848-852;

- 25 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 720, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 766-769 and 853-856;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 721, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 770-773 and 857-860;

- 30 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 722, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 774-775 and 861-862;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 723, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 776-778 and 863-865;

5 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 724, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 779 and 866;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 725, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 780-782 and 867-869;

10 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 726, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 783-785 and 870-872;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 727, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 786-788 and 873-875;

15 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 728, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 789 and 876;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 729, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 790-792 and 877-879;

20 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 730, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 793 and 880;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 731, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 794-795 and 881-882;

25 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 732, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 796-798 and 883-885;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 733, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 799 and 886;

30 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 734, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 800-802 and 887-889;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 735, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 803-804 and 890-891;

5 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 736, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 805-806 and 892-893;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 737, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 807 and 894;

10 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 738, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 808 and 895;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 739, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 809-810 and 896-897;

15 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 740, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 811-813 and 898-900;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 741, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 814-815 and 901-902;

20 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 742, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 816-818 and 903-905;

25 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 743, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 819-820 and 906-907;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 744, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 821-823 and 908-910;

30 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 745, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 824-825 and 911-912;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 746, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 826-828 and 913-915;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 747, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 829-831 and 916-918;

5 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 748, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 932-833 and 919-920;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 749, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 834 and 921; and

10 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 750, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 835-837 and 922-924.

14. The gene editing system according to claim 12 or 13, wherein:

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 735, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 803 and 890;

15 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 741, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 814 and 901; and

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 743, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 820 and 907.

20 15. A gene editing system comprising a main guide RNA (mgRNA) and a helper guide RNA (hgRNA), or at least one DNA polynucleotide encoding the mgRNA and/or the hgRNA,

wherein the mgRNA comprises an mgRNA spacer and the hgRNA comprises an hgRNA spacer of about 10 to about 20 nucleotides, wherein the nucleic acid sequence of the mgRNA spacer comprises a sequence selected from SEQ ID NOs: 925-961;

25 wherein the mgRNA spacer is capable of binding to a target sequence located in *AGT* gene; and

wherein the hgRNA spacer is capable of binding to a site on the *AGT* gene that is close to the target sequence of the mgRNA spacer.

16. The gene editing system of claim 15, wherein:

30 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 925, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 962-964 and 1034-1036;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 926, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 965-966 and 1037-1038;

5 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 927, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 967-968 and 1039-1040;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 928, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 969-970 and 1041-1042;

10 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 929, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 971-972 and 1043-1044;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 930, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 973-974 and 1045-1046;

15 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 931, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 975-977 and 1047-1049;

20 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 932, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 978-980 and 1050-1052;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 933, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 981 and 1053;

25 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 934, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 982-984 and 1054-1056;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 935, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 985-987 and 1057-1059;

30 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 936, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 988-989 and 1060-1061;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 937, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 990-991 and 1062-1063;

5 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 938, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 992-993 and 1064-1065;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 939, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 994-995 and 1066-1067;

10 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 940, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 996-997 and 1068-1069;

15 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 941, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 998-999 and 1070-1071;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 942, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1000-1001 and 1072-1073;

20 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 943, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1002-1003 and 1074-1075;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 944, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1004-1005 and 1076-1077;

25 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 945, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1006-1007 and 1078-1079;

30 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 946, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1008-1009 and 1080-1081;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 947, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1010-1011 and 1082-1083;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 948, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1012 and 1084;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 949, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1013 and 1085;

5 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 950, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1014-1015 and 1086-1087;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 951, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1016-1017 and
10 1088-1089;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 952, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1018-1019 and 1090-1091;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 953, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1020 and 1092;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 954, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1021-1022 and 1093-1094;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 955, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1023 and 1095;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 956, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1024 and 1096;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 957, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1025-1026 and
25 1097-1098;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 958, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1027-1028 and 1099-1100;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 959, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1029-1030 and 1101-1102;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 960, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1031 and 1103; and

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 961, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1032-1033 and 1104-1105.

17. The gene editing system according to claim 15 or 16, wherein:

5 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 925, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 962 and 1034;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 932, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 978-980 and 1050-1052;

10 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 935, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 986 and 1058; and

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 947, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1010 and 1082.

