

Example 11

Cell test of anti-IL17A 3VHHIgG1VK4B11 mutants blocking the ability of IL-17A to induce IL-6 production

The ability of IL-17 to induce the production of IL-6 by HT1080 human cells (ATCC:CCL-121) was used to analyze the neutralizing activity of VHHIgG1 candidates mut1 and mut4 regarding human recombinant IL-17A. Cells were grown on DMEM culture medium with added 10% inactivated fetal serum, gentamycin and glutamine. Aliquots of 5×10^4 cells per well were seeded in 96-well culture plates. Cells were allowed for attachment for 5 hours. The mixture of 40 ng/ml recombinant IL-17 and 20 ng/ml TNF- α was incubated with VHHIgG1 dilutions for 1 hour at 37°C. Then cytokine/antibody mixture was added to the cells and left overnight. The production of IL-6 by HT1080 cell culture was proportional to the amount of IL-17 added. The amount of the released IL-6 in cell supernatant samples was evaluated by ELISA technique using DuoSet ELISA Development System Human IL6 (RD System, Cat. No. DY206). The results of evaluation of the antagonistic properties of VHHIgG1 candidates are presented at Figure 14 in comparison with AIN457 (anti-IL-17A antibody by Novartis). The IC₅₀ value for mut1 was almost 30 times higher than that for the natural variant, while mut4 variant almost completely maintained its inhibiting capacity. The value of IC₅₀ for mut4 candidate was 30 ± 10 pM. Following the results of the present study and the overall physical-chemical and biological characteristics, the said candidate was selected for further development and optimization.

Example 12

Engineering of mut4VHHFab antibodies comprising human light chains

The total RNA of B-lymphocytes collected from 55 human donors was isolated with RNeasy Mini Kit, in accordance with the appropriate protocol (QIAGEN). RNA concentration was measured with Nanovue kit (GE Healthcare), and the quality of isolated RNA was tested by 1.5% agarose gel electrophoresis.

CLAIMS:

1. A humanized monoclonal IgG antibody that specifically binds to human IL-17A, wherein the variable domains are represented by a combination of V_{HH}-derivative with a variable domain of the light chain V_L, comprising

a) a derivative of Camelidae heavy chain variable domain (VHH) that comprises 3 hypervariable regions HCDR1, HCDR2 and HCDR3, wherein:

HCDR1 comprising the amino acid sequence of SEQ ID NO: 1:

G-T-F-A-T-X32-X33-X34 - X35, wherein

X32 is an amino acid selected from the group comprising S, N, K, R, E, W, Q, D, A, V and F;

X33 is an amino acid selected from the group comprising P or S;

X34 is an amino acid selected from the group comprising M and I;

X35 is an amino acid selected from the group comprising G, N, S, A, L, I, R, V and Q;

HCDR2 comprising the amino acid sequence of SEQ ID NO: 2:

X50-I-X52-X52a-S-G-X55-D-R-I-Y-A-D-S-V-K-G, wherein

X50 is an amino acid selected from the group comprising A, G and L;

X52 is an amino acid selected from the group comprising S, D and E;

X52a is an amino acid selected from the group comprising P and A;

X55 is an amino acid selected from the group comprising G, S, T, L, R, D, E, K, A and W;

HCDR3 comprising the amino acid sequence of SEQ ID NO: 3:

C-A- X94-X95- X96- X97-F-X99-X100-X100a- X100b - X100c - X100d - X100e - X100f – D- Y – D-S, wherein

X94 is an amino acid selected from the group comprising K, S, T, V, D and G;

X95 is an amino acid selected from the group comprising R and K;

X96 is an amino acid selected from the group comprising G, R, Y, H, D, W and K;

X97 is an amino acid selected from the group comprising R, A, V, S, L and H;

X99 is an amino acid selected from the group comprising D, E, G, A, R, V, K and Q;

X100 is an amino acid selected from the group comprising G, S and N;

X100a is an amino acid selected from the group comprising G, T, P, V, R, N and K;

X100b is an amino acid selected from the group comprising V, S, T, L, Y, A, H, G and I;

X100c is an amino acid selected from the group comprising Y, W and S;

X100d is an amino acid selected from the group comprising R, V, L, Y, A, W, K, G, Q and I;

X100e is an amino acid selected from the group comprising T, L, A and S;

X100f is an amino acid selected from the group comprising T, L, G, P, N, A, Q, F, I and D;

b) a variable domain of the light chain (VL) of a human antibody or a variable domain of the light chain of a humanized antibody.

