

Antibodies for IL-17C

Field of the invention

The present application relates to antibodies or antibody fragments which interact with human IL-17C. The invention also relates to nucleic acids, vectors and host cells capable of expressing said antibodies or fragments thereof, pharmaceutical compositions comprising said antibodies or fragments thereof and uses of said antibodies or fragments thereof for the treatment of specific diseases.

Background

IL-17C is a secreted homodimer of the IL17 protein family. *In vitro* it has been shown that IL-17C stimulates the release of TNF- α and IL-1 β from the monocytic cell line THP-1 (Li *et al.* (2000) Proc. Natl. Acad. Sci. U. S. A. 97, 773-8). IL-17C can induce the mRNA expression of inflammatory cytokines such as IL-1 β , IL-6 and IL-23 in peritoneal exudates cells (PECS) and the 3T3 cell line (Yamaguchi *et al.* (2007) J. Immunol 179, 7128-36).

The role of IL-17C as a proinflammatory cytokine relevant for host defense was postulated in several studies (Chang *et al.* (2011) Immunity 35, 611–621, Song *et al.* (2011) Nature Immunology 12, 12, Ramirez-Carrozzi *et al.* (2011) Nature Immunology 12, 12). Also a potential role in the progression of specific tumours and cancerous tissues was recently shown (Xinyang Song (2014) Immunity 40, 140–152).

Recently in WO 2013/057241 it was experimentally evaluated that inhibition of IL-17C is a promising approach to treat inflammatory disorders. However, respective antibodies used in WO 2013/057241 were surrogate antibodies specific for mouse IL-17C, but were shown not to be reactive to human IL-17C at all. In addition, further antibodies that antagonize IL-17C were already suggested (e.g. in WO 1999/060127), but are either polyclonal sera or surrogate antibodies which specifically bind to mouse IL-17C only.

Accordingly, a need exists to study and identify antibodies that bind to human IL-17C to ameliorate IL-17C related diseases or disorders in human.

Summary of the invention

The present disclosure provides novel antibodies and antibody fragments. The antibodies and antibody fragments disclosed herein bind to human IL-17C and also cross-react with IL-17C from the cynomolgus monkey and the mouse. In addition the disclosed antibodies inhibit binding of IL-17C to its receptor throughout the relevant species - human, mouse and cynomolgus monkey - with an IC_{50} concentration of 80 pM or less. As disclosed and exemplified herein, said antibodies proved to be effective in various *in vivo* mouse models for atopic dermatitis and psoriasis.

Thus, the disclosed antibodies or antibody fragments are superior in terms of effectiveness and provide well suited and promising compounds for the treatment of humans having, for example; atopic dermatitis or psoriasis.

The present disclosure provides antibodies or antibody fragments that bind to human IL-17C having CDR regions according to Table 1 of the present specification. The present disclosure also provides specific antibodies or antibody fragments having a variable heavy chain region and a variable light chain CDR regions comprising the amino acid sequences according to Table 1 of the present specification.

The present disclosure also provides specific antibodies or antibody fragments which compete with the specific antibodies or antibody fragments disclosed herein. The present disclosure also provides specific antibodies or antibody fragments which bind to the same epitope as the specific antibodies or antibody fragments disclosed herein.

The present disclosure also provides the isolated antibodies or antibody fragments of the present disclosure for use in medicine.

The present disclosure also provides also provides methods for treating a subject suffering from a disorder, such as an inflammatory disorder, by administering to said subject an effective amount of the antibodies or antibody fragments of the present disclosure. Preferably said subject is a human.

The present disclosure also provides pharmaceutical compositions comprising the isolated antibodies or antibody fragments of the present disclosure, and a pharmaceutically acceptable carrier.

The present disclosure also provides nucleic acids encoding the antibodies or antibody fragments of the present disclosure.

The present disclosure also provides vectors comprising nucleic acids encoding the antibodies or antibody fragment antibodies of the present disclosure.

The present disclosure also provides host cell comprising vector or nucleic acids encoding the antibodies or antibody fragments of the present disclosure.

There is utility in the claimed antibodies or antibody fragments. Furthermore, there is utility in the claimed method to identify such antibodies or fragments.

Utilization of the claimed antibodies or antibody fragments is to alter the biological activity of human IL-17C. In particular the claimed antibodies or antibody fragments are for therapeutic use, such as the treatment of inflammatory disorders like e.g. rheumatoid arthritis, psoriasis, pulmonary inflammation, COPD and/or the treatment of atopic dermatitis (AD), including moderate-to-severe AD.

Brief description of the drawings

Figure 1: MAB#1 dose-dependently prevents the ear thickening induced by topical application of MC903 on ear skin.

Data are expressed as mean values $\pm$ standard error of the mean (SEM) (n=8 per group). Statistical significance versus MC903+MOR03207 was calculated using ANOVA and Dunnett's multiple comparison test: * p<0.05; ** p<0.01; *** p<0.001. (DEX: dexamethasone; EtOH: ethanol)

Figure 2: MAB#1 dose-dependently reduces the ear inflammation induced by topical application of MC903 on ear skin.

Ear inflammation was assessed at Day 5 using in vivo imaging. Left panel: quantification of signal intensity in ears. Individual data points (n=8 per group) represent the average intensity

of both ears; data are also shown as mean values (horizontal lines) $\pm$ SEM. Statistical significance versus MC903+MOR03207 was calculated using ANOVA and Dunnett's multiple comparison test: * $p<0.05$; ** $p<0.01$; *** $p<0.001$. Right panel: representative images of mouse ears from animals from different treatment groups were acquired on the Bruker In-vivo Xtreme Imager 24h after injection of the Prosense 680 probe. (DEX: dexamethasone; EtOH: ethanol)

Figure 3: MAB#1 dose-dependently reduces the thickening of epidermal and dermal skin layer induced by topical application of MC903 on ear skin.

Data are presented as individual data points (n=8 per group) and mean values (horizontal lines) $\pm$ SEM. Statistical significance versus MC903+MOR03207 was calculated using ANOVA and Dunnett's multiple comparison test: * $p<0.05$; ** $p<0.01$; *** $p<0.001$. Left panel: data for epidermal thickness; Right panel: data for dermal thickness.

Figure 4: MAB#1 dose-dependently inhibits the MC903-mediated increase in TSLP and IL-33 expression in ear and TARC levels in plasma.

Data are presented as individual data points (n=8 per group) and mean values (horizontal lines) $\pm$ SEM. Statistical significance versus MC903+MOR03207 group was calculated using ANOVA and Dunnett's multiple comparison test: * $p<0.05$; ** $p<0.01$; *** $p<0.001$. Top left panel: data for TSLP protein expression in ear; Bottom left panel: data for IL-33 protein expression in ear; Top right panel: data for TARC protein levels in plasma.

Figure 5: Therapeutic administration of MAB#1 dose-dependently reduces the ear thickening induced by topical application of MC903 on ear skin.

Data are expressed as mean values $\pm$ SEM (n=10 per group). Statistical significance versus MC903+MOR03207 was calculated using ANOVA and Dunnett's multiple comparison test: * $p<0.05$; ** $p<0.01$; *** $p<0.001$. DEX: dexamethasone; EtOH: ethanol.

Figure 6: Therapeutic administration of MAB#1 dose-dependently reduces the ear inflammation induced by topical application of MC903 on ear skin.

Ear inflammation was assessed at Day 12 using *in vivo* imaging and the signal intensity in ears is graphically represented. Individual data points (n=10 per group) represent the average intensity of both ears; data are also shown as mean values (horizontal lines) $\pm$ SEM. Statistical significance versus MC903+MOR03207 was calculated using ANOVA and Dunnett's multiple comparison test: * $p<0.05$; ** $p<0.01$; *** $p<0.001$. DEX: dexamethasone; EtOH: ethanol.