15 18. A gene editing system comprising a main guide RNA (mgRNA) and a helper guide RNA (hgRNA), or at least one DNA polynucleotide encoding the mgRNA and/or the hgRNA,

wherein the mgRNA comprises an mgRNA spacer and the hgRNA comprises an hgRNA spacer of about 10 to about 20 nucleotides, wherein the nucleic acid sequence of the mgRNA spacer comprises a sequence selected from SEQ ID NOs: 1249-1251;

20 wherein the mgRNA spacer is capable of binding to a target sequence located in *APOC3* gene; and

wherein the hgRNA spacer is capable of binding to a site on the *APOC3* gene that is close to the target sequence of the mgRNA spacer.

19. The gene editing system of claim 18, wherein:

25 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 1249, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1252-1254, and 1259-1261;

30 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 1250, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1255-1256, and 1262-1263;

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 1251, the hgRNA spacer comprises a sequence selected from SEQ ID NOs: 1257-1258, and 1264-1265.

20. The gene editing system according to claim 18 or 19, wherein:

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 1266, the hgRNA spacer comprises a sequence selected from SEQ ID NO:1267.

5 when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 1268, the hgRNA spacer comprises a sequence selected from SEQ ID NO:1269.

when the mgRNA spacer comprises a sequence represented by SEQ ID NO: 1270, the hgRNA spacer comprises a sequence selected from SEQ ID NO: 1271.

21. The gene editing system according to claim 18 or 19, wherein

10 when the mgRNA comprises a sequence represented by SEQ ID NO: 1272, the hgRNA comprises a sequence selected from SEQ ID NO: 1273;

when the mgRNA comprises a sequence represented by SEQ ID NO: 1274, the hgRNA comprises a sequence selected from SEQ ID NO: 1275;

when the mgRNA comprises a sequence represented by SEQ ID NO: 1276, the hgRNA comprises a sequence selected from SEQ ID NO: 1277.

15 22. The gene editing system of any one of claims 1-21, comprising:

- a. the hgRNA comprising a CRISPR motif, the hgRNA spacer, and a first protein-binding motif, or a DNA polynucleotide encoding the hgRNA,
- b. the mgRNA comprising a second CRISPR motif and the mgRNA spacer, or a DNA polynucleotide encoding the mgRNA,
- 20 c. a first CRISPR-associated protein (Cas protein), or a polynucleotide encoding the first Cas protein, wherein the first Cas protein is capable of binding to the first CRISPR motif,
- d. a second Cas protein, or a polynucleotide encoding the second Cas protein, wherein the second Cas protein is capable of binding to the second CRISPR motif,
- 25 e. a first fusion protein comprising a nucleobase deaminase or a catalytic domain thereof and a first RNA binding domain, or a polynucleotide encoding the first fusion protein, wherein the nucleobase deaminase or the catalytic domain thereof and the first RNA binding domain are optionally connected by a linker, and wherein the first RNA binding domain is capable of binding to the
- 30 first protein-binding motif.

wherein the first Cas protein and second Cas protein are the same or different.

23. The gene editing system of claim 22, further comprising:

- a. a protease, or a polynucleotide encoding the protease, and
- b. a nucleobase deaminase inhibitor domain,

wherein the nucleobase deaminase inhibitor domain is connected to the nucleobase deaminase or the catalytic domain thereof in the first fusion protein optionally by a linker, and wherein there is a cleavage site for the protease between the nucleobase deaminase inhibitor domain and the nucleobase deaminase or the catalytic domain thereof.

24. The gene editing system of claim 23, further comprising:

a second fusion protein comprising the protease and a second RNA binding domain, or a polynucleotide encoding the second fusion protein,

wherein the protease and the second RNA binding domain are optionally connected by a linker,

wherein the mgRNA further comprises a second protein-binding motif,

and wherein the second RNA binding domain binds to the second protein-binding motif.

25. The gene editing system of claim 23, wherein the protease is split into a first protease fragment and a second protease fragment, wherein the first and/or second protease fragment alone is not able to cleave the cleavage site.

26. The gene editing system of claim 25, further comprising:

- a. a second fusion protein comprising the first protease fragment and a second RNA binding domain, or a polynucleotide encoding the second fusion protein, wherein the first protease fragment and the second RNA binding domain are optionally connected by a linker, and

- b. a third fusion protein comprising the second protease fragment and a third RNA binding domain, or a polynucleotide encoding the third fusion protein, wherein the second protease fragment and the third RNA binding domain are optionally connected by a linker,

wherein the mgRNA further comprises a second protein-binding motif and a third protein-binding motif,

wherein the second RNA binding domain is capable of binding to the second protein-binding motif, and

wherein the third RNA binding domain is capable of binding to the third protein-binding motif.