2. An antibody according to Claim 1, characterized by increased aggregation stability of V_{HH} -derivative compared to the native VHH antibody isolated from an immunized animal from Camelidae family.

3. An antibody according to Claim 1, wherein the variable domain of the light chain V_L is a human antibody derivative.

4. An antibody according to Claim 1, wherein the variable domain of the light chain V_L is a humanized fragment of an antibody, preferably mammalian.

5. An antibody according to Claim 1, wherein said antibody is one of any of the following isotypes: IgG1, IgG2, IgG3 or IgG4.

6. An antibody according to Claim 10, comprising a non-native modified Fc as a

part of IgG.

7. An antibody according to Claim 1, characterized by such aggregation stability that when used in concentrations over 10 mg/ml and stored for >6 months at a temperature of 4°C the content of aggregates increases by not more than 5% of their initial content in the solution.

8. An antibody according to Claim 1, characterized by such aggregation stability that when used in concentrations over 10 mg/ml and stored for >2 weeks at a temperature of 37°C the content of aggregates increases by not more than 5% of their initial content in the solution.

9. An antibody according to Claim 1, characterized by such aggregation stability that when used in concentrations over 10 mg/ml and stored for >48h at a temperature of 42°C the content of aggregates increases by not more than 5% of their initial content in the solution.

10. An antibody according to Claim 1, characterized by such aggregation stability that when used in concentrations over 10 mg/ml and stored for > 6 h at a temperature of 50°C the content of aggregates increases by not more than 5% of their initial content in the solution.

11. An antibody according to Claims 1-10 that specifically binds to human IL-17A, comprising:

a) A derivative of the heavy chain variable domain (V_{HH}) comprising 3 hypervariable regions HCDR1, HCDR2 и HCDR3, wherein:

HCDR1 comprising the amino acid sequence of G-T-F-A-T-S-P-M-G (SEQ ID NO: 4);

HCDR2 comprising the amino acid sequence of A-I-S-P-S-G-G- D-R-I-Y-

A-D-S-V-K-G (SEQ ID NO: 5);

HCDR3 comprising the amino acid sequence of C-A-V-R-R-R-F-D-G-T-S-Y-Y-T-G-D-Y-D-S (SEQ ID NO: 6);

b) A variable domain of the light chain (V_L) of a human antibody or a variable domain of the light chain of a humanized antibody.

12. An antibody according to Claim 11 that specifically binds to human IL-17A, comprising:

a) A derivative of the heavy chain variable domain (V_{HH}) comprising an amino acid sequence

QVQLVQSGGGLVQAGGSLRLSCAASGGTFATSPMGWLRQAPGKG
TEFVAAISPSGGDRIYADSVKGRFTISRDNAGYFIYLMNSLKPEDTAVYY
C AVRRRFDGTSYYTGDYDSWGQGTLLTVSS (SEQ ID NO: 7);

b) A variable domain of the light chain (V_L) of a human antibody or a variable domain of the light chain of a humanized antibody.

13. An antibody according to Claim 12 that specifically binds to human IL- 17A, comprising:

a) The VHH-derivative comprising the amino acid sequence of SEQ ID NO: 7;

b) The variable domain of the light chain (V_L) of a human antibody comprising the amino acid sequence of

EIVLTQSPGTLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLL
IYDASSRATGIPDRFSGSGSGTDFTLISRLEPEDFAVYYCQQYSYSPVTFG
Q GTKVEIKR (SEQ ID NO: 8).

14. An antibody according to Claims 1-10 that specifically binds human IL- 17A and comprises:

a) The heavy chain comprising the following amino acid sequence:

QVQLVQSGGGLVQAGGSLRLSCAASGGTFATSPMGWLRQAPGKGT

EFVAAISPSGGDRIYADSVKGRFTISRDNAGYFIYLQMNSLKPEDTAVYYC
AVRRRFDGTSYYTG DYDSWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGT
AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS
SSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVF
LFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP
REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG
QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
KTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSL
SLSPGK (SEQ ID NO: 9).

b) The variable domain of a human antibody light chain (V_L) comprising the following amino acid sequence:

EIVLTQSPGTLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRL
LIYDASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYSYSPVTFG
QGTEVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV
DNALQSGNSQESVTEQDSKDSSTLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC (SEQ ID NO: 10).

