CLAIMS

We claim:

1. A modified IgG class monoclonal antibody specific for IFNAR1, wherein said antibody comprises in the Fc region at least one amino acid substitution selected from the group consisting of L234F, L235E, and P331S, as numbered by the EU index as set forth in Kabat and wherein said antibody exhibits reduced affinity for at least one Fc ligand compared to an unmodified antibody.
2. The antibody of claim 1, wherein, said antibody is an IgG1 or IgG4 subclass.
3. The antibody of claim 2, wherein said antibody is an IgG1 class molecule.
4. The antibody of claim 3, wherein said antibody comprises an amino acid substitution of P331S.
5. The antibody of claim 3, wherein said antibody comprises the amino acid substitutions: L234F and L235E.
6. The antibody of claim 3, wherein said antibody comprises the amino acid substitutions: L234F, L235E and P331S.
7. The antibody of claim 3 wherein, said antibody is an IgG4 class molecule.
8. The antibody of claim 7 wherein, said antibody comprises an amino acid substitution of L235E of the Fc region.
9. The antibody of claim 7, wherein, said antibody further comprises in the Fc region amino acid substitution S228P.
10. The antibody of any of claims 1-9 wherein, said antibody comprises at least one complementarity determining region (CDR) selected from Table 2.
11. The antibody of any of claims 1-10, wherein, said antibody comprises:
    a. a human heavy chain variable region CDR1 comprising Seq ID NO: 31;
    b. a human heavy chain variable region CDR2 comprising Seq ID NO: 32;
    c. a human heavy chain variable region CDR3 comprising Seq ID NO: 33;
    d. a human light chain variable region CDR1 comprising Seq ID NO: 34;
    e. a human light chain variable region CDR2 comprising Seq ID NO: 35; and
    f. a human light chain variable region CDR3 comprising Seq ID NO: 36.
12. The antibody of any of claims 1-10, wherein, said antibody comprises:
    a. a human heavy chain variable region CDR1 comprising Seq ID NO: 1;
    b. a human heavy chain variable region CDR2 comprising Seq ID NO: 2;
    c. a human heavy chain variable region CDR3 comprising Seq ID NO: 3;

d. a human light chain variable region CDR1 comprising Seq ID NO: 4;

e. a human light chain variable region CDR2 comprising Seq ID NO: 5; and

f. a human light chain variable region CDR3 comprising Seq ID NO: 6.

13. The antibody of any of claims 1-10, wherein, said antibody comprises:

a. a human heavy chain variable region CDR1 comprising Seq ID NO: 11;

b. a human heavy chain variable region CDR2 comprising Seq ID NO: 12;

c. a human heavy chain variable region CDR3 comprising Seq ID NO: 13;

d. a human light chain variable region CDR1 comprising Seq ID NO: 14;

e. a human light chain variable region CDR2 comprising Seq ID NO: 15; and

f. a human light chain variable region CDR3 comprising Seq ID NO: 16.

14. The antibody of any of claims 1-10, wherein, said antibody comprises:

a. a human heavy chain variable region CDR1 comprising Seq ID NO: 21;

b. a human heavy chain variable region CDR2 comprising Seq ID NO: 22;

c. a human heavy chain variable region CDR3 comprising Seq ID NO: 23;

d. a human light chain variable region CDR1 comprising Seq ID NO: 24;

e. a human light chain variable region CDR2 comprising Seq ID NO: 25; and

f. a human light chain variable region CDR3 comprising Seq ID NO: 26.

15. The antibody of any of claims 1-10, wherein, said antibody comprises:

a. a human heavy chain variable region comprising the amino acid sequence of Seq ID No: 38; and

b. a human light chain variable region comprising the amino acid sequence of Seq ID No: 40.

16. The antibody of any of claims 1-10, wherein, said antibody comprises:

a. a human heavy chain variable region comprising the amino acid sequence of Seq ID No: 8; and

b. a human light chain variable region comprising the amino acid sequence of Seq ID No: 10.

17. The antibody of any of claims 1-10, wherein, said antibody comprises:

a. a human heavy chain variable region comprising the amino acid sequence of Seq ID No: 18; and

b. a human light chain variable region comprising the amino acid sequence of Seq ID No: 20.

18. The antibody of any of claims 1-10, wherein, said antibody comprise:

a. a human heavy chain variable region comprising the amino acid sequence of Seq ID No: 28; and
b. a human light chain variable region comprising the amino acid sequence of Seq ID No: 30.