27. The gene editing system of claim 26, wherein the second and third RNA binding domains are the same or different, and the second and third protein-binding motifs are the same or different.

28. The gene editing system of claim 25, further comprising:

a second fusion protein comprising the first protease fragment and a second RNA binding domain, or a polynucleotide encoding the second fusion protein,

wherein the first protease fragment and the second RNA binding domain are optionally connected by a linker,

wherein the mgRNA further comprises a second protein-binding motif, and

wherein the second RNA binding domain is capable of binding to the second protein-binding motif.

29. The gene editing system of any one of claims 19-24, wherein the protease is a TEV protease, a TuMV protease, a PPV protease, a PVY protease, a ZIKV protease, or a WNV protease.

30. The gene editing system in claim 29, wherein the protease is a TEV protease comprising a sequence of SEQ ID NO: 195.

31. The gene editing system in claim 30, wherein the first TEV protease fragment comprises a sequence of SEQ ID NO: 196 or 197.

32. The gene editing system in any one of claims 23-31, wherein the nucleobase deaminase inhibitor is an inhibitory domain of a nucleobase deaminase.

33. The gene editing system in any one of claims 23-32, wherein the nucleobase deaminase inhibitor is an inhibitory domain of a cytidine deaminase.

34. The gene editing system in claim 33, wherein the inhibitory domain of a cytidine deaminase comprises an amino acid sequence selected from SEQ ID NO: 1145-1234.

35. The gene editing system in claim 33, wherein the inhibitory domain of a cytidine deaminase comprises an amino acid sequence selected from SEQ ID NO: 1145 and 1146.

36. The gene editing system in any one of claims 22-35, wherein the nucleotide deaminase of the first fusion protein is a cytidine deaminase.

37. The gene editing system in claim 36, wherein the cytidine deaminase is selected from the group consisting of APOBEC3A (A3A), APOBEC3B (A3B), APOBEC3C (A3C), APOBEC3D (A3D), APOBEC3F (A3F), APOBEC3G (A3G), APOBEC3H (A3H), APOBEC1 (A1), APOBEC3 (A3), APOBEC2 (A2), APOBEC4 (A4), and AICDA (AID).
38. The gene editing system in claim 36, wherein the cytidine deaminase comprises an amino acid sequence of any one of SEQ ID NOs: 159-194.
39. The gene editing system in claim 36, wherein the cytidine deaminase is a human cytidine deaminase, a monkey cytidine deaminase, or mouse cytidine deaminase.
40. The gene editing system in claim 39, wherein the catalytic domain of the cytidine deaminase is a mouse A3 cytidine deaminase domain 1 (mA3-CDA1) or human A3B cytidine deaminase domain 2 (hA3B-CDA2).
41. The gene editing system in claim 40, wherein the catalytic domain has at least 85% sequence identity to amino acid residues 35-141 of SEQ ID NO: 1143 and comprises at least one substitution, relative to SEQ ID NO: 1143, at a residue selected from the group consisting of Y35, K40, W102, and N66 or a combination thereof.
42. The gene editing system of claim 41, wherein the substitution is selected from the group consisting of Y35D, K40H, W102Y, N66A, N66L, N66V and N66Q or a combination thereof.
43. The gene editing system of claim 41, wherein the substitution is Y35D.
44. The gene editing system of claim 41, wherein the catalytic domain comprises the amino acid sequence of SEQ ID NO: 1235.
45. The gene editing system of claim 41, wherein the substitution is K40H and W102Y.
46. The gene editing system of claim 41, wherein the catalytic domain comprises the amino acid sequence of SEQ ID NO: 1236.
47. The gene editing system of claim 41, wherein the substitution is K40H.
48. The gene editing system of claim 41, wherein the catalytic domain comprises the amino acid sequence of SEQ ID NO: 1237.
49. The gene editing system of claim 41, wherein the substitution is N66A.
50. The gene editing system of claim 41, wherein the catalytic domain comprises the amino acid sequence of SEQ ID NO: 1238.
51. The gene editing system of claim 41, wherein the substitution is N66L.

