CLAIMS

1. A hybrid nuclease molecule comprising a first nuclease domain and an Fc domain, wherein the first nuclease domain is operatively coupled to the Fc domain.

2. The hybrid nuclease molecule of claim 1, wherein the hybrid nuclease molecule is a polypeptide, wherein the amino acid sequence of the first nuclease domain comprises a human, wild-type RNase amino acid sequence as set forth in SEQ ID NO:149, wherein the amino acid sequence of the Fc domain comprises a human, wild-type IgG1 Fc domain amino acid sequence as set forth in SEQ ID NO:145.

3. The hybrid nuclease molecule of claim 1, wherein the hybrid nuclease molecule is a polypeptide consisting of SEQ ID NO:163.

4. The hybrid nuclease molecule of claim 1, wherein the hybrid nuclease molecule comprises wild-type, human DNase1 linked to wild-type, human IgG1.

5. The hybrid nuclease molecule of claim 1, wherein the hybrid nuclease molecule comprises human DNase1 G105R A114F linked to wild-type, human IgG1.

6. The hybrid nuclease molecule of claim 1, wherein the hybrid nuclease molecule comprises wild-type, human RNase1 linked to wild-type, human IgG1 linked to wild-type, human DNase1.

7. The hybrid nuclease molecule of claim 1, wherein the hybrid nuclease molecule comprises wild-type, human RNase1 linked to wild-type, human IgG1 linked to human DNase1 G105R A114F.

8. The hybrid nuclease molecule of claim 1, wherein the Fc domain binds to an Fc receptor on a human cell.

9. The hybrid nuclease molecule of claim 1, wherein the serum half-life of the molecule is significantly longer than the serum half-life of the first nuclease domain alone.

10. The hybrid nuclease molecule of claim 1, wherein the nuclease activity of the first nuclease domain of the molecule is the same or greater than the nuclease domain alone.

11. The hybrid nuclease molecule of claim 1, wherein administration of the molecule to a mouse increases the survival rate of the mouse as measured by a mouse Lupus model assay.

12. The hybrid nuclease molecule of claim 1, wherein the molecule further comprises a first linker domain, and wherein the first nuclease domain is operatively coupled to the Fc domain by the first linker domain.

13. The hybrid nuclease molecule of claim 12, wherein the hybrid nuclease molecule is a polypeptide, wherein the amino acid sequence of the first nuclease domain comprises a RNase amino acid sequence, wherein the first linker domain is between 5 and 32 amino acids in length, wherein the amino acid sequence of the Fc domain comprises a human, Fc domain amino acid sequence, and wherein the first linker domain is coupled to the C-terminus of the first nuclease domain and the N-terminus of the Fc domain.

14. The hybrid nuclease molecule of claim 12, wherein the hybrid nuclease molecule is a polypeptide, wherein the amino acid sequence of the first nuclease domain comprises a human RNase amino acid sequence, wherein the first linker domain is a NLG peptide between 5 and 32 amino acids in length, wherein the amino acid sequence of the Fc domain comprises a human, wild-type Fc domain amino acid sequence, and wherein the first linker domain is coupled to the C-terminus of the first nuclease domain and the N-terminus of the Fc domain.

15. The hybrid nuclease molecule of claim 1, further comprising a leader sequence.

16. The hybrid nuclease molecule of claim 15, wherein the hybrid nuclease molecule is a polypeptide, and wherein the leader sequence is human VK3LP peptide, and wherein the leader sequence is coupled to the N-terminus of the first nuclease domain.

17. The hybrid nuclease molecule of claim 1, wherein the molecule is a polypeptide.

18. The hybrid nuclease molecule of claim 1, wherein the molecule is a polynucleotide.

19. The hybrid nuclease molecule of claim 1, wherein the first nuclease domain comprises an RNase.

20. The hybrid nuclease molecule of claim 19, wherein the RNase is a human RNase.

21. The hybrid nuclease molecule of claim 19, wherein the hybrid nuclease molecule is a polypeptide, and wherein the RNase is a polypeptide comprising an amino acid sequence at least 90% similar to an RNase amino acid sequence set forth in Table 2.

22. The hybrid nuclease molecule of claim 19, wherein the RNase is human pancreatic RNase1.

23. The hybrid nuclease molecule of claim 1, wherein the first nuclease domain comprises a DNase.

24. The hybrid nuclease molecule of claim 23, wherein the DNase is a human DNase.

25. The hybrid nuclease molecule of claim 23, wherein the hybrid nuclease molecule is a polypeptide, and wherein the DNase is a polypeptide comprising an amino acid sequence at least 90% similar to a DNase amino acid sequence set forth in Table 2.

26. The hybrid nuclease molecule of claim 23, wherein the DNase is selected from the group consisting of human DNase I, TREX1, and human DNase 1L3.

27. The hybrid nuclease molecule of claim 1, wherein the Fc domain is a human Fc domain.

28. The hybrid nuclease molecule of claim 1, wherein the Fc domain is a wild-type Fc domain.

29. The hybrid nuclease molecule of claim 1, wherein the Fc domain is a mutant Fc domain.

30. The hybrid nuclease molecule of claim 1, wherein the Fc domain is a human IgG1 Fc domain.

31. The hybrid nuclease molecule of claim 1, wherein the hybrid nuclease molecule is a polypeptide, and wherein the Fc domain is a polypeptide comprising an amino acid sequence at least 90% similar to an Fc domain amino acid sequence set forth in Table 2.