Figure 7: Therapeutic administration of MAB#1 dose-dependently reduces the thickening of epidermal and dermal skin layer induced by topical administration of MC903 on ear skin.

Data are presented as individual data points (n=10 per group) and mean values (horizontal lines) $\pm$ SEM. Statistical significance versus MC903+MOR03207 was calculated using ANOVA and Dunnett's multiple comparison test: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Left panel: data for epidermal thickness; Right panel: data for dermal thickness. DEX: dexamethasone; EtOH: ethanol.

Figure 8: Therapeutic administration of MAB#1 dose-dependently reduces the dermal infiltration of eosinophils, T cells and mast cells.

Data are presented as individual data points (n=10 per group) and mean values (horizontal lines) $\pm$ SEM. Statistical significance versus MC903+MOR03207 was calculated using ANOVA and Dunnett's multiple comparison test: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Top left panel: data for eosinophils; Top right panel: data for mast cells; Bottom left panel: data for T cells. DEX: dexamethasone; EtOH: ethanol.

Figure 9: Therapeutic administration of MAB#1 reduces expression of IL-33, IL-4 and S100A9, which were still increased at Day 16 (11 days after stopping MC903 application).

Data are presented as individual data points (n=10 per group) and mean values (horizontal lines) $\pm$ SEM. Statistical significance versus MC903+MOR03207 group was calculated using ANOVA and Dunnett's multiple comparison test: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Top left panel: data for S100A9 mRNA expression in ear; Bottom left panel: data for IL-4 mRNA expression in ear; Top right panel: data for IL-33 protein levels in ear.

Figure 10: MAB#1 reduces macroscopic clinical signs of AD-like inflammation in the spontaneous & chronic Flaky Tail model

Clinical scoring of cutaneous inflammation for each mouse was done at start (week 0) and at end (week 6) of treatment. Data are the mean $\pm$ SD for each treatment group (n=8 per group). Statistical significance versus the isotype antibody treated group was calculated using ANOVA and Dunnett's multiple comparison test (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$).

Figure 11: MAB#1 reduces eczematous-like eyelid inflammation in the spontaneous & chronic Flaky Tail model.

Skin eyelid inflammation was scored at end of the treatment (week 6). Data are the mean $\pm$ SD for each treatment group (n=8 per group). Statistical significance versus the isotype antibody treated group was calculated using ANOVA and Dunnett's multiple comparison test (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$).

Detailed description of the invention

The disclosure pertains to a number of antibodies or antibody fragments that recognize human IL-17C.

Definitions:

The term "IL-17C" refers to a protein known as interleukin 17C.

Human IL-17C has the amino acid sequence of (UniProt Q9P0M4):

MTLLPGLLFTWLHTCLAHHDPSLRGHPHSHGTPHCYSAEELPLGQAPPHLLA
RGAKWGQALPVALVSSLEAASHRGRHERPSATTQCPVLRPEEVLEADTHQR
SISPWRYRVDTDDEDRYPQKLAF AECLCRGCIDARTGRETAALNSVRLQLSLV
LRRRPCSRDGSGLPTPGAF AFHTEFIHVPVGCTCVLPRSV (SEQ ID No.: 1)

Mouse IL-17C has the amino acid sequence of (UniProt Q8K4C5):

MSLLLLGWLPTGMTHQDPPSWGKPRSHRTLRCYSAEELSHGQAPPHLLTRS
ARWEQALPVALVASLEATGHRRQHEGPLAGTQCPVLRPEEVLEADTHERSIS
PWRYRIDTDENRYPQKLAVAECLCRGCINAKTGRETAALNSVQLQLSLVLR
QPCSRDGTADPTPGSF AFHTEFIRVPVGCTCVLPRSTQ (SEQ ID No.: 2)

Cynomolgus monkey IL-17C has the amino acid sequence of (XP_005592825.1):

MTLLPGLLFTWLHACLAHQDPFLRGHPHSHGTPRCYSAEELPLGQAPPHLLA
RGAKWGQALPVALVSSLEAAGHRRRHDRPSAATQCPVLRPEEVLEADTHQR

SISPWRYRVDTDED RYPQKLAF AECLCRGCIDPRTGRETAALNSVRLLQSLLV
LRRRPCSRDGSGLPTPGAFAFHTEFIRVPVGCTCVLPRSV (SEQ ID No.: 3)

The term "IL17RA" refers to a protein known as interleukin 17 receptor A. Human IL17RA has the amino acid sequence of (UniProt Q96F46):

MGAARSPPSAVPGPLLGLLLLLLGV LAPGGASLRLLDHRALVCSQPGLNCTVKNSTC
LDDSWIHPRNLTPSSPKDLQIQLHFAHTQQGDLFPVAHIEWTLQTDASILYLEGAELS
VLQLNTNERLCVRFEFLSKLRHHHRRWRFTFSHFVDPDQEYEVTVHHLPKPIPDG
DPNHQSKNFLVPDCEHARMKVTTPCMSSGSLWDPNITVETLEAHQLRVSFTLWNES
THYQILLTSFPHMENHSCFEHMHIPAPRPEEFHQRSNVTLTRNLKGCCRHHQVQIQ
PFFSSCLNDCLRHSATVSCPEMPDTPEPIPDYMWPLWVYWFITGISILLVGSVILLIVCM
TWRLAGPGSEKYSDDTKYTDGLPAADLIPPLKPRKWIIYSADHPLYVDVVLKFAQ
FLLTACGTEVALDLLEEQAISEAGVMTWVGRQKQEMVESNSKIIVLCSRGTRAKWQ
ALLGRGAPVRLRCDHGKPVGDLFTAAMNMILPDFKRPACFGTYVVCYFSEVSCDGD
VPDLFGAAPRYPLMDRFEEVYFRIQDLEMFQPGRMHRVGELSGDNYLRSPGGRQL
RAALDRFRDWQVRCPDWFECENLYSADDQDAPSLDEEVFEEPLLPPGTGIVKRAPL
VREPGSQACLAIDPLVGEEGGA AVAKLEPHLQPRGQPAPQPLHTLVLAEEGALVA
AVEPGPLADGA AVRLALAGEGEACPLL GSPGAGRNSVLF LPVPDPEDSPLGSSTPMA
SPDLLPEDVREHLEGLMLSLFEQSLSCQAQG GCSR PAMVLTDPHTPYEEEEQRQSV
QSDQGYISRSSQPPEGLTEMEEEEEEEQDPGKPALPLSPEDLESRLSLQRQLLFR
QLQKNSGWD TMGSESEGPSA (SEQ ID No.: 4)

The term "IL17RE" refers to a protein known as interleukin 17 receptor E. Human IL17RE has the amino acid sequence of (UniProt Q8NFR9):

MGSSRLAALLPLLLIVIDLSDSAGIGFRHLPHWNTRCPLASHTDDSFTGSSAYIPCRT
WWALFSTKPWCVRVWHCSRCLCQHLLSGGSLQRGLFHLLVQKSKKSSTFKFYRR
HKMPAPAQRKLLPRRHLSEKSHHISIPSPDISHKGLRSKRTQPSDPETWESLPRLDS
QRHGGPEFSFDLLPEARAIRVTISSGPEVSVRLCHQWALECEELSSPYDVQKIVSGG
HTVELPYEFLLPCLCIEASYLQEDTVRRKKCPFQSWPEAYGSDFWKSVHFTDYSQH
TQMVMALTLCPLKLEAALCQRHDWHTLCKDLPNATARES DGWYVLEKVDLHPQL
CFKFSFGNSSHVECPHQTGSLTSWNVSM DTAQQLILHFSSRMHATFSAAWSPLPG
LGQDTLVPPVYTVSQARGSSPVSLDIIPFLRPGCCVLVWRSDVQFAWKHLLCPDVS
YRHLGLLILALLALLTLLGWVLALTCRRPQSGPGPARPVLLLHAADSEAQRRLVGALA
ELLRAALGGGRDVIVDLWEGRHVARVGPLPWLWAARTRVAREQGTVLLWWSGADL
RPVSGPD PRAAPLLALLHAAPRPLLLLAYFSRLCAKGDIPPLRALPRYRLLRDLPRL

