Summary ~~of the Invention~~

One aspect of the ~~invention~~ disclosure is a bispecific antibody comprising a first antigen-binding site that specifically binds to human TWEAK and a second antigen-binding site that specifically binds to human IL17.

In one embodiment of the disclosure ~~invention~~ the bispecific antibody inhibits

a) TWEAK induced proliferation of human fibroblast-like synoviocytes-rheumatoid arthritis (HFLS-RA) with an IC50 value of 0.2 nM or lower; and

b) IL17 induced IL6 cytokine stimulation of human fibroblast-like synoviocytes-rheumatoid arthritis (HFLS-RA) with an IC50 value of 3.0 nM or lower; and

c) IL17 induced IL8 cytokine stimulation of human fibroblast-like synoviocytes-rheumatoid arthritis (HFLS-RA) with an IC50 value of 2.0 nM or lower.

In one embodiment of the disclosure ~~invention~~ the bispecific antibody comprising a first antigen-binding site that specifically binds to human TWEAK and a second antigen-binding site that specifically binds to human IL17 is a bivalent, bispecific antibody.

In one embodiment of the disclosure ~~invention~~ the bispecific antibody comprising a first antigen-binding site that specifically binds to human TWEAK and a second antigen-binding site that specifically binds to human IL17 is characterized in that

i) said first antigen-binding site comprises

a) CDR1H of SEQ ID NO:17, CDR2H of SEQ ID NO:18, CDR3H of SEQ ID NO:19, and CDR1L of SEQ ID NO:20, CDR2L of SEQ ID NO:21, CDR3L of SEQ ID NO:22; or

b) CDR1H of SEQ ID NO:1, CDR2H of SEQ ID NO:2, CDR3H of SEQ ID NO:3, and CDR1L of SEQ ID NO:4, CDR2L of SEQ ID NO:5, CDR3L of SEQ ID NO:6; or

c) CDR1H of SEQ ID NO:9, CDR2H of SEQ ID NO:10, CDR3H of SEQ ID NO:11, and CDR1L of SEQ ID NO:12, CDR2L of SEQ ID NO:13, CDR3L of SEQ ID NO:14; and

ii) said second antigen-binding site comprises

CDR1H of SEQ ID NO:47, CDR2H of SEQ ID NO:48, CDR3H of SEQ ID NO:49, and CDR1L of SEQ ID NO:50, CDR2L of SEQ ID NO:51, CDR3L of SEQ ID NO:52.

In ~~one embodiment~~another aspect of the disclosure ~~invention~~ is a chimeric or humanized variant of the such bispecific antibody.

In one embodiment of the disclosure ~~invention~~ the bispecific antibody comprising a first antigen-binding site that specifically binds to human TWEAK and a second antigen-binding site that specifically binds to human IL17 is characterized in that

i) said first antigen-binding site comprises

a variable heavy chain domain (VH) of SEQ ID NO:25, of SEQ ID NO:26, of SEQ ID NO:27, of SEQ ID NO:28, of SEQ ID NO:29, of SEQ ID NO:30, of SEQ ID NO:31, of SEQ ID NO:32, of SEQ ID NO:33, of SEQ ID NO:34, or of SEQ ID NO:35, and a variable light chain domain of SEQ ID NO:26, of SEQ ID NO:37, of SEQ ID NO:38, of SEQ ID NO:39, of SEQ ID NO:40, of SEQ ID NO:41, of SEQ ID NO:42, of SEQ ID NO:43, of SEQ ID NO:44, of SEQ ID NO:45, or of SEQ ID NO:46; and

ii) said second antigen-binding site comprises

a variable heavy chain domain (VH) of SEQ ID NO:55, or of SEQ ID NO:56, and a variable light chain domain of SEQ ID NO:57, or of SEQ ID NO:58.

In one embodiment of the disclosure ~~invention~~ the bispecific antibody comprising a first antigen-binding site that specifically binds to human TWEAK and a second antigen-binding site that specifically binds to human IL17 is characterized in that

i) said first antigen-binding site comprises

a variable heavy chain domain (VH) of SEQ ID NO:28, and a variable light chain domain of SEQ ID NO:37; and

ii) said second antigen-binding site comprises

a) a variable heavy chain domain (VH) of SEQ ID NO:56, and a variable light chain domain of SEQ ID NO:58; or

b) a variable heavy chain domain (VH) of SEQ ID NO:55, and a variable light chain domain of SEQ ID NO:57.

