CLAIMS

1. A polypeptide comprising an RNase, a DNase, and a variant Fc domain, wherein the RNase is operatively coupled, optionally with a linker, to the variant Fc domain, and wherein the DNase is operatively coupled, optionally with a linker, to the variant Fc domain, 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, 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 RNase is a human RNase, such as a human pancreatic RNase 1; and/or

(b) the DNase is selected from the group consisting of a Type 1 human DNase, a human DNase 1L3, or human TREX1; and/or

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

(d) a leader sequence, such as the human VK3LP peptide, is coupled to the N-terminus of the RNase or the N-terminus of the DNase.

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

(a) the Fc domain comprises a modified hinge domain comprising at least one substitution, optionally wherein the modified hinge domain comprises a mutation in one or more of the three hinge cysteines, such as SCC or SSS; and/or

(b) wherein the Fc domain comprises a modified CH2 domain comprising at least one substitution, optionally wherein the substitution is selected from the group consisting ofP238S, P331S, N297S or a combination thereof.

4. The polypeptide of claim 1 or claim 2, 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; and/or

(b) wherein the DNase comprises a human DNase, optionally DNase 1, optionally comprising an amino acid sequence set forth in SEQ ID NO: 139, SEQ ID NO:143, or SEQ ID NO:142 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:143, or SEQ ID NO:142; and/or

(c) the 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 substitution,

optionally wherein the modified hinge domain comprises a mutation in one or more of the three cysteines, such as SCC or SSS; and/or optionally comprising one or more Fc mutations selected from P238S, P331S, K322S, and N297S.

5. The polypeptide of claim 1, wherein;

the polypeptide 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:153, optionally without its leader sequence; optionally wherein the Fc domain comprises a modified hinge domain comprising at least one substitution, optionally wherein the modified hinge domain comprises a mutation in one or more of the three hinge cysteines, such as SCCor SSS; and/or a modified CH2 domain comprising at least one substitution selected from the group consisting of P238S, P331S, N297S or combination thereof.

6. The polypeptide of any preceding claim, wherein:

the RNase is operatively coupled to the 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 is operatively coupled to the N-terminus of the Fc domain, optionally with a linker; and /or wherein the RNase is operatively coupled to the C-terminus of the Fc domain, optionally with a linker; and/or wherein the polypeptide comprises a human VK3LP peptide leader sequence coupled to the N-terminus of the RNase.

7. The polypeptide of any preceding claim, wherein:

the DNase is operatively coupled to the Fc domain via a second linker domain, optionally wherein the second linker domain is a polypeptide linker, such as an NLG peptide; and/or wherein the DNase is operatively coupled to the N-terminus of the Fc domain, optionally with a linker; and/or wherein the DNase is operatively coupled to the C-terminus of the Fc domain, optionally with a linker; and/or wherein the polypeptide comprises a human VK3LP peptide leader sequence coupled to the N-terminus of the DNase.

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

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

10. A recombinant expression vector comprising a nucleic acid molecule according to claim 9.

11. A host cell transformed with the recombinant expression vector according to claim 10.

12. A method of making the polypeptide of any of claims 1 to 7, 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.

13. A dimeric polypeptide comprising a polypeptide of any of claims 1-7, optionally a homodimer.

14. A composition comprising the dimeric polypeptide of claim 13 and a pharmaceutically acceptable excipient.

15. A polypeptide of any of claims 1 to 7, the composition of claim 8, the dimeric polypeptide of claim 13 or the composition of claim 14 for use in a method for treating or preventing a condition associated with an abnormal immune response; optionally wherein the condition is an autoimmune disease, optionally systemic lupus erythematosus (SLE), or optionally selected from the group consisting of insulin-dependent diabetes mellitus, multiple sclerosis, experimental autoimmune encephalomyelitis, rheumatoid arthritis, experimental autoimmune arthritis, myasthenia gravis, thy- roiditis, an experimental form of uveoretinitis, Hashimoto's thyroiditis, primary myxoedema, thyrotoxicosis, pernicious anaemia, autoimmune atrophic gastritis, Addison's disease, premature menopause, male infertility, juvenile diabetes, Good pasture's syndrome, pemphigus vulgaris, pemphigoid, sympathetic ophthalmia, phacogenic uveitis, autoim- mune haemolytic anameia, idiopathic leucopenia, primary biliary cirrhosis, active chronic hepatitis Hbs-ve, cryp- togenic cirrhosis, ulcerative colitis, Sjogren's syndrome, scleroderma, Wegener's granulomatosis, polymyositis, dermatomyositis, discoid LE, systemic lupus erythematosus (SLE), and connective tissue disease.

16. A polypeptide of any of claims 1 to 7, the composition of claim 8, the dimeric polypeptide of claim 13, or the composition of claim 14 for use in a method for treating or preventing SLE.

17. A polypeptide of any of claims 1 to 7, the composition of claim 8, the dimeric polypeptide of claim 13, or the composition of claim 14 for use in a method for treating or preventing Sjogren's syndrome.

18. A polypeptide of any of claims 1 to 7, the composition of claim 8, the dimeric polypeptide of claim 13, or the composition of claim 14 for use in a method for treating or preventing lupus nephritis.

19. Use of a polypeptide of any of claims 1 to 7, the composition of claim 8, the dimeric polypeptide of claim 13, or the composition of claim 14 in the manufacture of a medicament for treating or preventing a condition associated with an abnormal immune response; optionally wherein the condition is an autoimmune disease, optionally systemic lupus erythematosus (SLE), or optionally selected from the group consisting of insulin-dependent diabetes mellitus, multiple sclerosis, experimental autoimmune encephalomyelitis, rheumatoid arthritis, experimental autoimmune arthritis, myasthenia gravis, thy- roiditis, an experimental form of uveoretinitis, Hashimoto's thyroiditis, primary myxoedema, thyrotoxicosis, pernicious anaemia, autoimmune atrophic gastritis, Addison's disease, premature menopause, male infertility, juvenile diabetes, Good pasture's syndrome, pemphigus vulgaris, pemphigoid, sympathetic ophthalmia, phacogenic uveitis, autoim- mune haemolytic anameia, idiopathic leucopenia, primary biliary cirrhosis, active chronic hepatitis Hbs-ve, cryp- togenic cirrhosis, ulcerative colitis, Sjogren's syndrome, scleroderma, Wegener's granulomatosis, polymyositis, dermatomyositis, discoid LE, systemic lupus erythematosus (SLE), and connective tissue disease.

20. Use of a polypeptide of any of claims 1 to 7, the composition of claim 8, the dimeric polypeptide of claim 13, or the composition of claim 14 in the manufacture of a medicament for treating or preventing SLE.

21. Use of a polypeptide of any of claims 1 to 7, or the composition of claim 8, the dimeric polypeptide of claim 13, or the composition of claim 14 in the manufacture of a medicament for treating or preventing Sjogren's syndrome.

22. Use of a polypeptide of any of claims 1 to 7, or the composition of claim 8, the dimeric polypeptide of claim 13, or the composition of claim 14 in the manufacture of a medicament for treating or preventing lupus nephritis.