LRALDARPF AEATSWGRLGARQRRQSRLELC SRLEREAARLADLG (SEQ ID No.: 5)

Murine IL17RE has the amino acid sequence of (UniProt Q8BH06):

MGSPRLAALLLSLPLLLIGLAVSARVACPCLRSWTS HCLLAYRVDKRFAGLQWGW F
 PLLVRKSKSPPKFEDYWRHRT PASFQRKLLGSPSLSEESHRI SIPSSAISHRGQRTK
 RAQPSAAEGREHLPEAGSQKCGGPEFSFDLLPEVQAVRVTIPAGPKASVRLCYQW
 ALECEDLSSPFD TQKIVSGGHTVDLPYEFLPCM CIEASYLQEDTVRRKKCPFQSWP
 EAYGSDFWQSIRFTDYSQHNQMVMALT LRCPLKLEASLCWRQDPLTPCETLPNATA
 QESEGWYILENVDLHPQLCFKFSFENSSHVECPHQSGSLPSWTVSMDTQAQQLTL
 HFSSRTYATFSAAWS DPGLGPDTPMPPVYSISQTQGSVPVTLDLIIPFLRQENCILVW
 RSDVHFAWKHVLC PDVSHRHLGLLILALLALTALVGWVLVLLGRRL LPGSGRTRPVLL
 LHAADSEAQRRLVGALAE LLRTALGGGRDVIVDLWEGTHVARIGLPWLWAARERV
 AREQGTVLLLWNCAGPSTACSGDPQAASLRTL LCAAPRPLLLAYFSRLCAKGDIPRP
 LRALPRYRLLRDLPRLLRALDAQPATLASSWSHLGAKRCLKNRLEQCHLLELEAAKD
 DYQGSTNSPCGFSCL (SEQ ID No.: 6)

The terms "antagonist of IL-17C" and an "IL-17C antagonist", are used interchangeably herein and refer to any molecule which inhibits the activity or function of IL-17C. The term "IL-17C antagonist" includes, but is not limited to, antibodies or antibody fragments specifically binding to IL-17C. Preferably, an IL-17C antagonist in the present disclosure is an antibody specific for human IL-17C. Such an antibody may be of any type, such as a murine, a rat, a chimeric, a humanized or a human antibody.

The term "antibody" as used herein refers to a protein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds which interacts with an antigen. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FR's arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The

constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component (C1q) of the classical complement system. The term "antibody" includes for example, monoclonal antibodies, human antibodies, humanized antibodies, camelised antibodies and chimeric antibodies. The antibodies can be of any isotype (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass. Both the light and heavy chains are divided into regions of structural and functional homology.

The phrase "antibody fragment", as used herein, refers to one or more portions of an antibody that retain the ability to specifically interact with (e.g., by binding, steric hindrance, stabilizing spatial distribution) an antigen. Examples of binding fragments include, but are not limited to, a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; a F(ab)₂ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consisting of the VH and CH1 domains; a Fv fragment consisting of the VL and VH domains of a single arm of an antibody; a dAb fragment (Ward *et al.*, (1989) *Nature* 341:544-546), which consists of a VH domain; and an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (scFv); see e.g., Bird *et al.*, (1988) *Science* 242:423-426; and Huston *et al.*, (1988) *Proc. Natl. Acad. Sci.* 85:5879-5883). Such single chain antibodies are also intended to be encompassed within the term "antibody fragment". These antibody fragments are obtained using conventional techniques known to those of skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies. Antibody fragments can also be incorporated into single domain antibodies, maxibodies, minibodies, intrabodies, diabodies, triabodies, tetrabodies, v-NAR and bis-scFv (see, e.g., Hollinger and Hudson, (2005) *Nature Biotechnology* 23:1126-1136). Antibody fragments can be grafted into scaffolds based on polypeptides such as Fibronectin type III (Fn3) (see U.S. Pat. No. 6,703,199, which describes fibronectin polypeptide monobodies). Antibody fragments can be incorporated into single chain molecules comprising a pair of tandem Fv segments (VH-CH1-VH-CH1) which, together with complementary light chain polypeptides, form a pair of antigen-binding sites (Zapata *et al.*, (1995) *Protein Eng.* 8:1057-1062; and U.S. Pat. No. 5,641,870).

A "human antibody" or "human antibody fragment", as used herein, includes antibodies and antibody fragments having variable regions in which both the framework and CDR regions are derived from sequences of human origin. Furthermore, if the antibody contains a constant

region, the constant region also is derived from such sequences. Human origin includes, e.g., human germline sequences, or mutated versions of human germline sequences or antibody containing consensus framework sequences derived from human framework sequences analysis, for example, as described in Knappik *et al.*, (2000) J Mol Biol 296:57-86).

The structures and locations of immunoglobulin variable domains, e.g., CDRs, may be defined using well known numbering schemes, e.g., the Kabat numbering scheme, the Chothia numbering scheme, or a combination of Kabat and Chothia (see, e.g., Sequences of Proteins of Immunological Interest, U.S. Department of Health and Human Services (1991), eds. Kabat *et al.*; Lazikani *et al.*, (1997) J. Mol. Bio. 273:927-948); Kabat *et al.*, (1991) Sequences of Proteins of Immunological Interest, 5th edit., NIH Publication no. 91-3242 U.S. Department of Health and Human Services; Chothia *et al.*, (1987) J. Mol. Biol. 196:901-917; Chothia *et al.*, (1989) Nature 342:877-883; and Al-Lazikani *et al.*, (1997) J. Mol. Biol. 273:927-948.

A "humanized antibody" or "humanized antibody fragment" is defined herein as an antibody molecule which has constant antibody regions derived from sequences of human origin and the variable antibody regions or parts thereof or only the CDRs are derived from another species. For example a humanized antibody can be CDR-grafted, wherein the CDRs of the variable domain are from a non-human origin, while one or more frameworks of the variable domain are of human origin and the constant domain (if any) is of human origin.

The term "chimeric antibody" or "chimeric antibody fragment" is defined herein as an antibody molecule which has constant antibody regions derived from, or corresponding to, sequences found in one species and variable antibody regions derived from another species. Preferably, the constant antibody regions are derived from, or corresponding to, sequences found in humans, and the variable antibody regions (e.g. VH , VL , CDR or FR regions) are derived from sequences found in a non-human animal, e.g. a mouse, rat, rabbit or hamster.

The term "isolated" refers to a compound, which can be e.g. an antibody or antibody fragment, that is substantially free of other antibodies or antibody fragments having different antigenic specificities. Moreover, an isolated antibody or antibody fragment may be substantially free of other cellular material and/or chemicals. Thus, in some aspects, antibodies provided are isolated antibodies which have been separated from antibodies with a different specificity. An isolated antibody may be a monoclonal antibody. An isolated antibody may be a recombinant monoclonal antibody. An isolated antibody that specifically binds to an epitope, isoform or variant of a target may, however, have cross-reactivity to other related antigens, e.g., from other species (e.g., species homologs).