In one embodiment of the disclosure ~~invention~~ the bispecific antibody comprising a first antigen-binding site that specifically binds to human TWEAK and a second antigen-binding site that specifically binds to human IL17 is characterized in that

i) said first antigen-binding site comprises

a variable heavy chain domain (VH) of SEQ ID NO:28, and a variable light chain domain of SEQ ID NO:37; and

ii) said second antigen-binding site comprises

a variable heavy chain domain (VH) of SEQ ID NO:56, and a variable light chain domain of SEQ ID NO:58.

In one embodiment of the disclosure ~~invention~~ the bispecific antibody comprising a first antigen-binding site that specifically binds to human TWEAK and a second antigen-binding site that specifically binds to human IL17 is characterized in that

i) said first antigen-binding site comprises

a variable heavy chain domain (VH) of SEQ ID NO:28, and a variable light chain domain of SEQ ID NO:37; and

ii) said second antigen-binding site comprises

a variable heavy chain domain (VH) of SEQ ID NO:55, and a variable light chain domain of SEQ ID NO:57.

In one embodiment the bispecific antibody which binds to TWEAK and IL17 and being characterized by the above mentioned amino acid sequences and amino acid

sequence fragments is of human IgG1 isotype, in one embodiment with mutations L234A and L235A, in one embodiment with mutations L234A, L235A and P329G.

In one embodiment the bispecific antibody which binds to TWEAK and IL17 and being characterized by the above mentioned amino acid sequences and amino acid sequence fragments is of human IgG4 isotype, in one embodiment with mutations S228P and L235E, in one embodiment with mutations S228P, L235E and P329G.

A further ~~embodiment~~ aspect of the disclosure ~~invention~~ is a pharmaceutical composition comprising a bispecific antibody according to the disclosure~~invention~~.

A further ~~embodiment~~ aspect of the disclosure ~~invention~~ is the use of a bispecific antibody according to the disclosure ~~invention~~ for the manufacture of a pharmaceutical composition.

A further ~~embodiment~~ aspect of the disclosure ~~invention~~ is a nucleic acid encoding a bispecific antibody according to the disclosure~~invention~~.

A further embodiment of the disclosure ~~invention~~ is a nucleic acid encoding a heavy chain variable domain and/or a light chain variable domain of a bispecific antibody according to the disclosure~~invention~~.

The disclosure ~~invention~~ further provides expression vectors containing nucleic acid according to the disclosure ~~invention~~ capable of expressing said nucleic acid in a prokaryotic or eukaryotic host cell, and host cells containing such vectors for the recombinant production of such an antibody. A further aspect of the disclosure are expression vectors characterized by comprising a nucleic acid according to the disclosure for the expression of the bispecific antibody according to the disclosure in a prokaryotic or eukaryotic host cell.

A further aspect of the ~~The~~ disclosure ~~invention further comprises~~ is a prokaryotic or eukaryotic host cell comprising a vector according to the disclosure ~~invention~~.

A further aspect of the ~~The~~ disclosure ~~invention further~~ comprises a method for the production of a recombinant chimeric, human or humanized antibody according to the disclosure~~invention~~, characterized by expressing a nucleic acid according to the disclosure ~~invention~~ in a prokaryotic or eukaryotic host cell and recovering said antibody from said cell or the cell culture supernatant. The disclosure ~~invention~~ further comprises the antibody obtainable by such a recombinant method.

Antibodies according to the disclosure ~~invention~~ show benefits for patients in need of a TWEAK and IL17 targeting therapy. The antibodies according to the ~~invention~~ disclosure have new and inventive properties causing a benefit for a patient suffering from a cancer disease, especially suffering from colon, lung, or pancreatic cancer or from

inflammatory diseases, especially from autoimmune diseases, rheumatoid arthritis, psoratic arthritis, muscle diseases, e.g. muscular dystrophy, multiple sclerosis, chronic kidney diseases, bone diseases, e.g. bone degeneration in multiple myeloma, systemic lupus erythematosus, lupus nephritis, and vascular injury.