15. An antibody according to Claim 1, wherein said antibody has the binding affinity to human IL-17A characterized with K_D of 10^{-10} M and lower.

16. An antibody according to Claim 1, wherein the kinetic association constant $k_{on}(1/Mc)$ for human IL-17A is not less than 10^5 1/Msec.

17. An antibody according to Claim 1, wherein the kinetic dissociation constant $dis(1/s)$ for human IL-17A is not more than 10^{-5} 1/sec.

18. An antibody according to Claim 1, wherein said antibody inhibits the activity of human IL-17A by no less than 50 %.

19. An antibody according to Claim 1, wherein said antibody is produced by

mammalian, yeast or bacterial cells.

20. Fragment of an antibody according to Claims 1- 19.

21. Fragment of an antibody according to Claim 20, wherein said fragment is represented by a light chain, heavy chain, and variable domains of the light and/or heavy chain that are a part of an antibody sequence, which includes a bio-specific antibody variant.

22. Fragment of an antibody according to Claim 21, wherein said fragment is represented by a light chain, heavy chain, and variable domains of the light and/or heavy chain that are parts of Fab.

23. Fragment of an antibody according to Claim 21, wherein said fragment is represented by a light chain, heavy chain, and variable domains of the light and/or heavy chain that are parts of scFv.

24. Methods of production of antibodies according to any of Claims 1 - 19 or fragments thereof according to Claims 20-23, involving phases selected from the following: directed mutagenesis, display methods, genetic engineering, biochemistry and high-performance biotechnology methods, which can include the methods for directed mutagenesis at different positions of the VHH domain of Camelidae antibodies.

25. A DNA construct encoding an antibody according to any of Claims 1 - 19 or an antibody fragment according to any of Claims 20-23.

26. An expression vector comprising one or several DNA constructs according to Claim 25.

27. A cell line comprising the expression vector according to Claim 26 or DNA

construct according to Claim 25.

28. Method of production of a humanized monoclonal antibody according to Claims 1- 19 or an antibody fragment according to Claims 20-23, which involves incubation of a cell line according to Claim 27 in a culture medium under the conditions sufficient to obtain said antibody or fragment thereof, followed by the isolation and purification of obtained antibody or its active fragment.

29. A host cell comprising the vector according to Claim 26.

30. Method of production of an antibody according to any of Claims 1-19 or an antibody fragment according to Claims 20-23, which involves incubation of a cell line according to Claim 29 in a culture medium under the conditions sufficient to obtain said antibody or fragment thereof, followed by isolation and purification of obtained antibody or its active fragment

31. A pharmaceutical composition comprising an antibody according to any of Claims 1-19 or fragments thereof according to Claims 20-23, in combination with one or several pharmaceutically suitable excipients, diluents or carriers.

32. A pharmaceutical composition according to Claim 31, further comprising active pharmaceutical ingredients selected from TNF- α inhibitors.

33. A pharmaceutical composition according to Claim 31, to be used in the therapy of IL-17A-mediated disease or disorder.

34. A pharmaceutical composition according to Claim 33, wherein an IL-17A-mediated disease or disorder is selected from: rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, psoriatic arthritis, reactive arthritis, spondyloarthropathy, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, inflammatory bowel disease, asthma, allergic disorders, psoriasis, dermatitis, systemic sclerosis,