The term "recombinant antibody", as used herein, includes all antibodies that are prepared, expressed, created or segregated by means not existing in nature. For example antibodies isolated from a host cell transformed to express the antibody, antibodies selected and isolated from a recombinant, combinatorial human antibody library, and antibodies prepared, expressed, created or isolated by any other means that involve splicing of all or a portion of a human immunoglobulin gene, sequences to other DNA sequences or antibodies isolated from an animal (e.g., a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom. Preferably, such recombinant antibodies have variable regions in which the framework and CDR regions are derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies can be subjected to in vitro mutagenesis (or, when an animal transgenic for human Ig sequences is used, in vivo somatic mutagenesis) and thus the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and related to human germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire in vivo. A recombinant antibody may be a monoclonal antibody. In an embodiment, the antibodies and antibody fragment disclosed herein are isolated from the Ylanthia® antibody library as disclosed in US 13/321,564 or US 13/299,367, which both herein are incorporated by reference.

The term "monoclonal antibody" as used herein refers to a preparation of antibody molecules of single molecular composition. A monoclonal antibody composition displays a unique binding site having a unique binding specificity and affinity for particular epitopes.

As used herein the term "binds specifically to", "specifically binds to", is "specific to/for" or "specifically recognizes", or the like, refers to measurable and reproducible interactions such as binding between a target and an antibody or antibody fragment, which is determinative of the presence of the target in the presence of a heterogeneous population of molecules including biological molecules. For example, an antibody or antibody fragment that specifically binds to a target (which can be an antigen or an epitope of an antigen) is an antibody or antibody fragment that binds this target with greater affinity, avidity, more readily, and/or with greater duration than it binds to other targets. In certain embodiments, an antibody or antibody fragment specifically binds to an epitope on a protein that is conserved among the protein from different species. In another embodiment, specific binding can include, but does not require exclusive binding. The antibodies or antibody fragments disclosed herein specifically bind to human IL-17C. Preferably, the disclosed antibodies or antibody fragments specific for human IL-17C specifically bind to IL-17C of another species, such as IL-17C from mouse, rat, rhesus monkey and/or cynomolgus monkey. Even more preferred the antibodies or antibody fragments disclosed herein are specific for human IL-17C, cynomolgus monkey IL-17C and

mouse IL-17C. Methods for determining whether two molecules specifically bind are well known in the art and include, for example, a standard ELISA assay. The scoring may be carried out by standard color development (e.g. secondary antibody with horseradish peroxidase and tetramethyl benzidine with hydrogen peroxide). The reaction in certain wells is scored by the optical density, for example, at 450 nm. Typical background (=negative reaction) may be 0.1 OD; typical positive reaction may be 1 OD. This means the difference positive/negative can be more than 5-fold. Typically, determination of binding specificity is performed by using not a single reference antigen, but a set of about three to five unrelated antigens, such as milk powder, BSA, transferrin or the like.

The term "avidity" is used to describe the combined strength of multiple bond interactions between proteins. Avidity is distinct from affinity which describes the strength of a single bond. As such, avidity is the combined synergistic strength of bond affinities (functional affinity) rather than the sum of bonds. With the antibodies of the present disclosure, both antigen-binding sites from the VH/VL pairs simultaneously interact with IL-17C. Whilst each single binding interaction may be readily broken (depending on the relative affinity), because many binding interactions are present at the same time, transient unbinding of a single site does not allow the molecule to diffuse away, and binding of that site is likely to be reinstated. The overall effect is synergistic, strong binding of antigen to antibody.

As used herein, the term "affinity" refers to the strength of interaction between the polypeptide and its target at a single site. Within each site, the binding region of the polypeptide interacts through weak non-covalent forces with its target at numerous sites; the more interactions, the stronger the affinity.

The term " K_D ", as used herein, refers to the dissociation constant, which is obtained from the ratio of K_d to K_a (i.e. K_d/K_a) and is expressed as a molar concentration (M). K_D values for antigen binding moieties like e.g. monoclonal antibodies can be determined using methods well established in the art. Methods for determining the K_D of an antigen binding moiety like e.g. a monoclonal antibody are SET (soluble equilibrium titration) or surface plasmon resonance using a biosensor system such as a Biacore® system. In the present disclosure an antibody specific to IL-17C typically has a dissociation rate constant (K_D) (k_{off}/k_{on}) of less than $5 \times 10^{-2}M$, less than $10^{-2}M$, less than $5 \times 10^{-3}M$, less than $10^{-3}M$, less than $5 \times 10^{-4}M$, less than $10^{-4}M$, less than $5 \times 10^{-5}M$, less than $10^{-5}M$, less than $5 \times 10^{-6}M$, less than $10^{-6}M$, less than $5 \times 10^{-7}M$, less than $10^{-7}M$, less than $5 \times 10^{-8}M$, less than $10^{-8}M$, less than $5 \times 10^{-9}M$, less than $10^{-9}M$, less than $5 \times 10^{-10}M$, less than $10^{-10}M$, less than $5 \times 10^{-11}M$, less than $10^{-11}M$, less than

$5 \times 10^{-12} \text{M}$, less than 10^{-12}M , less than $5 \times 10^{-13} \text{M}$, less than 10^{-13}M , less than $5 \times 10^{-14} \text{M}$, less than 10^{-14}M , less than $5 \times 10^{-15} \text{M}$, or less than 10^{-15}M or lower.

"Cross competes" means the ability of an antibody, antibody fragment or other antigen-binding moieties to interfere with the binding of other antibodies, antibody fragments or antigen-binding moieties to a specific antigen in a standard competitive binding assay. The ability or extent to which an antibody, antibody fragment or other antigen-binding moieties is able to interfere with the binding of another antibody, antibody fragment or antigen-binding moieties to a specific antigen, and, therefore whether it can be said to cross-compete according to the invention, can be determined using standard competition binding assays. One suitable assay involves the use of the Biacore technology (e.g. by using the BIAcore 3000 instrument (Biacore, Uppsala, Sweden)), which can measure the extent of interactions using surface plasmon resonance technology. Another assay for measuring cross-competing uses an ELISA-based approach. A high throughput process for "epitope binning" antibodies based upon their cross-competition is described in International Patent Application No. WO 2003/48731. Cross-competition is present if the antibody or antibody fragment under investigation reduces the binding of one of the antibodies described in Table 1 to IL-17C by 60% or more, specifically by 70% or more and more specifically by 80% or more and if one of the antibodies described in Table 1 reduces the binding of said antibody or antibody fragment to IL-17C by 60% or more, specifically by 70% or more and more specifically by 80% or more.

The term "epitope" includes any proteinaceous region which is specifically recognized by an antibody or fragment thereof or a T-cell receptor or otherwise interacts with a molecule. Generally epitopes are of chemically active surface groupings of molecules such as amino acids or carbohydrate or sugar side chains and generally may have specific three-dimensional structural characteristics, as well as specific charge characteristics. As will be appreciated by one of skill in the art, practically anything to which an antibody can specifically bind could be an epitope.

"Binds the same epitope as" means the ability of an antibody, antibody fragment or other antigen-binding moiety to bind to a specific antigen and binding to the same epitope as the exemplified antibody when using the same epitope mapping technique for comparing the antibodies. The epitopes of the exemplified antibody and other antibodies can be determined using epitope mapping techniques. Epitope mapping techniques are well known in the art. For example, conformational epitopes are readily identified by determining spatial conformation of amino acids such as by, e.g., hydrogen/deuterium exchange, x-ray crystallography and two-dimensional nuclear magnetic resonance.

Compositions of the present disclosure may be used for therapeutic or prophylactic applications. The present disclosure, therefore, includes a pharmaceutical composition containing an antibody (or functional antibody fragment) as disclosed herein and a pharmaceutically acceptable carrier or excipient therefor. In a related aspect, the present disclosure provides a method for treating an inflammatory disorder. Such method contains the steps of administering to a subject in need thereof an effective amount of the pharmaceutical composition that contains an antibody (or functional antibody fragment) as described or contemplated herein.