19. The antibody of any of claims 1-18, wherein, said antibody comprises the light chain constant region sequence of Seq ID No: 41.

20. The antibody of any of claims 1-18, wherein, said antibody comprises the heavy chain constant region of Seq ID No: 42.

21. The antibody of any of claims 1-18, wherein, said antibody comprises the light chain constant region having the amino acid sequence of SEQ ID No:41 and the heavy chain constant region having the amino acid sequence of Seq ID No: 42.

22. The antibody of any of claims 19-21, wherein, said antibody comprises a heavy chain amino acid sequence comprising allelic variation, wherein said allelic variation is at least one or more positions selected from the group consisting of 214, 221, 356 and 358 as defined by the EU index numbering system.

23. The antibody of any of the preceding claims wherein, said antibody is selected from the group consisting of: human antibody, humanized antibody, chimeric antibody, intrabody, and a synthetic antibody.

24. An isolated nucleic acid comprising a polynucleotide sequence encoding the antibody of any of the preceding claims.

25. The nucleic acid of claim 24 wherein, said nucleic acid is a replicable vector.

26. The nucleic acid of claim 25 wherein, said polynucleotide sequence is operably linked to a promoter.

27. A host cell comprising or transformed with the vector of claim 25 or 26.

28. A transgenic mouse comprising human immunoglobulin heavy and light chain transgenes, wherein the mouse expresses the antibody of any of claims 1-23.

29. A hybridoma prepared from the mouse of claim 28 wherein the hybridoma produces said antibody.

30. A pharmaceutical composition comprising the antibody of any of the claims 1-23, and a pharmaceutically acceptable excipient.

31. A method of treating a condition or a disease associated with an immune disorder, comprising administering to a subject in need thereof an effective amount of the composition of claim 30.

32. The method of claim 31 wherein said disease is a type I interferon mediated disease.

33. The method of claim 32 wherein said type I interferon is interferon alpha.

34. The method of claim 33 wherein said type I interferon mediated disease is associated with the type I interferon receptor.

35. The method of claim 31, wherein said disease or disorder is HIV infection of AIDS.

36. The method of claim 31, wherein said disease or disorder is systemic lupus erythematosus.

37. The method of claim 31, wherein said disease or disorder is Sjogren's syndrome.

38. The method of claim 31, wherein said disease or disorder is myositis.

39. The method of claim 31, wherein said disease or disorder is inflammatory myositis.

40. The method of claim 31, wherein said disease or disorder is polymyositis.

41. The method of claim 31, wherein said disease or disorder is dermatomyositis.

42. The method of claim 31, wherein said disease or disorder is inclusion body myositis.

43. The method of claim 31, wherein said disease or disorder is juvenile myositis.

44. The method of claim 31, wherein said disease or disorder is idiopathic inflammatory myositis.

45. The method of claim 31, wherein said disease or disorder is vasculitis.

46. The method of claim 31, wherein said disease or disorder is sarcoidosis.

47. The method of claim 31, wherein said disease or disorder is selected from the group consisting of: inflammatory bowel disease, multiple sclerosis, autoimmune thyroiditis, rheumatoid arthritis, insulin dependent diabetes mellitus, glomerulonephritis, and graft versus host disease.

48. The method of claim 31, wherein said disease or disorder is psoriasis or conditions resulting thereof.

49. The method of claim 31, wherein said disease or disorder is transplant rejection or graft versus host disease.

50. The method of claim 31 wherein said disease or disorder is selected from the group consisting of: Grave's disease, Hashimoto's thyroiditis, Crohn's disease, psoriasis, psoriatic arthritis, sympathetic opthalmitis, autoimmune oophoritis, autoimmune orchitis, autoimmune lymphoproliferative syndrome, antiphospholipid syndrome. Sjogren's syndrome, scleroderma, Addison's disease, polyendocrine deficiency syndrome, Guillan-Barre syndrome, immune thrombocytopenic purpura, pernicious anemia, myasthenia gravis, primary biliary cirrhosis, mixed connective tissue disease, vitiligo, autoimmune uveitis, autoimmune hemolytic anemia, autoimmune thrombopocytopenia, celiac disease, dermatitis herpetiformis, autoimmune hepatitis, pemphigus, pemphigus vulgaris,

pemphigus foliaceus, bullous pemphigoid, autoimmune myocarditis, autoimmune vasculitis, alopecia areata, autoimmune artherosclerosis, Behcet's disease, autoimmune myelopathy, autoimmune hemophelia, autoimmune interstitial cystitis, autoimmune diabetes isipidus, autoimmune endometriosis, relapsing polychondritis, ankylosing spondylitis, autoimmune urticaria, dermatomyositis, Miller-Fisher syndrome, IgA nephropathy, goodpastures syndrome, and herpes gestationis.