graft-versus-host disease, graft rejection, acute or chronic immune disease associated with organ grafting, sarcoidosis, atherosclerosis, chronic fatigue syndrome, Wegener's disease, Henoch-Schonlein purpura, microscopic polyangiitis with renal involvement, chronic active hepatitis, uveitis, cachexia, acute transverse myelitis, primary biliary cirrhosis, polyglandular autoimmune syndrome type I and type II, Schmidt's syndrome, acute respiratory distress syndrome, alopecia, alopecia areata, seronegative arthropathy, arthropathy, Reiter's syndrome, psoriatic arthropathy, arthropathy associated with ulcerative colitis, enteropathic synovitis, spondyloarthropathy, atheromatosis disease/coronary sclerosis, atopic allergy, autoimmune bullous disease, pemphigus, pemphigus foliaceus, pemphigoid, linear iga diseases, autoimmune hemolytic anemia, Coombs positive hemolytic anemia, Myalgic encephalomyelitis/chronic fatigue syndrome, chronic active hepatic inflammation, cranial giant arteritis, primary sclerosing hepatitis, cryptogenic autoimmune hepatitis, pulmonary fibrosis, cryptogenic fibrosing alveolitis, systemic scleroderma associated with interstitial lung disease, rheumatoid arthritis associated with interstitial lung disease, systemic lupus erythematosus associated with lung disease, dermatomyositis/polymyositis associated with lung disease, Sjogren disease associated with lung disease, ankylosing spondylitis associated with lung disease, diffuse pulmonary vasculitis, fibrosis, lung disease with lymphocyte infiltration, autoimmune hepatitis, autoimmune hepatitis type I (classic autoimmune or lupoid hepatitis), autoimmune hepatitis type II (associated with anti-LKM antibody), autoimmune hypoglycemia, acute graft-associated immune disease, chronic graft-associated immune disease, osteoarthritis, primary sclerosing cholangitis, type I psoriasis, type II psoriasis, discoid lupus erythematosus, multiple sclerosis (all types), sympathetic ophthalmia, pulmonary hypertension secondary to connective tissue disease, Goodpasture syndrome, pulmonary manifestations of polyarteritis nodosa, acute rheumatic fever, rheumatoid spondylitis, Still's disease, systemic scleroderma, Sjogren's Syndrome, Takayasu disease/arthritis, autoimmune thrombocytopenia, idiopathic thrombocytopenia, autoimmune thyroid disorders, hyperthyroid, autoimmune

hypothyroidism (Hashimoto disease), atrophic autoimmune hypothyroidism, phacogenic uveitis, primary vasculitis, vitiligo, acute hepatic disease, chronic hepatic disease, cholestasis, idiosyncratic hepatic disease, allergies and asthma, Th1-and Th2-mediated disease, malignancies comprising lung cancer, breast cancer, stomach cancer, bladder cancer, colorectal cancer, pancreatic cancer, ovarian cancer, prostate cancer and hematopoietic malignancies (leukemia and lymphomas), abetalipoproteinaemia, acute leukemia, acute lymphoblastic leukemia, acute myeloid leukemia, adenocarcinoma, allograft rejection, antiphospholipid syndrome, B-cell lymphoma, bone graft rejection, bone marrow transplant (BMT) rejection, Burkitt lymphoma, inflammatory response to bypass, cartilage graft rejection, chronic myelocytic leukemia (CML), chronic inflammatory pathologies, chronic lymphatic leukemia (CLL), rectocolic carcinoma, cystic fibrosis, cytokine therapy-induced disorders, demyelinating disease, dermatitis, dermatological conditions, any organ or tissue graft rejection, hairy-cell leukemia, heart transplant rejection, Hodgkin disease, idiopathic pulmonary fibrosis, antibody-mediated cytotoxicity, iridocyclitis /uveitis/optic neuritis, juvenile rheumatoid arthritis, renal transplant rejection, liver transplant rejection, lymphoedema, malignant lymphoma, malignant histiocytosis, malignant melanoma, mixed connective-tissue disease, monoclonal gammopathy, multiple myeloma, myelodysplastic syndrome, nasopharyngeal cancer, neonatal chronic lung disease, nephritis, nephrotic, neurodegenerative disorders, non-Hodgkin's lymphomas, osteoporosis, pancreatic graft rejection, pancreatic carcinoma, paraneoplastic disease /tumor-related hypercalcemia, parathyroid graft rejection, Raynaud's phenomenon and disease, Raynoud's disease, sarcoma, scleroderma disease, seronegative arthritis, skin allograft rejection, skin changes, small intestinal graft rejection, solid tumors, a comprehensive systemic inflammatory response syndrome, systemic-onset juvenile rheumatoid arthritis, T cells or FAB ALL, thrombocytopenia, toxicity, grafting, urticaria, vasculitis, heterograft rejection for any organ or tissue, acute coronary syndrome, adult-onset Stills disease, alopecia areata, anaphylaxis, antiphospholipid antibody syndrome, aplastic