The present disclosure provides therapeutic methods comprising the administration of a therapeutically effective amount of an IL-17C antibody as disclosed to a subject in need of such treatment. A "therapeutically effective amount" or "effective amount", as used herein, refers to the amount of an IL-17C antibody necessary to elicit the desired biological response. In accordance with the subject invention, the therapeutic effective amount is the amount of an IL-17C antibody necessary to treat and/or prevent a disease.

"Subject" or "species", as used in this context refers to any mammal, including rodents, such as mouse or rat, and primates, such as cynomolgus monkey (*Macaca fascicularis*), rhesus monkey (*Macaca mulatta*) or humans (*Homo sapiens*). Preferably the subject is a primate, most preferably a human.

Embodiments:

In one embodiment, the present disclosure refers to an antibody or antibody fragment specific for IL-17C wherein said antibody or antibody fragment comprises

- (a) a HCDR1 region comprising the amino acid sequence of SEQ ID No.: 7, a HCDR2 region comprising the amino acid sequence of SEQ ID No.: 8, a HCDR3 region comprising the amino acid sequence of SEQ ID No.: 9, a LCDR1 region comprising the amino acid sequence of SEQ ID No.: 13, a LCDR2 region comprising the amino acid sequence of SEQ ID No.: 14 and a LCDR3 region comprising the amino acid sequence of SEQ ID No.: 15, or
- (b) a HCDR1 region comprising the amino acid sequence of SEQ ID No.: 20, a HCDR2 region comprising the amino acid sequence of SEQ ID No.: 21, a HCDR3 region comprising the amino acid sequence of SEQ ID No.: 22, a LCDR1 region comprising the amino acid sequence of SEQ ID No.: 26, a LCDR2 region

comprising the amino acid sequence of SEQ ID No.: 27 and a LCDR3 region comprising the amino acid sequence of SEQ ID No.: 28.

In one embodiment, the present disclosure refers to an antibody or antibody fragment specific for IL-17C, wherein said antibody or antibody fragment comprises

the HCDR1 region of SEQ ID No.: 7, the HCDR2 region of SEQ ID No.: 8, the HCDR3 region of SEQ ID No.: 9, the LCDR1 region of SEQ ID No.: 13, the LCDR2 region of SEQ ID No.: 14 and the LCDR3 region of SEQ ID No.: 15, or

the HCDR1 region of SEQ ID No.: 20, the HCDR2 region of SEQ ID No.: 21, the HCDR3 region of SEQ ID No.: 22, the LCDR1 region of SEQ ID No.: 26, the LCDR2 region of SEQ ID No.: 27 and the LCDR3 region of SEQ ID No.: 28.

In another embodiment, the present disclosure refers to an antibody or antibody fragment specific for IL-17C wherein said antibody or antibody fragment comprises

(a) a HCDR1 region comprising the amino acid sequence of SEQ ID No.: 10, a HCDR2 region comprising the amino acid sequence of SEQ ID No.: 11, a HCDR3 region comprising the amino acid sequence of SEQ ID No.: 12, a LCDR1 region comprising the amino acid sequence of SEQ ID No.: 13, a LCDR2 region comprising the amino acid sequence of SEQ ID No.: 14 and a LCDR3 region comprising the amino acid sequence of SEQ ID No.: 15, or

(b) a HCDR1 region comprising the amino acid sequence of SEQ ID No.: 23, a HCDR2 region comprising the amino acid sequence of SEQ ID No.: 24, a HCDR3 region comprising the amino acid sequence of SEQ ID No.: 25, a LCDR1 region comprising the amino acid sequence of SEQ ID No.: 26, a LCDR2 region comprising the amino acid sequence of SEQ ID No.: 27 and a LCDR3 region comprising the amino acid sequence of SEQ ID No.: 28.

In a further embodiment, the present disclosure refers to an antibody or antibody fragment specific for IL-17C, wherein said antibody or antibody fragment comprises

the HCDR1 region of SEQ ID No.: 10, the HCDR2 region of SEQ ID No.: 11, the HCDR3 region of SEQ ID No.: 12, the LCDR1 region of SEQ ID No.: 13, the LCDR2 region of SEQ ID No.: 14 and the LCDR3 region of SEQ ID No.: 15, or

the HCDR1 region of SEQ ID No.: 23, the HCDR2 region of SEQ ID No.: 24, the HCDR3 region of SEQ ID No.: 25, the LCDR1 region of SEQ ID No.: 26, the LCDR2 region of SEQ ID No.: 27 and the LCDR3 region of SEQ ID No.: 28.

In one embodiment, the present disclosure refers to an antibody or antibody fragment specific for IL-17C wherein said antibody or antibody fragment comprises

- (a) a HCDR1 region comprising the amino acid sequence of SEQ ID No.: 7, a HCDR2 region comprising the amino acid sequence of SEQ ID No.: 8, a HCDR3 region comprising the amino acid sequence of SEQ ID No.: 9, a LCDR1 region comprising the amino acid sequence of SEQ ID No.: 13, a LCDR2 region comprising the amino acid sequence of SEQ ID No.: 14 and a LCDR3 region comprising the amino acid sequence of SEQ ID No.: 15, or
- (b) a HCDR1 region comprising the amino acid sequence of SEQ ID No.: 10, a HCDR2 region comprising the amino acid sequence of SEQ ID No.: 11, a HCDR3 region comprising the amino acid sequence of SEQ ID No.: 12, a LCDR1 region comprising the amino acid sequence of SEQ ID No.: 13, a LCDR2 region comprising the amino acid sequence of SEQ ID No.: 14 and a LCDR3 region comprising the amino acid sequence of SEQ ID No.: 15, or
- (c) a HCDR1 region comprising the amino acid sequence of SEQ ID No.: 20, a HCDR2 region comprising the amino acid sequence of SEQ ID No.: 21, a HCDR3 region comprising the amino acid sequence of SEQ ID No.: 22, a LCDR1 region comprising the amino acid sequence of SEQ ID No.: 26, a LCDR2 region comprising the amino acid sequence of SEQ ID No.: 27 and a LCDR3 region comprising the amino acid sequence of SEQ ID No.: 28.
- (d) a HCDR1 region comprising the amino acid sequence of SEQ ID No.: 23, a HCDR2 region comprising the amino acid sequence of SEQ ID No.: 24, a HCDR3 region comprising the amino acid sequence of SEQ ID No.: 25, a LCDR1 region comprising the amino acid sequence of SEQ ID No.: 26, a LCDR2 region comprising the amino acid sequence of SEQ ID No.: 27 and a LCDR3 region comprising the amino acid sequence of SEQ ID No.: 28.

In one embodiment, the present disclosure refers to an antibody or antibody fragment specific for IL-17C, wherein said antibody or antibody fragment comprises

the HCDR1 region of SEQ ID No.: 7, the HCDR2 region of SEQ ID No.: 8, the HCDR3 region of SEQ ID No.: 9, the LCDR1 region of SEQ ID No.: 13, the LCDR2 region of SEQ ID No.: 14 and the LCDR3 region of SEQ ID No.: 15, or

the HCDR1 region of SEQ ID No.: 10, the HCDR2 region of SEQ ID No.: 11, the HCDR3 region of SEQ ID No.: 12, the LCDR1 region of SEQ ID No.: 13, the LCDR2 region of SEQ ID No.: 14 and the LCDR3 region of SEQ ID No.: 15, or

the HCDR1 region of SEQ ID No.: 20, the HCDR2 region of SEQ ID No.: 21, the HCDR3 region of SEQ ID No.: 22, the LCDR1 region of SEQ ID No.: 26, the LCDR2 region of SEQ ID No.: 27 and the LCDR3 region of SEQ ID No.: 28, or

the HCDR1 region of SEQ ID No.: 23, the HCDR2 region of SEQ ID No.: 24, the HCDR3 region of SEQ ID No.: 25, the LCDR1 region of SEQ ID No.: 26, the LCDR2 region of SEQ ID No.: 27 and the LCDR3 region of SEQ ID No.: 28.

