91	hRNaseG88D-S	agactgccgcctgacaaacgactccaggtaccc
92	hRNAseG88D-AS	gggtacctggagtcgtttgtcaggcggcagtct
93	g4s5-5-1	GGC TCA GGT GGT GGA GGA TCT GGA GGA GGT GGC TCA GGT GGT GGA GGA TCT G
94	g4s5-2s	GTT AGA TCT CTC CGG AGG AGG TGG CTC AGG TGG TGG AGG ATC TGG A
95	g4s5-asxho	CTC GAG ACT CCC ACC TCC TCC AGA TCC TCC ACC ACC TGA GCC ACC T
96	g4s4-5'	AAA GAT CTC TCC GGA GGA GGT GGC TCA GGT GGT GGA GGA TCT GGA GGA GG
97	g4s4-3'	CTC GAG ACC GGT AGA ACC ACC TCC ACC ACT CCC ACC TCC TCC AGA TCC TC
98	g4s5-5	GTT AGA TCT CTC CGG AGG AGG TGG CTC A
99	g4s5-3	ACC GGT CTC GAG ACT CCC ACC TCC TCC AGA TC

TABLE 2

SEQ ID NO.	DESCRIPTION	SEQUENCE (NUCLEOTIDE SEQUENCES ARE 5′-3′)
100	g4s4lnk ("(G4S)4")	cggaggaggtggctcaggtggtggaggatctggaggaggtgggagtggtggaggtggttct
101	G4S5-1 ("(G4S)5")	cggaggaggtggctcaggtggtggaggatctggaggaggtggctcaggtggtggaggatctggaggaggtgggagt
102	G4S5-2 ("(G4S)5")	cggaggaggtggctcaggtggtggaggatctggaggaggtggctcaggtggtggaggatctggaggaggtgggagt
103	3′hRNase G88D	gtcgacggagctagcagccccgtgaacgtgagcagccccagcgtgcaggatatccccttccctgggcaaggaatcccgggccaagaaattccagcggcagcatatggactcagacagttccccccagcagcagctccacctactgtaaccaaatgatgaggcgccggaatatgacacaggggcggtgcaaaccagtgaacacctttgtgcacgagccctctggtagatgtccagaatgtctgtttccaggaaaaggtcacctgcaagaacgggcagggcaactgctacaagagcaactccagcatgcacatcacagactgccgcctgacaaacgactccaggtaccccaactgtgcataccggaccagcccgaaggagagacacatcattgtggcctgtgaagggagcccatatgtgccagtccactttgatgcttctgtggaggactctacctaataatctaga
104	hDNase1-3′-G105R;A114F	gatatcctgaagatcgcagccttcaacatccagacatttggggagaccaagatgtccaatgccaccctcgtcagctacattgtgcagatcctgagccgctatgacatcgccctggtccaggaggtcagagacagccacctgactgccgtggggaagctgctggacaacctcaatcaggatgcaccagacacctatcactacgtggtcagtgagccactgggacggaacagctataaggagcgctacctgttcgtgtacaggcctgaccaggtgtctgcggtggacagctactactacgatgatggctgcgagccctgcaggaacgacaccttcaaccgagagccattcattgtcaggttcttctcccggttcacagaggtcagggagtttgccattgttcccctgcatgcggccccgggggacgcagtagccgagatcgacgctctctatgacgtctacctggatgtccaagagaaatggggcttggaggacgtcatgttgatgggcgacttcaatgcgggctgcagctatgtgagaccctcccagtggtcatccatccgcctgtggacaagccccaccttccagtggctgatcccgacagcgctgacaccacagctacacccacgcactgtgcctatgacaggatcgtggttgcagggatgctgctccgaggcgccgttgttcccgactcggctcttcccttaacttccaggctgcctatggcctgagtgaccaactggcccaagccatcagtgaccactatccagtggaggtgatgctgaagtgataatctaga
105	hDNase1-3′-WT	Gatatcctgaagatcgcagccttcaacatccagacatttggggagaccaagatgtccaatgccaccctcgtcagctacattgtgcagatcctgagccgctatgacatcgccctggtccaggaggtcagagacagccacctgactgccgtggggaagctgctggacaacctcaatcaggatgcaccagacacctatcactacgtggtcagtgagccactgggacggaacagctataaggagcgctacctgttcgtgtacaggcctgaccaggtgtctgcggtggacagctactactacgatgatggctgcgagccctgcgggaacgacaccttcaaccgagagccagccattgtcaggttcttctcccggttcacagaggtcagggagtttgccattgttcccctgcatgcggccccgggggacgcagtagccgagatcgacgctctctatgacgtctacctggatgtccaagagaaatggggcttggaggacgtcatgttgatgggcgacttcaatgcgggctgcagctatgtgagaccc