51. The method of any of claims 31-50, further comprising administering at least one agent selected from the group consisting of: phototherapy, corticosteroids, prednisone, NSAIDS, plasmapheresis, immunosuppressants, methotrexate, retinoic acid, tioguanine, mycophenolate mofetil, fumaric esters, cyclophosphamide, azathioprine, cyclosporine, and immunoglobulins.

52. The method of any of claims 31-51 further comprising administering at least one agent selected from the group consisting of: alefacept (AMEVIVE™), etanercept (ENBREL®), adalimumab (HUMIRA®), infliximab (REMICADE®), belimumab (LYMPHOSTATB™), rituxumab (RITUXAN®), and efalizumab (RAPTIVA®).

53. A crystal comprising a human IgG Fc region, wherein the human IgG Fc region comprises at least one amino acid substitution selected from the group consisting of L234F, L235E, and P331S, as numbered by the EU index as set forth in Kabat and wherein said fragment exhibits reduced affinity for at least one Fc ligand compared to an unmodified Fc region.

54. The crystal of Claim 53, wherein the human IgG Fc region comprises the amino acid substitutions L234F, L235E and P331S.

55. The crystal of Claim 53, which is diffraction quality.

56. The crystal of Claim 53, which is a native crystal.

57. The crystal of Claim 53, which is characterized by an orthorhombic unit cell of a=50.18±0.2 Å, b=147.30±0.2 Å, and c=75.47 ±0.2 Å.

58. The crystal of Claim 53, which has a space group of $C222_1$.

59. A modified monoclonal antibody, wherein said antibody comprises in the Fc region the amino acid substitutions L234F, L235E, and P331S, as numbered by the EU index as set forth in Kabat and wherein said antibody exhibits reduced affinity for at least one Fc ligand compared to an unmodified antibody.

60. A fusion protein comprising a modified Fc region, wherein said Fc region comprises the amino acid substitutions L234F, L235E, and P331S, as numbered by the EU index as set

forth in Kabat and wherein said Fc region exhibits reduced affinity for at least one Fc ligand compared to an Fc region.

61. A method of making the antibody of any of claims 1-23 or 59.

62. The antibody of any of claims 1-23 or 59, wherein said antibody is an internalizing antibody.

63. The fusion protein of claim 60, wherein said fusion protein is an internalizing fusion protein.

64. The fusion protein of claim 63, wherein said fusion protein specifically binds IFNAR1.

65. The antibody of any of claims 1-23, 59, or 62, wherein said antibody exhibits reduced or ablated antibody dependent cell-mediated cytotoxicity (ADCC) as compared to said unmodified antibody.

66. The antibody of any of claims 1-23, 59, or 62, wherein said antibody exhibits reduced or ablated complement mediated cytotoxicity (CDC) as compared to said unmodified antibody.

67. The antibody of any of claims 1-23, 59, or 62, wherein said antibody exhibits reduced or ablated ADCC and CDC as compared to said unmodified antibody.

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35 40 45

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35 40 45

Gly Glu Ile Ile Leu Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80

Asn Leu Thr Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
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Gly Ile Ile Tyr Pro Gly Asp Ser Asp Ile Arg Tyr Ser Pro Ser Phe
    50                  55                  60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Thr Thr Ala Tyr
65                  70                  75                  80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg His Asp Ile Glu Gly Phe Asp Tyr Trp Gly Arg Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115
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<210> 39
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<400> 39
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120

cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca
180

gacaggttaa gtggcagtgg gtctgggaca gacttcactc tcaccatcac cagactggag
240

cctgaagatt ttgcagtgta ttactgtcag cagtatgata gctcagcgat caccttcggc
300

caagggacac gactggagat taaa
324

<210> 40
<211> 108
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<220>
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<400> 40

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Phe Phe Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Leu Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asp Ser Ser Ala
85 90 95

Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 41
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
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<400> 41

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1 5 10 15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
20 25 30

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Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
        35                  40                  45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
    50                  55                  60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65                  70                  75                  80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
                85                  90                  95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
            100                 105
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<210> 42
<211> 330
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct

<400> 42

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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110
```

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Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                325                 330
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<210> 43
<211> 41

<212> DNA
<213> Artificial Sequence

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<400> 43
cgtgcccagc acctgaattc gagggggggac cgtcagtctt c
41

<210> 44
<211> 41
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<400> 44
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41

<210> 45
<211> 41
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<400> 45
ccaacaaagc cctcccagcc tccatcgaga aaaccatctc c
41

<210> 46
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<400> 46
ggagatggtt ttctcgatgg aggctgggag ggctttgttg g
41

<210> 47
<211> 31
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<400> 47
ggtcccccat gcccaccatg cccagcacct g
31

<210> 48
<211> 31
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<400> 48
caggtgctgg gcatggtggg catgggggac c
31

<210> 49
<211> 33
<212> DNA
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<220>
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33

<210> 50
<211> 33
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<220>
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<400> 50
gactgatggt ccccctcga actcaggtgc tgg
33

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<110> MedImmune LLC.

<120> Anti-IFNAR1 antibodies with reduced Fc ligand affinity

<130> IA161PCT

<150> US 61/006,962
<151> 2008-02-08

<150> US 61/034,618
<151> 2008-03-07

<150> US 61/049,970
<151> 2008-05-02

<160> 50

<170> PatentIn version 3.5

<210> 1
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Arg Ala Ser Gln Gly Ile Tyr Ser Val Leu Ala
1 5 10

<210> 2
<211> 7
<212> PRT
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<220>
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<400> 2

Asp Ala Ser Arg Leu Glu Ser
1 5

<210> 3
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct

<400> 3

Gln Gln Phe Asn Ser Tyr Ile Thr
1 5

<210> 4
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct

<400> 4

Gly Tyr Phe Trp Ser
1 5

<210> 5
<211> 16
<212> PRT
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<220>
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<400> 5

Glu Ile Asp His Ser Gly Lys Thr Asn Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 6
<211> 10
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<213> Artificial Sequence

<220>
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<400> 6

Glu Ser Lys Tyr Tyr Phe Gly Leu Asp Val
1 5 10

<210> 7
<211> 354
<212> DNA
<213> Artificial Sequence

<220>
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60

acctgcgctg tctatggtgg gtccttcagt ggttatttct ggagctggat ccgccagccc
120

ccagggaagg ggctggagtg gattggggaa atcgatcaca gtggaaagac caactacaat
180

ccgtccctca agagtcgagt taccatatca gtagacacgt ccaagaacca ggtctccctg
240

aagctgagct ctgtgaccgc cgcggacacg gctgtgtatt actgtgcgag agaaagcaag
300

tactacttcg gtttggacgt ctggggccaa gggaccacgg tcaccgtcac ctca
354

<210> 8
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
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<400> 8

Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr
20 25 30

Phe Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Asp His Ser Gly Lys Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Val Ser Leu
65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Glu Ser Lys Tyr Tyr Phe Gly Leu Asp Val Trp Gly Gln Gly Thr
100 105 110

Thr Val Thr Val Thr Ser
115

<210> 9
<211> 318
<212> DNA
<213> Artificial Sequence

<220>
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60

atcacttgcc gggcaagtca gggcatttac agtgttttag cctggtatca gcagaaacca
120

gggaaaactc ctaagctcct gatctatgat gcctcccgtt tggaaagtgg ggtcccatca
180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct
240

gaagattttg caacttatta ctgtcaacag tttaatagtt acatcacctt cggccaaggg
300

acacgactgg agattaaa
318

<210> 10
<211> 106
<212> PRT
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<220>
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<400> 10

Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Tyr Ser Val
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Thr Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Arg Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Asn Ser Tyr Ile Thr
85 90 95

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 11
<211> 11
<212> PRT
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<220>
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<400> 11