In another embodiment of the present disclosure the antibody or antibody fragment specifically binds to human IL-17C.

In another embodiment of the present disclosure the antibody or antibody fragment is a monoclonal antibody or antibody fragment.

In another embodiment of the present disclosure the antibody or antibody fragment is a human, humanized or chimeric antibody or antibody fragment. In another embodiment of the present disclosure the antibody or antibody fragment is of the IgG isotype. In another embodiment the antibody or antibody fragment is IgG1.

In one embodiment, the present disclosure refers to an antibody or antibody fragment specific for IL-17C, wherein said antibody or antibody fragment comprises

the HCDR1 region of SEQ ID No.: 7, the HCDR2 region of SEQ ID No.: 8, the HCDR3 region of SEQ ID No.: 9, the LCDR1 region of SEQ ID No.: 13, the LCDR2 region of SEQ ID No.: 14 and the LCDR3 region of SEQ ID No.: 15, and further comprises a heavy chain of SEQ ID No.: 17 or a light chain of SEQ ID No.: 16, or

the HCDR1 region of SEQ ID No.: 10, the HCDR2 region of SEQ ID No.: 11, the HCDR3 region of SEQ ID No.: 12, the LCDR1 region of SEQ ID No.: 13, the LCDR2 region of SEQ ID No.: 14 and the LCDR3 region of SEQ ID No.: 15 and further comprises a heavy chain of SEQ ID No.: 17 or a light chain of SEQ ID No.: 16, or

the HCDR1 region of SEQ ID No.: 20, the HCDR2 region of SEQ ID No.: 21, the HCDR3 region of SEQ ID No.: 22, the LCDR1 region of SEQ ID No.: 26, the LCDR2 region of SEQ ID No.: 27 and the LCDR3 region of SEQ ID No.: 28 and further comprises a heavy chain of SEQ ID No.: 30 or a light chain of SEQ ID No.: 29, or

the HCDR1 region of SEQ ID No.: 23, the HCDR2 region of SEQ ID No.: 24, the HCDR3 region of SEQ ID No.: 25, the LCDR1 region of SEQ ID No.: 26, the LCDR2 region of SEQ ID No.: 27 and the LCDR3 region of SEQ ID No.: 28, and further comprises a heavy chain of SEQ ID No.: 30 or a light chain of SEQ ID No.: 29.

In one embodiment, the present disclosure refers to an antibody or antibody fragment specific for IL-17C, wherein said antibody or antibody fragment comprises a heavy chain of SEQ ID No.: 17 and a light chain of SEQ ID No.: 16.

In one embodiment, the present disclosure refers to an antibody or antibody fragment specific for IL-17C, wherein said antibody or antibody fragment comprises a heavy chain of SEQ ID No.: 30 and a light chain of SEQ ID No.: 29.

In a further embodiment, the present disclosure refers to an antibody or antibody fragment specific for IL-17C, wherein said antibody or antibody fragment comprises a heavy chain of SEQ ID No.: 43 and a light chain of SEQ ID No.: 42.

In one embodiment, the present disclosure refers to an antibody or antibody fragment specific for IL-17C, wherein said antibody or antibody fragment comprises a heavy chain of SEQ ID No.: 56 and a light chain of SEQ ID No.: 55.

In another embodiment of the present disclosure the antibody or antibody fragment is an isolated antibody or antibody fragment.

In another embodiment of the present disclosure the antibody or antibody fragment is a recombinant antibody or antibody fragment.

In one embodiment, the present disclosure refers to an antibody or antibody fragment specific for IL-17C for use in the treatment of a disorder or condition associated with the undesired presence of IL-17C.

In one embodiment, the present disclosure refers to a nucleic acid composition comprising a nucleic acid sequence or a plurality of nucleic acid sequences encoding an antibody or antibody fragment specific for IL-17C, wherein said antibody or antibody fragment comprises

the HCDR1 region of SEQ ID No.: 7, the HCDR2 region of SEQ ID No.: 8, the HCDR3 region of SEQ ID No.: 9, the LCDR1 region of SEQ ID No.: 13, the LCDR2 region of SEQ ID No.: 14 and the LCDR3 region of SEQ ID No.: 15, or

the HCDR1 region of SEQ ID No.: 10, the HCDR2 region of SEQ ID No.: 11, the HCDR3 region of SEQ ID No.: 12, the LCDR1 region of SEQ ID No.: 13, the LCDR2 region of SEQ ID No.: 14 and the LCDR3 region of SEQ ID No.: 15, or

the HCDR1 region of SEQ ID No.: 20, the HCDR2 region of SEQ ID No.: 21, the HCDR3 region of SEQ ID No.: 22, the LCDR1 region of SEQ ID No.: 26, the LCDR2 region of SEQ ID No.: 27 and the LCDR3 region of SEQ ID No.: 28, or

the HCDR1 region of SEQ ID No.: 23, the HCDR2 region of SEQ ID No.: 24, the HCDR3 region of SEQ ID No.: 25, the LCDR1 region of SEQ ID No.: 26, the LCDR2 region of SEQ ID No.: 27 and the LCDR3 region of SEQ ID No.: 28.

In another embodiment, the present disclosure refers to a vector composition comprising a vector or a plurality of vectors comprising the nucleic acid sequence or plurality of nucleic acid sequences encoding an antibody or antibody fragment as disclosed in Table 1.

In one embodiment, the present disclosure refers to a cell comprising a vector composition comprising a vector or a plurality of vectors comprising the nucleic acid sequence or plurality of nucleic acid sequences encoding an antibody or antibody fragment as disclosed in Table 1.

In another embodiment, the present disclosure refers to a pharmaceutical composition comprising an antibody or antibody fragment as disclosed in Table 1 and a pharmaceutically acceptable carrier or excipient.

In one embodiment, said antibody or antibody fragment specific for IL-17C blocks the binding of IL-17C to the receptor of IL-17C. In a further embodiment, said antibody or antibody fragment specific for IL-17C blocks the binding of IL-17C to the receptor of IL-17C, wherein said receptor is IL17RE. In another embodiment the present disclosure refers to an antibody or antibody fragment specific for IL-17C, wherein said antibody or antibody fragment blocks the binding of IL-17C to IL17RE. In another embodiment said antibody or antibody fragment comprises the HCDR1 region of SEQ ID No.: 7, the HCDR2 region of SEQ ID No.: 8, the HCDR3 region of SEQ ID No.: 9, the LCDR1 region of SEQ ID No.: 13, the LCDR2 region of SEQ ID No.: 14 and the LCDR3 region of SEQ ID No.: 15, or

the HCDR1 region of SEQ ID No.: 10, the HCDR2 region of SEQ ID No.: 11, the HCDR3 region of SEQ ID No.: 12, the LCDR1 region of SEQ ID No.: 13, the LCDR2 region of SEQ ID No.: 14 and the LCDR3 region of SEQ ID No.: 15, or

the HCDR1 region of SEQ ID No.: 20, the HCDR2 region of SEQ ID No.: 21, the HCDR3 region of SEQ ID No.: 22, the LCDR1 region of SEQ ID No.: 26, the LCDR2 region of SEQ ID No.: 27 and the LCDR3 region of SEQ ID No.: 28, or

the HCDR1 region of SEQ ID No.: 23, the HCDR2 region of SEQ ID No.: 24, the HCDR3 region of SEQ ID No.: 25, the LCDR1 region of SEQ ID No.: 26, the LCDR2 region of SEQ ID No.: 27 and the LCDR3 region of SEQ ID No.: 28.