anemia, coronary sclerosis, atopic eczema, atopic dermatitis, autoimmune dermatitis, autoimmune disorder associated with streptococcus infection, autoimmune enteropathy, autoimmune hearing loss, autoimmune lymphoproliferative syndrome (ALPS), autoimmune myocarditis, autoimmune premature ovarian failure, bullous pemphigoid, catastrophic antiphospholipid syndrome, celiac disease, cervical spondylosis, cicatrical pemphigoid, clinically isolated syndrome (CIS) with the risk for multiple sclerosis, erythema multiform, severe erythema multiform, gestational pemphigoid, inflammatory demyelinating disease, idiopathic pulmonary fibrosis/ usual interstitial pneumonia, iritis, , keratitis, motor neuron disease, mucosal pemphigoid, non-A, non-B hepatitis, optic neuritis, ovarian cancer, oligoarticular JIA, polyarteritis nodosa, polychondritis, polymyalgia rheumatica, poliosis, polyarticular juvenile idiopathic arthritis, polymyositis, polymyalgia rheumatica (PMR), prostate and rectal cancer and hematopoietic malignancies (leukemia and lymphoma), relapsing neuromyelitis optica, rheumatic heart disease, SAPHO (synovitis, acne, pustulosis, hyperostosis and osteitis), scleroderma, secondary amyloidosis, ankylosing spondylitis, systemic inflammation response syndrome, cranial arteritis, urticaria, vasculitis, and Yersinia- or Salmonella-associated arthropathy.

35. An isolated antibody according to Claims 1-19 or fragment thereof according to Claims 20-23 for use in the treatment of IL-17A-mediated disease or disorder, characterized by its administration of a therapeutically effective amount to a patient who needs such a treatment.

36. An isolated antibody according to Claims 1-19 or fragment thereof according to Claims 20-23 for use in the treatment of IL-17A-mediated disease or disorder according to Claim 35, wherein an IL-17A-mediated disease or disorder is selected from: rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, psoriatic arthritis, reactive arthritis, spondyloarthropathy, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, inflammatory bowel disease, asthma, allergic

disorders, psoriasis, dermatitis, systemic sclerosis, graft-versus-host disease, graft rejection, acute or chronic immune disease associated with organ grafting, sarcoidosis, atherosclerosis, chronic fatigue syndrome, Wegener's disease, Henoch-Schonlein purpura, microscopic polyangiitis with renal involvement, chronic active hepatitis, uveitis, cachexia, acute transverse myelitis, primary biliary cirrhosis, polyglandular autoimmune syndrome type I and type II, Schmidt's syndrome, acute respiratory distress syndrome, alopecia, alopecia areata, seronegative arthropathy, arthropathy, Reiter's syndrome, psoriatic arthropathy, arthropathy associated with ulcerative colitis, enteropathic synovitis, spondyloarthropathy, atheromatosis disease/coronary sclerosis, atopic allergy, autoimmune bullous disease, pemphigus, pemphigus foliaceus, pemphigoid, linear iga diseases, autoimmune hemolytic anemia, Coombs positive hemolytic anemia, Myalgic encephalomyelitis/chronic fatigue syndrome, chronic active hepatic inflammation, cranial giant arteritis, primary sclerosing hepatitis, cryptogenic autoimmune hepatitis, pulmonary fibrosis, cryptogenic fibrosing alveolitis, systemic scleroderma associated with interstitial lung disease, rheumatoid arthritis associated with interstitial lung disease, systemic lupus erythematosus associated with lung disease, dermatomyositis/polymyositis associated with lung disease, Sjogren disease associated with lung disease, ankylosing spondylitis associated with lung disease, diffuse pulmonary vasculitis, fibrosis, lung disease with lymphocyte infiltration, autoimmune hepatitis, autoimmune hepatitis type I (classic autoimmune or lupoid hepatitis), autoimmune hepatitis type II (associated with anti-LKM antibody), autoimmune hypoglycemia, acute graft-associated immune disease, chronic graft-associated immune disease, osteoarthritis, primary sclerosing cholangitis, type I psoriasis, type II psoriasis, discoid lupus erythematosus, multiple sclerosis (all types), sympathetic ophthalmia, pulmonary hypertension secondary to connective tissue disease, Goodpasture syndrome, pulmonary manifestations of polyarteritis nodosa, acute rheumatic fever, rheumatoid spondylitis, Still's disease, systemic scleroderma, Sjogren's Syndrome, Takayasu disease/arthritis, autoimmune thrombocytopenia, idiopathic thrombocytopenia, autoimmune thyroid disorders,