TABLE 2		
SEQ ID NO.	**DESCRIPTION**	**SEQUENCE (NUCLEOTIDE SEQUENCES ARE 5′-3′)**
		tctccgggtaaagtcgacggagctagcagccccgtgaacgtgagcagccccagc gtgcaggatatcatgggccctggagctcgcagacagggcaggattgtgcaggga aggcctgagatgtgcttctgcccacccccctaccccactccctccccttcggatc ttaacactgggcactcacacacccaccccatgctcctctccaggctcagcagca ggtacgtacccaaccatgggctcgcaggccctgcccccggggcccatgcagacc ctcatctttttcgacatggaggccactggcttgcccttctcccagcccaaggtc acggagctgtgcctgctggctgtccacagatgtgccctggagagccccccccacc tctcaggggccacctcccacagttcctccaccaccgcgtgtggtagacaagctc tccctgtgtgtggctccggggaaggcctgcagccctgcagccagcgagatcaca ggtctgagcacagctgtgctggcagcgcatgggcgtcaatgttttgatgacaac ctggccaacctgctcctagccttcctgcggcgccagccacagccctggtgcctg gtggcacacaatggtgaccgctacgacttccccctgctccaagcagagctggct atgctgggcctcaccagtgctctggatggtgccttctgtgtggatagcatcact gcgctgaaggccctggagcgagcaagcagcccctcagaacacggcccaaggaag agctacagcctaggcagcatctacactcgcctgtatgggcagtcccctccagac tcgcacacggctgagggtgatgtcctggccctgctcagcatctgtcagtggaga ccacaggccctgctgcggtgggtggatgctcacgccaggcctttcggcaccatc aggcccatgtatggggtcacagcctctgctaggaccaaatgataatctaga
207	huVK3LP-hDNase1L3-hIgG1-WT-NLG-hTREX1-72AA	metpaqllfllllwlpdttgmricsfnvrsfgeskqedknamdvivkvikrcdi ilvmeikdsnnricpilmeklnrnsrrgitynyvissrlgrntykeqyaflyke klvsvkrsyhyhdyqdgdadvfsrepfvvwfqsphtavkdfviiplhttpetsv keidelvevytdvkhrwkaenfifmgdfnagcsyvpkkawknirlrtdprfvwl igdqedttvkkstncaydrivlrgqeivssvvpksnsvfdfqkayklteeeald vsdhfpvefklqssraftnskksvtlrkktkskrsdlepkssdkthtcppcpap ellggpsvflfppkpkdtlmisrtpevtcvvvdvshedpevkfnwyvdgvevhn aktkpreeqynstyrvvsvltvlhqdwlngkeykckvsnkalpapiektiskak gqprepqvytlppsrdeltknqvsltclvkgfypsdiavewesngqpennyktt ppvldsdgsfflyskltvdksrwqqgnvfscsvmhealhnhytqkslslspgkv dgasspvnvsspsvqdimgpgarrqgrivqgrpemcfcppptplpplriltlgt htptpcsspgsaagtyptmgsqalppgpmqtliffdmeatglpfsqpkvtelcl lavhrcalespptsqgpppptvpppprvvdklslcvapgkacspaaseitglsta vlaahgrqcfddnlanlllaflrrqpqpwclvahngdrydfpllqaelamlglt saldgafcvdsitalkalerasspsehgprksyslgsiytrlygqsppdshtae gdvlallsicqwrpqallrwvdaharpfgtirpmygvtasartk*
208	(G4S)10	ggggsggggsggggsggggsggggsggggsggggsggggsggggsggggs
209	(G4S)3	ggggsggggsggggs
210	(G4S)	ggggs
211	(G4S)6	ggggsggggsggggsggggsggggsggggs
212	OligodT 18mer	ttttttttttttttttttt
213	mRNase-mIgG2a P238S, K322S, P331S (nucleotide sequence)	gttaagcttg ccacc atg ggt ctg gag aag tcc ctc att ctg ttt cca ttg ttt ttc ctg ctg ctt gga tgg gtc cag cct tcc ccg ggc agg gaa tct gca gca cag aag ttt cag cgg cag cac atg gat cca gat ggt tcc tcc atc aac agc ccc acc tac tgc aac caa atg atg aaa cgc cgg gat atg aca aat ggg tca tgc aag ccc gtg aac acc ttc gtg cat gag ccc ttg gca gat gtc cag gcc gtc tgc tcc cag gaa aat gtc acc tgc aag aac agg aag agc aac tgc tac aag agc agc tct gcc ctg cac atc act gac tgc cac ctg aag ggc aac tcc aag tat ccc aac tgt gac tac aag acc act caa tac cag aag cac atc att gtg gcc tgt gaa ggg aac ccc tac gta cca gtc cac ttt gat gct act gtg ctc