In another embodiment said antibody or antibody fragment comprises a heavy chain of SEQ ID No.: 17 and a light chain of SEQ ID No.: 16 or a heavy chain of SEQ ID No.: 30 and a light chain of SEQ ID No.: 29 or a heavy chain and a light chain that has at least 60%, at least 70 %, at least 80%, at least 90% or at least 95% identity to the a heavy chain of SEQ ID No.: 17 or 30 and to the light chain of SEQ ID No.: 16 or 29.

In another embodiment the present disclosure refers to an antibody or antibody fragment specific for IL-17C wherein said antibody or antibody fragment bivalently binds to an IL-17C homodimer and forms a complex consisting of said antibody or antibody fragment and one IL-17C homodimer and wherein said antibody or antibody fragment blocks the binding of IL-17C to IL17RE.

In certain embodiments, said antibody or antibody fragment specific for IL-17C blocks the binding of IL-17C to one or more receptors of IL-17C. In another embodiment said antibody or antibody fragment comprises the HCDR1 region of SEQ ID No.: 7, the HCDR2 region of SEQ ID No.: 8, the HCDR3 region of SEQ ID No.: 9, the LCDR1 region of SEQ ID No.: 13, the LCDR2 region of SEQ ID No.: 14 and the LCDR3 region of SEQ ID No.: 15, or

the HCDR1 region of SEQ ID No.: 10, the HCDR2 region of SEQ ID No.: 11, the HCDR3 region of SEQ ID No.: 12, the LCDR1 region of SEQ ID No.: 13, the LCDR2 region of SEQ ID No.: 14 and the LCDR3 region of SEQ ID No.: 15, or

the HCDR1 region of SEQ ID No.: 20, the HCDR2 region of SEQ ID No.: 21, the HCDR3 region of SEQ ID No.: 22, the LCDR1 region of SEQ ID No.: 26, the LCDR2 region of SEQ ID No.: 27 and the LCDR3 region of SEQ ID No.: 28, or

the HCDR1 region of SEQ ID No.: 23, the HCDR2 region of SEQ ID No.: 24, the HCDR3 region of SEQ ID No.: 25, the LCDR1 region of SEQ ID No.: 26, the LCDR2 region of SEQ ID No.: 27 and the LCDR3 region of SEQ ID No.: 28.

In another embodiment said antibody or antibody fragment comprises a heavy chain of SEQ ID No.: 17 and a light chain of SEQ ID No.: 16 or a heavy chain of SEQ ID No.: 30 and a light chain of SEQ ID No.: 29 or a heavy chain and a light chain that has at least 60%, at least 70 %, at least 80%, at least 90% or at least 95% identity to the a heavy chain of SEQ ID No.: 17 or 30 and to the light chain of SEQ ID No.: 16 or 29.

In alternative embodiments, said antibody or antibody fragment specific for the receptor of IL-17C blocks the binding of IL-17C to receptors of IL-17C, wherein the receptors of IL-17C include IL17RE and IL17RA. In alternative embodiments, said antibody or antibody fragment specific for the receptor of IL-17C blocks the binding of IL-17C to IL17RE and IL17RA. In certain embodiments, said antibody or antibody fragment specific for IL-17C blocks the binding of IL-17C to IL17RE with an IC_{50} concentration of less than 100nM, 90nM, 80nM, 70nM, 60nM, 50nM, 40nM, 30nM, 20nM, 10nM, 9nM, 8nM, 7nM, 6nM, 5nM, 4nM, 3nM, 2nM, 1nM, 100pM, 90pM, 80pM, 70pM, 60pM, 50pM, 40pM, 30pM, 20pM, 10pM, 9pM, 8pM, 7pM, 6pM, 5pM, 4pM, 3pM, 2pM or 1pM. In certain aspects the IC_{50} concentration can be determined by ELISA; SET, FACS or MSD (Meso Scale Discovery). In another aspect the IC_{50} concentration can be determined by the method as described herein in Example 3. In another embodiment said antibody or antibody fragment comprises a heavy chain of SEQ ID No.: 17 and a light chain of SEQ ID No.: 16 or a heavy chain of SEQ ID No.: 30 and a light chain of SEQ ID No.: 29 or a heavy chain and a light chain that has at least 60%, at least 70 %, at least 80%, at least 90% or at least 95% identity to the a heavy chain of SEQ ID No.: 17 or 30 and to the light chain of SEQ ID No.: 16 or 29.

In one embodiment the disclosed antibody or antibody fragment is specific for human IL-17C. In a further embodiment the disclosed antibody or antibody fragment specific for IL-17C is cross-reactive with IL-17C of another species, such as IL-17C from mouse, rat, rhesus monkey and/or cynomolgus monkey. In another embodiment the antibody or antibody fragment is specific for human IL-17C, cynomolgus monkey IL-17C and mouse IL-17C. In a further embodiment the antibody or antibody fragment is specific for human IL-17C, cynomolgus monkey IL-17C and mouse IL-17C. In another embodiment the antibody or antibody fragment is specific for human IL-17C, cynomolgus monkey IL-17C and mouse IL-17C, wherein said antibody or antibody fragment comprises

the HCDR1 region of SEQ ID No.: 7, the HCDR2 region of SEQ ID No.: 8, the HCDR3 region of SEQ ID No.: 9, the LCDR1 region of SEQ ID No.: 13, the LCDR2 region of SEQ ID No.: 14 and the LCDR3 region of SEQ ID No.: 15, or

the HCDR1 region of SEQ ID No.: 10, the HCDR2 region of SEQ ID No.: 11, the HCDR3 region of SEQ ID No.: 12, the LCDR1 region of SEQ ID No.: 13, the LCDR2 region of SEQ ID No.: 14 and the LCDR3 region of SEQ ID No.: 15, or

the HCDR1 region of SEQ ID No.: 20, the HCDR2 region of SEQ ID No.: 21, the HCDR3 region of SEQ ID No.: 22, the LCDR1 region of SEQ ID No.: 26, the LCDR2 region of SEQ ID No.: 27 and the LCDR3 region of SEQ ID No.: 28, or

the HCDR1 region of SEQ ID No.: 23, the HCDR2 region of SEQ ID No.: 24, the HCDR3 region of SEQ ID No.: 25, the LCDR1 region of SEQ ID No.: 26, the LCDR2 region of SEQ ID

No.: 27 and the LCDR3 region of SEQ ID No.: 28. In another embodiment said antibody or antibody fragment comprises a heavy chain of SEQ ID No.: 17 and a light chain of SEQ ID No.: 16 or a heavy chain of SEQ ID No.: 30 and a light chain of SEQ ID No.: 29 or a heavy chain and a light chain that has at least 60%, at least 70 %, at least 80%, at least 90% or at least 95% identity to the a heavy chain of SEQ ID No.: 17 or 30 and to the light chain of SEQ ID No.: 16 or 29.

In yet another embodiment the disclosed antibody or antibody fragment specifically binds to human IL-17C, cynomolgus monkey IL-17C and mouse IL-17C and blocks the binding of human IL-17C, cynomolgus monkey IL-17C and mouse IL-17C to its specific receptor IL17RE with an IC_{50} concentration of less than 100nM, 90nM, 80nM, 70nM, 60nM, 50nM, 40nM, 30nM, 20nM, 10nM, 9nM, 8nM, 7nM, 6nM, 5nM, 4nM, 3nM, 2nM, 1nM, 100pM, 90pM, 80pM, 70pM, 60pM, 50pM, 40pM, 30pM, 20pM, 10pM, 9pM, 8pM, 7pM, 6pM, 5pM, 4pM, 3pM, 2pM or 1pM. In another aspect said antibody is in IgG1 format. In another embodiment said IC_{50} concentration is determined in a Receptor Inhibition Assay as described herein in Example 3.