hyperthyroid, autoimmune hypothyroidism (Hashimoto disease), atrophic autoimmune hypothyroidism, phacogenic uveitis, primary vasculitis, vitiligo, acute hepatic disease, chronic hepatic disease, cholestasis, idiosyncratic hepatic disease, allergies and asthma, Th1-and Th2-mediated disease, malignancies comprising lung cancer, breast cancer, stomach cancer, bladder cancer, colorectal cancer, pancreatic cancer, ovarian cancer, prostate cancer and hematopoietic malignancies (leukemia and lymphomas), abetalipoproteinaemia, acute leukemia, acute lymphoblastic leukemia, acute myeloid leukemia, adenocarcinoma, allograft rejection, antiphospholipid syndrome, B-cell lymphoma, bone graft rejection, bone marrow transplant (BMT) rejection, Burkitt lymphoma, inflammatory response to bypass, cartilage graft rejection, chronic myelocytic leukemia (CML), chronic inflammatory pathologies, chronic lymphatic leukemia (CLL), rectocolic carcinoma, cystic fibrosis, cytokine therapy-induced disorders, demyelinating disease, dermatitis, dermatological conditions, any organ or tissue graft rejection, hairy-cell leukemia, heart transplant rejection, Hodgkin disease, idiopathic pulmonary fibrosis, antibody-mediated cytotoxicity, iridocyclitis /uveitis/optic neuritis, juvenile rheumatoid arthritis, renal transplant rejection, liver transplant rejection, lymphoedema, malignant lymphoma, malignant histiocytosis, malignant melanoma, mixed connective-tissue disease, monoclonal gammopathy, multiple myeloma, myelodysplastic syndrome, nasopharyngeal cancer, neonatal chronic lung disease, nephritis, nephrotic, neurodegenerative disorders, non-Hodgkin's lymphomas, osteoporosis, pancreatic graft rejection, pancreatic carcinoma, paraneoplastic disease /tumor-related hypercalcemia, parathyroid graft rejection, Raynaud's phenomenon and disease, Raynoud's disease, sarcoma, scleroderma disease, seronegative arthritis, skin allograft rejection, skin changes, small intestinal graft rejection, solid tumors, a comprehensive systemic inflammatory response syndrome, systemic-onset juvenile rheumatoid arthritis, T cells or FAB ALL, thrombocytopenia, toxicity, grafting, urticaria, vasculitis, heterograft rejection for any organ or tissue, acute coronary syndrome, adult-onset Stills disease, alopecia areata, anaphylaxis, antiphospholipid antibody syndrome, aplastic

anemia, coronary sclerosis, atopic eczema, atopic dermatitis, autoimmune dermatitis, autoimmune disorder associated with streptococcus infection, autoimmune enteropathy, autoimmune hearing loss, autoimmune lymphoproliferative syndrome (ALPS), autoimmune myocarditis, autoimmune premature ovarian failure, bullous pemphigoid, catastrophic antiphospholipid syndrome, celiac disease, cervical spondylosis, cicatrical pemphigoid, clinically isolated syndrome (CIS) with the risk for multiple sclerosis, erythema multiform, severe erythema multiform, gestational pemphigoid, inflammatory demyelinating disease, idiopathic pulmonary fibrosis/ usual interstitial pneumonia, iritis, , keratitis, motor neuron disease, mucosal pemphigoid, non-A, non-B hepatitis, optic neuritis, ovarian cancer, oligoarticular JIA, polyarteritis nodosa, polychondritis, polymyalgia rheumatica, poliosis, polyarticular juvenile idiopathic arthritis, polymyositis, polymyalgia rheumatica (PMR), prostate and rectal cancer and hematopoietic malignancies (leukemia and lymphoma), relapsing neuromyelitis optica, rheumatic heart disease, SAPHO (synovitis, acne, pustulosis, hyperostosis and osteitis), scleroderma, secondary amyloidosis, ankylosing spondylitis, systemic inflammation response syndrome, cranial arteritis, urticaria, vasculitis, and Yersinia- or Salmonella-associated arthropathy.

37. An isolated antibody according to Claims 1-19 or fragment thereof according to Claims 20-23 for use in the treatment of IL-17A-mediated disease or disorder according to 36, further comprising the administration of TNF- α inhibitors.