Arg Ala Thr Gln Asp Ile Ser Ile Ala Leu Val
1 5 10

<210> 12
<211> 7
<212> PRT
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<220>
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<400> 12

Asp Ala Ser Gly Leu Gly Ser
1 5

<210> 13
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct

<400> 13

Gln Gln Phe Asn Ser Tyr Pro Tyr Thr
1 5

<210> 14
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
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<400> 14

Asn Tyr Tyr Trp Ser
1 5

<210> 15
<211> 16
<212> PRT
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<220>
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<400> 15

Glu Ile Ile Leu Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 16
<211> 10
<212> PRT
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<220>
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<400> 16

Glu Ser Lys Trp Gly Tyr Tyr Phe Asp Ser
1 5 10

<210> 17
<211> 354
<212> DNA
<213> Artificial Sequence

<220>
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60

acctgcgctg tctatggtgg gtccttcagt aattactact ggagctggat ccgccagccc
120

ccagggaagg ggctggagtg gattggggaa atcattctta gtggaagcac caactacaac
180

ccgtccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg
240

aacctgacct ctgtgaccgc cgcggacacg gctgtgtatt actgtgcgag agagtctaaa
300

tggggttact actttgactc ctggggccag ggaaccctgg tcaccgtctc ctca
354

<210> 18
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct

<400> 18

Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Asn Tyr
20 25 30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Ile Leu Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80

Asn Leu Thr Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Glu Ser Lys Trp Gly Tyr Tyr Phe Asp Ser Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 19
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
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60

atcacttgcc gggcaactca ggacattagc attgctttag tctggtatca gcagaaacca
120

gggaaagctc ctgagctcct gatctatgat gcctccggtt tgggaagtgg ggtcccatca
180

aggttcagcg gcagtggatc tggcacagat ttcactctca ccatcagcag cctgcagcct
240

gaagattttg caacttatta ctgtcaacag tttaatagtt acccgtacac ttttggccag
300

gggaccaagc tggagatcaa a
321

<210> 20
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
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<400> 20

Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Thr Gln Asp Ile Ser Ile Ala
20 25 30

Leu Val Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Glu Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Gly Leu Gly Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Asn Ser Tyr Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 21
<211> 12
<212> PRT

<213> Artificial Sequence

<220>
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<400> 21

Arg Ala Ser Gln Ser Val Ser Ser Ser Phe Phe Ala
1 5 10

<210> 22
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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<400> 22

Gly Ala Ser Ser Arg Ala Thr
1 5

<210> 23
<211> 10
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<220>
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<400> 23

Gln Gln Tyr Tyr Asp Ser Ser Ala Ile Thr
1 5 10

<210> 24
<211> 5
<212> PRT
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<220>
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<400> 24

Asn Tyr Trp Ile Ala
1 5

<210> 25
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
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<400> 25

Ile Ile Tyr Pro Gly Asp Ser Asp Ile Arg Tyr Ser Pro Ser Phe Gln
1 5 10 15

Gly

<210> 26
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
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<400> 26

His Asp Ile Glu Gly Phe Asp Tyr
1 5

<210> 27
<211> 351
<212> DNA
<213> Artificial Sequence

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<400> 27
gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc
60

tcctgtaagg gttctggata catctttacc aattactgga tcgcctgggt gcgccagatg
120

cccggtaaag gcctggagtc gatggggatc atctatcctg gtgactctga tatcagatac
180

agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcac caccgcctac
240

ctgcagtgga gcagtctgaa ggcctcagac accgccatgt attactgtgc gagacatgac
300

atagaggggt ttgactactg gggccgggga accctggtca ccgtctcctc a
351

<210> 28
<211> 117
<212> PRT

<213> Artificial Sequence

<220>
<223> synthetic construct

<400> 28

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ile Phe Thr Asn Tyr
20 25 30

Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Ser Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Ile Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Thr Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg His Asp Ile Glu Gly Phe Asp Tyr Trp Gly Arg Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 29
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<220>
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<400> 29
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60

ctctcctgca gggccagtca gagtgttagc agcagcttct tcgcctggta ccagcagaaa
120

cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca
180

gacaggttaa gtggcagtgg gtctgggaca gacttcactc tcaccatcac cagactggag
240

cctgaagatt ttgcagtgta ttactgtcag cagtatgata gctcagcgat caccttcggc
300

caagggacac gactggagat taaa
324

<210> 30
<211> 108
<212> PRT
<213> Artificial Sequence

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<400> 30

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Phe Phe Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Leu Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asp Ser Ser Ala
85 90 95

Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 31