A further ~~embodiment~~ aspect of the disclosure ~~invention~~ is a bispecific antibody according to the disclosure ~~invention~~ for use in the treatment of cancer, inflammatory diseases, autoimmune diseases, rheumatoid arthritis, psoratic arthritis, muscle diseases, e.g. muscular dystrophy, multiple sclerosis, chronic kidney diseases, bone diseases, e.g. bone degeneration in multiple myeloma, systemic lupus erythematosus, lupus nephritis, and vascular injury. The bispecific antibody according to the disclosure may be for use in , ~~especially for~~ the treatment of systemic lupus erythematosus, lupus nephritis.

A further ~~embodiment~~ aspect of the disclosure ~~invention~~ is use of a bispecific antibody according to the disclosure ~~invention~~ for manufacture of a medicament for the treatment of cancer, inflammatory diseases, autoimmune diseases, rheumatoid arthritis, psoratic arthritis, muscle diseases, e.g. muscular dystrophy, multiple sclerosis, chronic kidney diseases, bone diseases, e.g. bone degeneration in multiple myeloma, systemic lupus erythematosus, lupus nephritis, and vascular injury. There may be provided use of a bispecific antibody according to the disclosure for manufacture of a medicament, ~~especially~~ for the treatment of systemic lupus erythematosus, lupus nephritis.

The disclosure ~~invention~~ further provides a method for treating a patient suffering from cancer, especially from colon, lung, or pancreatic cancer or from inflammatory diseases, especially from autoimmune diseases, rheumatoid arthritis, psoratic arthritis, muscle diseases, e.g. muscular dystrophy, multiple sclerosis, chronic kidney diseases, bone diseases, e.g. bone degeneration in multiple myeloma, systemic lupus erythematosus, lupus nephritis, and vascular injury, comprising administering to a patient diagnosed as having such a disease (and therefore being in need of such a therapy) an effective amount of the bispecific antibody which binds to TWEAK and IL17 according to the disclosure ~~invention~~. The antibody is administered preferably in a pharmaceutical composition.

The disclosure ~~invention~~ further comprises a pharmaceutical composition comprising an antibody according to the disclosure ~~invention~~, optionally together with a buffer and/or an adjuvant useful for the formulation of antibodies for pharmaceutical purposes.

The disclosure ~~invention~~ further provides a pharmaceutical composition comprising an antibody according to the disclosure ~~invention~~ in a pharmaceutically acceptable carrier. In one

embodiment, the pharmaceutical composition may be included in an article of manufacture or kit.

The bispecific antibodies according to the disclosure ~~invention~~ show benefits for human patients in need of a TWEAK and IL17 targeting therapy and have valuable properties.

The antibodies according to the disclosure ~~invention~~ have valuable properties causing a benefit for a patient suffering from such a disease, especially suffering from inflammatory diseases such as rheumatoid arthritis or lupus nephritis. Such valuable properties include the simultaneous inhibition of both TWEAK and IL17 leading to complementary treatment benefits. There is a persistent high unmet medical need in RA as many patients fail to achieve a target of remission. Bispecific antibodies targeting both TWEAK and IL17 offer an opportunity for improved efficacy by inhibiting IL-17 and TWEAK thus providing complementary anti-inflammatory and anti-angiogenic activity and optimal impact on bone formation/resorption. TWEAK expression is significantly increased in synovial tissue of RA and PsA patients – mainly in $CD55^+$ synoviocytes and $CD168^+$ macrophages. (Van Kuijk, et al., Ann Rheum Dis 69 (2010) 301-304). IL-17A is produced in inflamed synovial tissue with lower IL-17 in TNF responders and higher IL-17 levels in TNF-non-responders (Moran, et al., Arthritis & Rheumatism 11 (2009) R113). In addition, available data supports a role for IL-17 and TWEAK in kidney inflammation with effects on mesangial cells, tubular epithelial cells, endothelial cells, elevated chemokines, cytokines, neutrophil infiltration and positive correlations of IL-17 and TWEAK with disease activity. Urinary TWEAK levels correlate with renal SLEDAI scores, TWEAK is elevated during flares and specific to renal disease (Schwartz, et al., J Autoimmunity 27 (2006) 242-25). In addition, TWEAK blockade reduces kidney inflammation in in a model of acute kidney injury (AKI) (Sanz, et al., J Amer Soc Nephrol 19 (2008) 695-703). Elevated IL-17 is detected in tissues from lupus patients and IL-17 is detected in affected kidneys from patients with SLE (Crispin, et al., J Immunol. 181 (2008) 8761–8766).