32. The hybrid nuclease molecule of claim 12, wherein the hybrid nuclease molecule is a polypeptide, and wherein the first linker domain has a length of about 1 to about 50 amino acids.

33. The hybrid nuclease molecule of claim 12, wherein the hybrid nuclease molecule is a polypeptide, and wherein the first linker domain has a length of about 5 to about 32 amino acids.

34. The hybrid nuclease molecule of claim 12, wherein the hybrid nuclease molecule is a polypeptide, and wherein the first linker domain has a length of about 15 to about 25 amino acids.

35. The hybrid nuclease molecule of claim 12, wherein the hybrid nuclease molecule is a polypeptide, and wherein the first linker domain has a length of about 20 to about 32 amino acids.

36. The hybrid nuclease molecule of claim 12, wherein the hybrid nuclease molecule is a polypeptide, and wherein the first linker domain has a length of about 20 amino acids.

37. The hybrid nuclease molecule of claim 12, wherein the hybrid nuclease molecule is a polypeptide, and wherein the first linker domain has a length of about 25 amino acids.

38. The hybrid nuclease molecule of claim 12, wherein the hybrid nuclease molecule is a polypeptide, and wherein the first linker domain has a length of about 18 amino acids.

39. The hybrid nuclease molecule of claim 12, wherein the hybrid nuclease molecule is a polypeptide, and wherein the first linker domain comprises a gly/ser peptide.

40. The hybrid nuclease molecule of claim 39, wherein the gly/ser peptide is of the formula $(Gly_4Ser)n$, wherein n is a positive integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10.

41. The hybrid nuclease molecule of claim 39, wherein the gly/ser peptide comprises $(Gly_4Ser)3$, $(Gly_4Ser)4$, or $(Gly_4Ser)5$.

42. The hybrid nuclease molecule of claim 12, wherein the hybrid nuclease molecule is a polypeptide, and wherein the first linker domain comprises an NLG peptide.

43. The hybrid nuclease molecule of claim 12, wherein the hybrid nuclease molecule is a polypeptide, and wherein the first linker domain comprises an N-linked glycosylation site.

44. The hybrid nuclease molecule claim 1, wherein the hybrid nuclease molecule is a polypeptide, and wherein the first nuclease domain is linked to the N-terminus of the Fc domain.

45. The hybrid nuclease molecule claim 1, wherein the hybrid nuclease molecule is a polypeptide, and wherein the first nuclease domain is linked to the C-terminus of the Fc domain.

46. The hybrid nuclease molecule of claim 1, further comprising a second nuclease domain.

47. The hybrid nuclease molecule of claim 46, wherein the first and second nuclease domains are distinct nuclease domains.

48. The hybrid nuclease molecule of claim 46, wherein the first and second nuclease domains are the same nuclease domains.

49. The hybrid nuclease molecule of claim 46, wherein the hybrid nuclease molecule is a polypeptide, and wherein the second nuclease domain is linked to the C-terminus of the Fc domain.

50. The hybrid nuclease molecule of claim 46, wherein the hybrid nuclease molecule is a polypeptide, and wherein the second nuclease domain is linked to the N-terminus of the Fc domain.

51. The hybrid nuclease molecule of claim 46, wherein the hybrid nuclease molecule is a polypeptide, and wherein the second nuclease domain is linked to the C-terminus of the first nuclease domain.

52. The hybrid nuclease molecule of claim 46, wherein the hybrid nuclease molecule is a polypeptide, and wherein the second nuclease domain is linked to the N-terminus of the first nuclease domain.

53. A dimeric polypeptide comprising a first polypeptide and a second polypeptide, wherein the first polypeptide comprises a first nuclease domain and an Fc domain, wherein the first nuclease domain is operatively coupled to the Fc domain.

54. The dimeric polypeptide of claim 53, wherein the second polypeptide is a second hybrid nuclease molecule comprising a second nuclease domain and a second Fc domain, wherein the second nuclease domain is operatively coupled to the second Fc domain.

55. A pharmaceutical composition comprising at least one hybrid nuclease molecule and/or at least one dimeric polypeptide according to any one of claims 1-54, and a pharmaceutically acceptable excipient.

56. A nucleic acid molecule encoding the hybrid nuclease molecule according to claim 17.

57. A recombinant expression vector comprising a nucleic acid molecule according to claim 56.

58. A host cell transformed with the recombinant expression vector according to claim 57.

59. A method of making the hybrid nuclease molecule of claim 1, comprising: providing a host cell comprising a nucleic acid sequence that encodes the hybrid nuclease molecule; and maintaining the host cell under conditions in which the hybrid nuclease molecule is expressed.

60. A method for treating or preventing a condition associated with an abnormal immune response, comprising administering to a patient in need thereof an effective amount of an isolated hybrid nuclease molecule of claim 1.

61. The method of claim 60, wherein the condition is an autoimmune disease.

62. The method of claim 61, wherein the autoimmune disease is 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.

63. The method of claim 61, wherein the autoimmune disease is SLE.

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.