TABLE 2		
SEQ ID NO.	**DESCRIPTION**	**SEQUENCE (NUCLEOTIDE SEQUENCES ARE 5′-3′)**
		gag ccc aga ggt ctc aca atc aag ccc tct cct cca tgc aaa tgc cca gca cct aac ctc ttg ggt gga tca tcc gtc ttc atc ttc cct cca aag atc aag gat gta ctc atg atc tcc ctg agc ccc atg gtc aca tgt gtg gtg gtg gat gtg agc gag gat gac cca gac gtc cag atc agc tgg ttt gtg aac aac gtg gaa gta cac aca gct cag aca caa acc cat aga gag gat tac aac agt act ctc cgg gtg gtc agt gcc ctc ccc atc cag cac cag gac tgg atg agt ggc aag gag ttc aaa tgc tcg gtc aac aac aaa gac ctc cca gcg tcc atc gag aga acc atc tca aaa ccc aga ggg cca gta aga gct cca cag gta tat gtc ttg cct cca cca gca gaa gag atg act aag aaa gag ttc agt ctg acc tgc atg atc aca ggc ttc tta cct gcc gaa att gct gtg gac tgg acc agc aat ggg cgt aca gag caa aac tac aag aac acc gca aca gtc ctg gac tct gat ggt tct tac ttc atg tac agc aag ctc aga gta caa aag agc act tgg gaa aga gga agt ctt ttc gcc tgc tca gtg gtc cac gag ggt ctg cac aat cac ctt acg act aag agc ttc tct cgg act ccg ggt aaa tgataatcta gaa
214	mRNase-mIgG2a P238S, K322S, P331S (amino acid sequence)	Met Gly Leu Glu Lys Ser Leu Ile Leu Phe Pro Leu Phe Phe Leu Leu Leu Gly Trp Val Gln Pro Ser Pro Gly Arg Glu Ser Ala Ala Gln Lys Phe Gln Arg Gln His Met Asp Pro Asp Gly Ser Ser Ile Asn Ser Pro Thr Tyr Cys Asn Gln Met Met Lys Arg Arg Asp Met Thr Asn Gly Ser Cys Lys Pro Val Asn Thr Phe Val His Glu Pro Leu Ala Asp Val Gln Ala Val Cys Ser Gln Glu Asn Val Thr Cys Lys Asn Arg Lys Ser Asn Cys Tyr Lys Ser Ser Ser Ala Leu His Ile Thr Asp Cys His Leu Lys Gly Asn Ser Lys Tyr Pro Asn Cys Asp Tyr Lys Thr Thr Gln Tyr Gln Lys His Ile Ile Val Ala Cys Glu Gly Asn Pro Tyr Val Pro Val His Phe Asp Ala Thr Val Leu Glu Pro Arg Gly Leu Thr Ile Lys Pro Ser Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu Leu Gly Gly Ser Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser Pro Met Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp Pro Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu Phe Lys Cys Ser Val Asn Asn Lys Asp Leu Pro Ala Ser Ile Glu Arg Thr Ile Ser Lys Pro Arg Gly Pro Val Arg Ala Pro Gln Val Tyr Val

CLAIMS

1. A polypeptide comprising a first nuclease domain, a second nuclease domain, and a variant Fc domain, wherein the first and second nuclease domains are operably linked, optionally with a linker, to each other in series to form a tandem array, wherein said tandem array of nuclease domains is operably linked, optionally with a linker, to either the C-terminus or the N-terminus of the variant Fc domain, wherein the first nuclease domain is an RNAse and the second nuclease domain is a DNase, and wherein the variant Fc domain is a variant human IgG1 Fc domain comprising an amino acid substitution which decreases binding, compared to wild-type, to an Fcγ receptor or a complement protein or both, and wherein the polypeptide has a reduced effector function optionally selected from the group consisting of opsonization, phagocytosis, complement dependent cytotoxicity, and antibody-dependent cellular cytotoxicity.