52. The gene editing system of claim 41, wherein the catalytic domain comprises the amino acid sequence of SEQ ID NO: 1239.
53. The gene editing system of claim 41, wherein the substitution is N66V.
54. The gene editing system of claim 41, wherein the catalytic domain comprises the amino acid sequence of SEQ ID NO: 1240.
55. The gene editing system of claim 41, wherein the substitution is N66Q.
56. The gene editing system of claim 41, wherein the catalytic domain comprises the amino acid sequence of SEQ ID NO: 1241.
57. The gene editing system in any one of claims 22-35, wherein the nucleotide deaminase of the first fusion protein is an adenosine deaminase.
58. The gene editing system in claim 57, wherein the adenosine deaminase is selected from tRNA-specific adenosine deaminase (TadA), adenosine deaminase tRNA specific 1 (ADAT1), adenosine deaminase tRNA specific 2 (ADAT2), adenosine deaminase tRNA specific 3 (ADAT3), adenosine deaminase RNA specific B1 (ADARB1), adenosine deaminase RNA specific B2 (ADARB2), adenosine monophosphate deaminase 1 (AMPD1), adenosine monophosphate deaminase 2 (AMPD2), adenosine monophosphate deaminase 3 (AMPD3), adenosine deaminase (ADA), adenosine deaminase 2 (ADA2), adenosine deaminase like (ADAL), adenosine deaminase domain containing 1 (ADAD1), adenosine deaminase domain containing 2 (ADAD2), and adenosine deaminase RNA specific (ADAR).
59. The gene editing system in claim 58, wherein the adenosine deaminase comprises an amino acid sequence selected from SEQ ID NO: 66-158.
60. The gene editing system of any one of claims 22-59, wherein the first fusion protein further comprises an uracil glycosylase inhibitor (UGI).
61. The gene editing system of any one of claims 22-60, wherein the Cas protein is Cas9, a dead Cas9 (dCas9), or a Cas9 nickase (nCas9) selected from the group consisting of SpCas9, FnCas9, St1Cas9, St3Cas9, NmCas9, SaCas9, AsCpf1, LbCpf1, FnCpf1, VQR Cas9, EQR Cas9, VRER Cas9, Cas9-NG, xCas9, eCas9, SpCas9-HF1, HypaCas9, HiFiCas9, sniper-Cas9, SpG, SpRY, KKH SaCas9, CjCas9, Cas9-NRRH, Cas9-NRCH, Cas9-NRTH, SsCpf1, PcCpf1, BpCpf1, LiCpf1, PmCpf1, Lb2Cpf1, PbCpf1, PeCpf1, PdCpf1, MbCpf1, EcCpf1, CmtCpf1, BsCpf1, BhCas12b, AkCas12b, BsCas12b, AmCas12b, AaCas12b, RfxCas13d, LwaCas13a, PspCas13b, PguCas13b, and RanCas13b.

62. The gene editing system of any one of claims 22-61, wherein the first protein-binding RNA motif and the first RNA binding domain, the second protein-binding RNA motif and the second RNA binding domain, and the third protein-binding RNA motif and the third RNA binding domain, are each independently selected from the group consisting of: a MS2 phage operator stem- loop and MS2 coat protein (MCP) or an RNA-binding section thereof,
- 5 a BoxB and N22P or an RNA-binding section thereof,
- a telomerase Ku binding motif and Ku protein or an RNA-binding section thereof,
- 10 a telomerase Sm7 binding motif and Sm7 protein or an RNA-binding section thereof,
- a PP7 phage operator stem - loop and PP7 coat protein (PCP) or an RNA-binding section thereof,
- a SfMu phage Com stem-loop and Com RNA binding protein or an RNA-binding section thereof, and
- 15 a non-natural RNA aptamer and corresponding aptamer ligand or an RNA-binding section thereof.
63. The gene editing system of any one of claims 1-62, wherein the mgRNA and/or the hgRNA comprise a dual-RNA structure.
- 20 64. The gene editing system of claim 63, wherein the dual-RNA structure is formed by a CRISPR RNA (crRNA) and a trans-activating crRNA (tracrRNA), wherein the crRNA comprises the spacer.
65. The gene editing system of claim 63 or 64, wherein the mgRNA comprises a mcrRNA and a first tracrRNA, and the mcrRNA comprises the mgRNA spacer,
- 25 wherein the hgRNA comprises a hcrRNA and a second tracrRNA, and the hcrRNA comprises the hgRNA spacer, and wherein the first tracrRNA and the second tracrRNA are same or different.
66. The gene editing system of claim 65, wherein the mcrRNA and the hcrRNA are
- a. SEQ ID NO: 1112 and SEQ ID NO: 1111, respectively; or
- 30 b. SEQ ID NO. 1114 and SEQ ID NO: 1113, respectively; or
- c. SEQ ID NO. 1116 and SEQ ID NO: 1115, respectively.
67. The gene editing system of claim 65, wherein the mcrRNA and the hcrRNA are