Low viscosity and high stability in terms of aggregation (>55°C) makes such antibodies suitable for high concentration formulation for a possible subcutaneous application (He, F., et al., J Pharm Sci.100 (2010) 1330-1340).

In one embodiment the bispecific antibodies according to the disclosure ~~invention~~ are additionally characterized by one or more of the following properties (as determined in Examples 4, 10, 11, 16, 17 and 19): the bispecific antibody

a) shows no cross reactivity with IL17B, IL17C, IL17D, IL17F (which means that the binding to IL17B, IL17C, IL17D and IL17F is 0% compared to the binding to IL17A , which is set as 100%);

b) inhibits IL17 induced IL8 cytokine stimulation of CCD-25SK cells with an IC50 value of 2.0 nM or lower (e.g. with an IC50 value between 2.0 nM and 0.0 nM);

c) inhibits IL17 induced IL6 cytokine stimulation of CCD-25SK cells with an IC50 value of 5.0 nM or lower (e.g. with an IC50 value between 5.0 nM and 0.0 nM); preferably with an IC50 value of 2.0 nM or lower;

d) human TWEAK/human Fn14 interaction with an IC50 value of 4.0 [ng/ml] or lower (e.g. with an IC50 value between 4.0 [ng/ml] and 0.0 [ng/ml]); preferably with an IC50 value of 3.0 [ng/ml] or lower;

e) binds to human TWEAK with an KD value of binding affinity of 0.1 nM or lower, and binds to human IL-17 with an KD value of binding affinity of 0.3 nM or lower; and /or

f) is capable to simultaneously bind to human <TWEAK> and human <IL17>, wherein the signal intensity (in RU) (in a surface plasmon resonance assay) of the binding of the bispecific TWEAK/IL17 antibody to a 1:1 mixture from human <TWEAK> and human <IL17> is at least the same or higher compared to the sum of a) the signal intensity (in RU) of the binding of the bispecific TWEAK/IL17 antibody to human <TWEAK> alone and b) the signal intensity (in RU) of the binding of the bispecific TWEAK/IL17 antibody to human <IL17> alone.

Description of the Figures

Figure 1a and b Two exemplary bispecific, bivalent antibody formats for the bispecific <TWEAK/IL17> antibodies according to the invention are shown.

Figure 2 One exemplary bispecific, tetravalent antibody format for the bispecific <TWEAK/IL17> antibodies according to the invention is shown.

17. An antibody according to claims 1 to 14 for use in the treatment of cancer, or inflammatory diseases, autoimmune diseases, rheumatoid arthritis, psoratic arthritis, muscle diseases, e.g. muscular dystrophy, multiple sclerosis, chronic kidney diseases, bone diseases, e.g. bone degeneration in multiple myeloma, systemic lupus erythematosus, lupus nephritis, and vascular injury.

18. Use of an antibody according to claims 1 to 14 for manufacture of a medicament for the treatment of cancer, or inflammatory diseases, autoimmune diseases, rheumatoid arthritis, psoratic arthritis, muscle diseases, e.g. muscular dystrophy, multiple sclerosis, chronic kidney diseases, bone diseases, e.g. bone degeneration in multiple myeloma, systemic lupus erythematosus, lupus nephritis, and vascular injury.

19. Nucleic acid encoding an antibody according to claims 1 to 14.

20. Expression vectors characterized by comprising a nucleic acid according to claim 19 for the expression of the bispecific antibody according to claims 1 to 14 in a prokaryotic or eukaryotic host cell.

21. Prokaryotic or eukaryotic host cell comprising a vector according to claim 20.

22. Method for the production of a recombinant antibody according to claims 1 to 14, characterized by expressing a nucleic acid according to claim 19 in a prokaryotic or eukaryotic host cell and recovering said antibody from said cell or the cell culture supernatant.

~~23. Method for the treatment of a patient suffering from cancer or from inflammatory diseases, autoimmune diseases, rheumatoid arthritis, psoratic arthritis, muscle diseases, e.g. muscular dystrophy, multiple sclerosis, chronic kidney diseases, bone diseases, e.g. bone degeneration in multiple myeloma, systemic lupus erythematosus, lupus nephritis, and vascular injury, characterized by administering to the patient an antibody according to claims 1 to 14.~~