2. The polypeptide of claim 1, wherein

(a) the first nuclease domain is a human RNase, such as a human pancreatic RNase 1; and/or

(b) the second nuclease domain is a human DNase selected from the group consisting of a Type 1 human DNase, a human DNase1L3, or human TREX1.

3. The polypeptide of claim 1 or claim 2, wherein:

(a) the variant Fc domain comprises a hinge domain, a CH2 domain and a CH3 domain; and/or

(b) the variant Fc domain comprises a modified hinge domain comprising at least one amino acid substitution, optionally wherein the modified hinge domain comprises a substitution of one or more of the three hinge cysteines with serine, such as SCC or SSS; and/or

(c) the variant Fc domain comprises a modified CH2 domain comprising at least one substitution, optionally wherein the substitution is selected from the group consisting of P238S, P331S, N297S or a combination thereof.

4. The polypeptide of any one of the preceding claims, wherein:

the RNase or DNase domain is operatively coupled to the variant Fc domain via a linker domain, optionally wherein the linker domain is a polypeptide linker, such as a Gly-Ser linker; and/or

wherein the RNase or DNase domain is operatively coupled to the N-terminus of the variant Fc domain, optionally with a linker; and/or

wherein the RNase or DNase domain is operatively coupled to the C-terminus of the variant Fc domain, optionally with a linker.

5. The polypeptide of any one of the preceding claims, wherein

(a) the RNase comprises an amino acid sequence at least 90% identical to the amino acid sequence set forth in SEQ ID NO:149, optionally without its leader sequence, or comprises 100 or more contiguous amino acids from SEQ ID NO. 149, wherein the RNase retains the activity of the RNase set forth in SEQ ID NO: 149; and/or

(b) the DNase comprises an amino acid sequence set forth in SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, or SEQ ID NO: 143, or comprising an amino acid sequence at least 90% identical to the amino acid sequence set forth in SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, or SEQ ID NO: 143, wherein the DNase retains the activity of a DNase set forth in SEQ ID NO: 139, 140, 141, 142, or 143; and/or

(c) the variant Fc domain comprises an amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% identical to the amino acid sequence set forth in SEQ ID NO:145, optionally comprising a modified hinge domain comprising at least one amino acid substitution, optionally wherein the modified hinge domain comprises a substitution of one or more of the three hinge cysteines with serine, such as SCC or SSS; and/or optionally comprising one or more Fc mutations selected from P238S, P331S, K322S, and N279S.

6. A composition comprising the polypeptide of any of the preceding claims and a pharmaceutically acceptable carrier.

7. A nucleic acid molecule encoding the polypeptide according to any of claims 1 to 5.

8. A recombinant expression vector comprising the nucleic acid molecule according to claim 7.

9. A host cell transformed with the recombinant expression vector according to claim 8.

10. A method of making the polypeptide of any of claims 1 to 5, comprising: providing a host cell comprising a nucleic acid sequence that encodes the polypeptide; and maintaining the host cell under conditions in which the polypeptide is expressed.

11. A dimeric polypeptide comprising the polypeptide of any one of claims 1 to 5, optionally a homodimer.

12. A composition comprising the dimeric polypeptide of claim 11 and a pharmaceutically acceptable carrier.

13. The polypeptide of any of claims 1 to 5, the composition of claim 6, the dimeric polypeptide of claim 11, or the composition of claim 12, for use in a method of treating systemic lupus erythematosus (SLE).

14. The polypeptide of any of claims 1 to 5, the composition of claim 6, the dimeric polypeptide of claim 11, or the composition of claim 12, for use in a method of treating Sjogren's syndrome.

15. The polypeptide of any of claims 1 to 5, the composition of claim 6, the dimeric polypeptide of claim 11, or the composition of claim 12, for use in a method of treating lupus nephritis.

16. Use of the polypeptide of any of claims 1 to 5, the composition of claim 6, the dimeric polypeptide of claim 11, or the composition of claim 12, in the manufacture of a medicament for treating systemic lupus erythematosus (SLE).

17. Use of the polypeptide of any of claims 1 to 5, the composition of claim 6, the dimeric polypeptide of claim 11, or the composition of claim 12, in the manufacture of a medicament for treating Sjogren's syndrome.

18. Use of the polypeptide of any of claims 1 to 5, the composition of claim 6, the dimeric polypeptide of claim 11, or the composition of claim 12, in the manufacture of a medicament for treating lupus nephritis.