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 and second nuclease domains are selected from an RNAse and 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 the first and second nuclease domains are selected from:

(a) a human RNase, such as a human pancreatic RNase 1; and/or

(b) 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 first or second nuclease 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 first or second nuclease domain is operatively coupled to the N-terminus of the variant Fc domain, optionally with a linker; and/or

wherein the first or second nuclease 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; and/or

(b) the DNase comprises an amino acid sequence set forth in SEQ ID NO: 139, 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: 142, or SEQ ID NO: 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. The polypeptide of any of claims 1 to 5 or the composition of claim 6, 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, thyroiditis, 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, Goodpasture's syndrome, pemphigus vulgaris, pemphigoid, sympathetic ophthalmia, phacogenic uveitis, autoimmune haemolytic anaemia, idiopathic leucopenia, primary biliary cirrhosis, active chronic hepatitis Hbs-ve, cryptogenic cirrhosis, ulcerative colitis, Sjogren's syndrome, scleroderma, Wegener's granulomatosis, polymyositis, dermatomyositis, discoid LE, systemic lupus erythematosus (SLE), and connective tissue disease.

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

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

14. The dimeric polypeptide of claim 12, or the composition of claim 13 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, thyroiditis, 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, Goodpasture's syndrome, pemphigus vulgaris, pemphigoid, sympathetic ophthalmia, phacogenic uveitis, autoimmune haemolytic anaemia, idiopathic leucopenia, primary biliary cirrhosis, active chronic hepatitis Hbs-ve, cryptogenic cirrhosis, ulcerative colitis, Sjogren's syndrome, scleroderma, Wegener's granulomatosis, polymyositis, dermatomyositis, discoid LE, systemic lupus erythematosus (SLE), and connective tissue disease.

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

16. The polypeptide of any of claims 1 to 5, the composition of claim 6, the dimeric polypeptide of claim 12, or the composition of claim 13, for use in a method of treating Sjogren's syndrome.

17. The polypeptide of any of claims 1 to 5, the composition of claim 6, the dimeric polypeptide of claim 12, or the composition of claim 13, for use in a method of treating lupus nephritis.

18. Use of a polypeptide of any of claims 1 to 5, the composition of claim 6, the dimeric polypeptide of claim 12, or the composition of claim 13 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, thyroiditis, 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, Goodpasture's syndrome, pemphigus vulgaris, pemphigoid, sympathetic ophthalmia, phacogenic uveitis, autoimmune haemolytic anaemia, idiopathic leucopenia, primary biliary cirrhosis, active chronic hepatitis Hbs-ve, cryptogenic cirrhosis, ulcerative colitis, Sjogren's syndrome, scleroderma, Wegener's granulomatosis, polymyositis, dermatomyositis, discoid LE, systemic lupus erythematosus (SLE), and connective tissue disease.

19. Use of the polypeptide of any of claims 1 to 5, the composition of claim 6, the dimeric polypeptide of claim 12, or the composition of claim 13, in the manufacture of a medicament for treating systemic lupus erythematosus (SLE).

20. Use of the polypeptide of any of claims 1 to 5, the composition of claim 6, the dimeric polypeptide of claim 12, or the composition of claim 13, in the manufacture of a medicament for treating Sjogren's syndrome.

21. Use of the polypeptide of any of claims 1 to 5, the composition of claim 6, the dimeric polypeptide of claim 12, or the composition of claim 13, in the manufacture of a medicament for treating lupus nephritis.