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<212> PRT
<213> Artificial Sequence

<220>
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<400> 31

Arg Ala Ser Gln Ser Val Ser Ser Ser Phe Phe Ala
1 5 10

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<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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<400> 32

Gly Ala Ser Ser Arg Ala Thr
1 5

<210> 33
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<212> PRT
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<400> 33

Gln Gln Tyr Asp Ser Ser Ala Ile Thr
1 5

<210> 34
<211> 5
<212> PRT
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<220>
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<400> 34

Asn Tyr Trp Ile Ala
1 5

<210> 35
<211> 17
<212> PRT
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<220>
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<400> 35

Ile Ile Tyr Pro Gly Asp Ser Asp Ile Arg Tyr Ser Pro Ser Phe Gln
1 5 10 15

Gly

<210> 36
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
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<400> 36

His Asp Ile Glu Gly Phe Asp Tyr
1 5

<210> 37
<211> 351
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tcctgtaagg gttctggata catctttacc aactactgga tcgcctgggt gcgccagatg
120

cccggtaaag gcctggagtc gatggggatc atctatcctg gtgactctga tatcagatac
180

agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcac caccgcctac
240

ctgcagtgga gcagtctgaa ggcctcagac accgccatgt attactgtgc gagacatgac
300

atagaggggt ttgactactg gggccgggga accctggtca ccgtctcctc a
351

<210> 38
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<212> PRT
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<400> 38

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Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1               5                   10                  15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ile Phe Thr Asn Tyr
            20                  25                  30

Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Ser Met
        35                  40                  45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Ile Arg Tyr Ser Pro Ser Phe
    50                  55                  60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Thr Thr Ala Tyr
65                  70                  75                  80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg His Asp Ile Glu Gly Phe Asp Tyr Trp Gly Arg Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115
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<210> 39
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<400> 39
gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc
60

ctctcctgca gggccagtca gagtgttagc agcagcttct tcgcctggta ccagcagaaa
120

cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca
180

gacaggttaa gtggcagtgg gtctgggaca gacttcactc tcaccatcac cagactggag
240

cctgaagatt ttgcagtgta ttactgtcag cagtatgata gctcagcgat caccttcggc
300

caagggacac gactggagat taaa
324

<210> 40
<211> 108
<212> PRT
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<220>
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<400> 40

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Phe Phe Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Leu Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asp Ser Ser Ala
85 90 95

Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 41
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct

<400> 41

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1 5 10 15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
20 25 30

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Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
        35                  40                  45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
    50                  55                  60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65                  70                  75                  80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
                85                  90                  95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
            100                 105
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<210> 42
<211> 330
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct

<400> 42

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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110
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Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
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Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
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Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
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Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
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CLAIMS

We claim:

1. A modified IgG class monoclonal antibody specific for IFNAR1, wherein said antibody comprises in the Fc region at least one amino acid substitution selected from the group consisting of L234F, L235E, and P331S, as numbered by the EU index as set forth in Kabat and wherein said antibody exhibits reduced affinity for at least one Fc ligand compared to an unmodified antibody.
2. The antibody of claim 1, wherein, said antibody is an IgG1 or IgG4 subclass.
3. The antibody of claim 2, wherein said antibody is an IgG1 class molecule.
4. The antibody of claim 3, wherein said antibody comprises an amino acid substitution of P331S.
5. The antibody of claim 3, wherein said antibody comprises the amino acid substitutions: L234F and L235E.