- a. SEQ ID NO. 1138 and SEQ ID NO: 1137, respectively; or
 - b. SEQ ID NO. 1140 and SEQ ID NO: 1139, respectively; or
 - c. SEQ ID NO. 1142 and SEQ ID NO: 1141, respectively.
- 5 68. The gene editing system of any one of claims 64-67, wherein the tracrRNA is SEQ ID NO: 1117 and 1242.
69. A polynucleotide encoding the hgRNA and/or the mgRNA in any one of claims 1-21.
70. A polynucleotide encoding all components except the first and the second Cas proteins in the gene editing system in any one of claims 22-69.
- 10 71. A polynucleotide encoding all components except the mgRNA and hgRNA in the gene editing system in any one of claims 22-69.
72. A polynucleotide encoding all components except the mgRNA, hgRNA, and the first and second Cas proteins in the gene editing system in any one of claims 22-69.
73. A kit comprising
- a. the polynucleotide in claim 70,
 - 15 b. a polynucleotide encoding the first and/or second Cas protein in any one of claims 22-68.
74. A kit comprising the polynucleotide in claim 69 and the polynucleotide in claims 71.
75. A kit comprising the polynucleotide in claim 72 and a polynucleotide encoding the mgRNA, hgRNA and the first and/or second Cas protein in any one of claims 22-68.
- 20 76. A vector comprising the polynucleotide in claim 69.
77. A vector comprising the polynucleotide in claim 70.
78. A vector comprising the polynucleotide in claim 71.
79. A vector comprising the polynucleotide in claim 72.
80. The vector of any one of claim 76-79, wherein the vector is selected from a plasmid, a 25 viral vector, and a lipid nanoparticle (LNP) vector, or a non-viral vector.
81. The vector of any one of claims 76-79, wherein the vector is an AAV vector.
82. A kit comprising:
- a. the vector in claim any one of claim 76-79,

- b. a vector comprising the polynucleotide encoding the first and/or second Cas protein in any one of claims 22-68.
83. A cell comprising the gene editing system in any one of claims 1-68.
84. A cell comprising the polynucleotide of claim 69 or 72.
- 5 85. The cell in claim 84, further comprising a polynucleotide encoding the first and/or second Cas protein in any one of claims 22-68.
86. A cell comprising the vector in any one of claims 76-79.
87. The cell in claim 86, further comprising a vector comprising a polynucleotide encoding the first and/or second Cas protein in any one of claims 22-68.
- 10 88. The cell of any one of claims 83-87, wherein the cell is a stem cell.
89. The cell in claim 88, wherein the stem cell is a pluripotent stem cell.
90. The cell in claim 89, wherein the pluripotent stem cell is an induced pluripotent stem cell (iPSC) or an embryonic stem cell.
91. The cell of any one of claims 83-87, wherein the cell is a somatic cell.
- 15 92. The cell in any one of claims 83-87, wherein the cell is a hepatocyte.
93. The cell in any one of claims 83-92, wherein the cell is a primary cell or a differentiated cell.
94. A composition comprising the gene editing system in any one of claims 1-68.
95. A composition comprising the cell in any one of claims 83-93.
- 20 96. A method for disrupting or regulating the expression of a gene selected from *PCSK9*, *ANGPTL3*, *ASGR1*, *LPA*, *AGT*, and *APOC3* gene in a cell, comprising introducing into the cell the gene editing system in any one of claims 1-68.
97. A method for disrupting or regulating the expression of *PCSK9* gene in a cell, comprising introducing into the cell the gene editing system in any one of claims 1-4.
- 25 98. A method for disrupting or regulating the expression of *ANGPTL3* gene in a cell, comprising introducing into the cell the gene editing system in any one of claims 5-8.
99. A method for disrupting or regulating the expression of *ASGR1* gene in a cell, comprising introducing into the cell the gene editing system in any one of claims 9-11.