6. The antibody of claim 3, wherein said antibody comprises the amino acid substitutions: L234F, L235E and P331S.
7. The antibody of claim 3 wherein, said antibody is an IgG4 class molecule.
8. The antibody of claim 7 wherein, said antibody comprises an amino acid substitution of L235E of the Fc region.
9. The antibody of claim 7, wherein, said antibody further comprises in the Fc region amino acid substitution S228P.
10. The antibody of any of claims 1-9 wherein, said antibody comprises at least one complementarity determining region (CDR) selected from Table 2.
11. The antibody of any of claims 1-10, wherein, said antibody comprises:
    a. a human heavy chain variable region CDR1 comprising Seq ID NO: 31;
    b. a human heavy chain variable region CDR2 comprising Seq ID NO: 32;
    c. a human heavy chain variable region CDR3 comprising Seq ID NO: 33;
    d. a human light chain variable region CDR1 comprising Seq ID NO: 34;
    e. a human light chain variable region CDR2 comprising Seq ID NO: 35; and
    f. a human light chain variable region CDR3 comprising Seq ID NO: 36.
12. The antibody of any of claims 1-10, wherein, said antibody comprises:
    a. a human heavy chain variable region CDR1 comprising Seq ID NO: 1;
    b. a human heavy chain variable region CDR2 comprising Seq ID NO: 2;
    c. a human heavy chain variable region CDR3 comprising Seq ID NO: 3;

d. a human light chain variable region CDR1 comprising Seq ID NO: 4;

e. a human light chain variable region CDR2 comprising Seq ID NO: 5; and

f. a human light chain variable region CDR3 comprising Seq ID NO: 6.

13. The antibody of any of claims 1-10, wherein, said antibody comprises:

a. a human heavy chain variable region CDR1 comprising Seq ID NO: 11;

b. a human heavy chain variable region CDR2 comprising Seq ID NO: 12;

c. a human heavy chain variable region CDR3 comprising Seq ID NO: 13;

d. a human light chain variable region CDR1 comprising Seq ID NO: 14;

e. a human light chain variable region CDR2 comprising Seq ID NO: 15; and

f. a human light chain variable region CDR3 comprising Seq ID NO: 16.

14. The antibody of any of claims 1-10, wherein, said antibody comprises:

a. a human heavy chain variable region CDR1 comprising Seq ID NO: 21;

b. a human heavy chain variable region CDR2 comprising Seq ID NO: 22;

c. a human heavy chain variable region CDR3 comprising Seq ID NO: 23;

d. a human light chain variable region CDR1 comprising Seq ID NO: 24;

e. a human light chain variable region CDR2 comprising Seq ID NO: 25; and

f. a human light chain variable region CDR3 comprising Seq ID NO: 26.

15. The antibody of any of claims 1-10, wherein, said antibody comprises:

a. a human heavy chain variable region comprising the amino acid sequence of Seq ID No: 38; and

b. a human light chain variable region comprising the amino acid sequence of Seq ID No: 40.

16. The antibody of any of claims 1-10, wherein, said antibody comprises:

a. a human heavy chain variable region comprising the amino acid sequence of Seq ID No: 8; and

b. a human light chain variable region comprising the amino acid sequence of Seq ID No: 10.

17. The antibody of any of claims 1-10, wherein, said antibody comprises:

a. a human heavy chain variable region comprising the amino acid sequence of Seq ID No: 18; and

b. a human light chain variable region comprising the amino acid sequence of Seq ID No: 20.

18. The antibody of any of claims 1-10, wherein, said antibody comprise:

a. a human heavy chain variable region comprising the amino acid sequence of Seq ID No: 28; and

b. a human light chain variable region comprising the amino acid sequence of Seq ID No: 30.

19. The antibody of any of claims 1-18, wherein, said antibody comprises the light chain constant region sequence of Seq ID No: 41.

20. The antibody of any of claims 1-18, wherein, said antibody comprises the heavy chain constant region of Seq ID No: 42.

21. The antibody of any of claims 1-18, wherein, said antibody comprises the light chain constant region having the amino acid sequence of SEQ ID No:41 and the heavy chain constant region having the amino acid sequence of Seq ID No: 42.

22. The antibody of any of claims 19-21, wherein, said antibody comprises a heavy chain amino acid sequence comprising allelic variation, wherein said allelic variation is at least one or more positions selected from the group consisting of 214, 221, 356 and 358 as defined by the EU index numbering system.

23. The antibody of any of the preceding claims wherein, said antibody is selected from the group consisting of: human antibody, humanized antibody, chimeric antibody, intrabody, and a synthetic antibody.

24. An isolated nucleic acid comprising a polynucleotide sequence encoding the antibody of any of the preceding claims.

25. The nucleic acid of claim 24 wherein, said nucleic acid is a replicable vector.

26. The nucleic acid of claim 25 wherein, said polynucleotide sequence is operably linked to a promoter.

27. A host cell comprising or transformed with the vector of claim 25 or 26.

28. A transgenic mouse comprising human immunoglobulin heavy and light chain transgenes, wherein the mouse expresses the antibody of any of claims 1-23.

29. A hybridoma prepared from the mouse of claim 28 wherein the hybridoma produces said antibody.

30. A pharmaceutical composition comprising the antibody of any of the claims 1-23, and a pharmaceutically acceptable excipient.

31. A method of making the antibody of any of claims 1-23.

32. The antibody of any of claims 1-23, wherein said antibody is an internalising antibody.