100. A method for disrupting or regulating the expression of *LPA* gene in a cell, comprising introducing into the cell the gene editing system in any one of claims 12-14.
101. A method for disrupting or regulating the expression of *AGT* gene in a cell, comprising introducing into the cell the gene editing system in any one of claims 15-17.
102. A method for disrupting or regulating the expression of *APOC3* gene in a cell, comprising introducing into the cell the gene editing system in any one of claims 18-21.
103. A method for disruption or regulation the expression of two or more genes selected from *PCSK9*, *ANGPTL3*, *ASGR1*, *LPA*, *AGT*, and *APOC3* gene in a cell, comprising introducing into the cell two or more gene editing systems, wherein when the two or more genes include the *PCSK9* gene, the two or more gene editing systems include the gene editing systems in any one of claims 1-4, wherein when the two or more genes include the *ANGPTL3* gene, the two or more gene editing systems include the gene editing systems in any one of claims 5-8, wherein when the two or more genes include the *ASGR1* gene, the two or more gene editing systems include the gene editing systems in any one of claims 9-11, wherein when the two or more genes include the *LPA* gene, the two or more gene editing systems include the gene editing systems in any one of claims 12-14, wherein when the two or more genes include the *AGT* gene, the two or more gene editing systems include the gene editing systems in any one of claims 15-17, wherein when the two or more genes include the *APOC3* gene, the two or more gene editing systems include the gene editing systems in any one of claims 18-21.
104. The method of claim 103, wherein the expression of two genes selected from *PCSK9*, *ANGPTL3*, *ASGR1*, *LPA*, *AGT*, and *APOC3* gene are disrupted or regulated.
105. The method of claim 104, wherein the two genes are *PCSK9* gene and *ANGPTL3* gene.
106. The method of claim 103, wherein the expression of three genes selected from *PCSK9*, *ANGPTL3*, *ASGR1*, *LPA*, *AGT*, and *APOC3* gene are disrupted or regulated.
107. A method for regulating Low-Density Lipoprotein cholesterol (LDL-C) metabolism in a subject, comprising introducing into a cell of the subject the gene editing system according to any one of claims 1-11 and 18-21.

108. A method for treating hypercholesterolemia in a subject, comprising introducing into a cell of the subject a therapeutically effective amount of the gene editing system according to any one of claims 1-11 and 18-21.
- 5 109. A method for lowering LDL-C level in a subject, comprising introducing into a cell of the subject the gene editing system according to any one of claims 1-11 and 18-21.
110. A method for regulating triglyceride-rich remnant particles and/or lipoprotein(a) (Lp(a)) metabolism in a subject, comprising introducing into a cell of the subject the gene editing system according to any one of claims 9-14 and 18-21.
- 10 111. A method for lowering the level of triglyceride-rich remnant particles and/or lipoprotein(a) (Lp(a)) in a subject, comprising introducing into a cell of the subject the gene editing system according to any one of claims 9-14 and 18-21.
112. A method for regulating blood pressure in a subject, comprising introducing into a cell of the subject the gene editing system according to any one of claims 15-17.
- 15 113. A method for reducing the expression of angiotensinogen in a subject, comprising introducing into a cell of the subject the gene editing system according to any one of claims 15-17.
114. A method for treating hypertension in a subject, comprising introducing into a cell of the subject a therapeutically effective amount of the gene editing system according to any one of claims 15-17.
- 20 115. A method for treating cardiovascular disease (CVD) in a subject, comprising introducing into the subject a therapeutically effective amount of the gene editing system according to any one of claims 1-68.
116. A method for treating cardiovascular disease (CVD), comprising lowering blood lipid level with a method of claim 109, lowering the level of circulating lipoprotein particles with a method of claim 111, or lowering blood pressure with a method of claim 113.
- 25 117. The method in claim 116, wherein the cardiovascular disease is associated with the expression of genes selected from *PCSK9*, *ANGPTL3*, *ASGR1*, *LPA*, *AGT*, and *APOC3* gene.
- 30 118. The method in claim 116, wherein the cardiovascular disease is selected from atherosclerosis, congestive heart failure, peripheral vascular disease, cerebrovascular disease, rheumatic heart disease, arrhythmia, hypertension, and coronary artery disease.

119. The method in any one of claims 96-114, wherein the cell is a stem cell.
120. The method in claim 119, wherein the stem cell is a pluripotent stem cell.
121. The method in claim 120, wherein the pluripotent stem cell is an induced pluripotent stem cell (iPSC) or an embryonic stem cell.
- 5 122. The method in any one of claims 96-114, wherein the cell is somatic cell.
123. The method in any one of claims 96-114, wherein the cell is a hepatocyte.
124. The method in any one of claims 96-114, wherein the cell is a primary cell or a differentiated cell.