In yet another embodiment the disclosed antibody or antibody fragment specifically binds to human IL-17C and blocks the binding of human IL-17C to human IL17RE with an IC_{50} concentration of less than 100nM, 90nM, 80nM, 70nM, 60nM, 50nM, 40nM, 30nM, 20nM, 10nM, 9nM, 8nM, 7nM, 6nM, 5nM, 4nM, 3nM, 2nM, 1nM, 100pM, 90pM, 80pM, 70pM, 60pM, 50pM, 40pM, 30pM, 20pM, 10pM, 9pM, 8pM, 7pM, 6pM, 5pM, 4pM, 3pM, 2pM or 1pM. In another aspect said antibody is in IgG1 format. In another embodiments said IC_{50} concentration is determined in a Receptor Inhibition Assay as described herein in Example 3.

In yet another embodiment the disclosed antibody or antibody fragment specifically binds to cynomolgus monkey IL-17C and blocks the binding of cynomolgus monkey IL-17C to cynomolgus monkey IL17RE with an IC_{50} concentration of less than 100nM, 90nM, 80nM, 70nM, 60nM, 50nM, 40nM, 30nM, 20nM, 10nM, 9nM, 8nM, 7nM, 6nM, 5nM, 4nM, 3nM, 2nM, 1nM, 100pM, 90pM, 80pM, 70pM, 60pM, 50pM, 40pM, 30pM, 20pM, 10pM, 9pM, 8pM, 7pM, 6pM, 5pM, 4pM, 3pM, 2pM or 1pM. In another aspect said antibody is in IgG1 format. In another embodiments said IC_{50} concentration is determined in a Receptor Inhibition Assay as described herein in Example 3.

In yet another embodiment the disclosed antibody or antibody fragment specifically binds to human IL-17C, cynomolgus monkey IL-17C and mouse IL-17C, and blocks the binding of human IL-17C, cynomolgus monkey IL-17C and mouse IL-17C, to human IL17RE,

cynomolgus monkey IL17RE and mouse IL17RE, respectively, each with an IC₅₀ concentration of less than 100nM, 90nM, 80nM, 70nM, 60nM, 50nM, 40nM, 30nM, 20nM, 10nM, 9nM, 8nM, 7nM, 6nM, 5nM, 4nM, 3nM, 2nM, 1nM, 100pM, 90pM, 80pM, 70pM, 60pM, 50pM, 40pM, 30pM, 20pM, 10pM, 9pM, 8pM, 7pM, 6pM, 5pM, 4pM, 3pM, 2pM or 1pM. In a preferred embodiment said antibody or antibody fragment comprises

the HCDR1 region of SEQ ID No.: 7, the HCDR2 region of SEQ ID No.: 8, the HCDR3 region of SEQ ID No.: 9, the LCDR1 region of SEQ ID No.: 13, the LCDR2 region of SEQ ID No.: 14 and the LCDR3 region of SEQ ID No.: 15, or

the HCDR1 region of SEQ ID No.: 10, the HCDR2 region of SEQ ID No.: 11, the HCDR3 region of SEQ ID No.: 12, the LCDR1 region of SEQ ID No.: 13, the LCDR2 region of SEQ ID No.: 14 and the LCDR3 region of SEQ ID No.: 15, or

the HCDR1 region of SEQ ID No.: 20, the HCDR2 region of SEQ ID No.: 21, the HCDR3 region of SEQ ID No.: 22, the LCDR1 region of SEQ ID No.: 26, the LCDR2 region of SEQ ID No.: 27 and the LCDR3 region of SEQ ID No.: 28, or

the HCDR1 region of SEQ ID No.: 23, the HCDR2 region of SEQ ID No.: 24, the HCDR3 region of SEQ ID No.: 25, the LCDR1 region of SEQ ID No.: 26, the LCDR2 region of SEQ ID No.: 27 and the LCDR3 region of SEQ ID No.: 28. In another embodiment said antibody or antibody fragment comprises a heavy chain of SEQ ID No.: 17 and a light chain of SEQ ID No.: 16 or a heavy chain of SEQ ID No.: 30 and a light chain of SEQ ID No.: 29 or a heavy chain and a light chain that has at least 60%, at least 70 %, at least 80%, at least 90% or at least 95% identity to the heavy chain of SEQ ID No.: 17 or 30 and to the light chain of SEQ ID No.: 16 or 29. In another aspect said antibody is in IgG1 format. In another embodiments said IC₅₀ concentration is determined in a Receptor Inhibition Assay as described herein in Example 3.

In yet another embodiment the disclosed antibody or antibody fragment inhibits human IL-17C, cynomolgus monkey IL-17C and mouse IL-17C driven activation of a NF-κB reporter gene in NIH3T3 cells with an IC₅₀ concentration of less than 100pM, 90pM, 80pM, 70pM, 60pM, 50pM, 40pM, 30pM, 20pM, 10pM, 9pM, 8pM, 7pM, 6pM, 5pM, 4pM, 3pM, 2pM or 1pM. In a preferred embodiment said antibody or antibody fragment comprises

the HCDR1 region of SEQ ID No.: 7, the HCDR2 region of SEQ ID No.: 8, the HCDR3 region of SEQ ID No.: 9, the LCDR1 region of SEQ ID No.: 13, the LCDR2 region of SEQ ID No.: 14 and the LCDR3 region of SEQ ID No.: 15, or

the HCDR1 region of SEQ ID No.: 10, the HCDR2 region of SEQ ID No.: 11, the HCDR3 region of SEQ ID No.: 12, the LCDR1 region of SEQ ID No.: 13, the LCDR2 region of SEQ ID No.: 14 and the LCDR3 region of SEQ ID No.: 15, or

the HCDR1 region of SEQ ID No.: 20, the HCDR2 region of SEQ ID No.: 21, the HCDR3 region of SEQ ID No.: 22, the LCDR1 region of SEQ ID No.: 26, the LCDR2 region of SEQ ID No.: 27 and the LCDR3 region of SEQ ID No.: 28, or

the HCDR1 region of SEQ ID No.: 23, the HCDR2 region of SEQ ID No.: 24, the HCDR3 region of SEQ ID No.: 25, the LCDR1 region of SEQ ID No.: 26, the LCDR2 region of SEQ ID No.: 27 and the LCDR3 region of SEQ ID No.: 28. In another embodiment said antibody or antibody fragment comprises a heavy chain of SEQ ID No.: 17 and a light chain of SEQ ID No.: 16 or a heavy chain of SEQ ID No.: 30 and a light chain of SEQ ID No.: 29 or a heavy chain and a light chain that has at least 60%, at least 70 %, at least 80%, at least 90% or at least 95% identity to the heavy chain of SEQ ID No.: 17 or 30 and to the light chain of SEQ ID No.: 16 or 29. In another aspect said antibody is in IgG1 format. In another embodiments said IC₅₀ concentration is determined in a IL-17C-driven NF-κB reporter assay as described herein in Example 4.

In one embodiment the disclosed antibody or antibody fragment is specific for human IL-17C encoded by the amino acid sequence of SEQ ID No.: 1. In one embodiment the disclosed antibody or antibody fragment is specific for a polypeptide comprising the amino acid sequence of SEQ ID No.: 1. In a further embodiment said monoclonal antibody or antibody fragment is a monoclonal antibody specific for a polypeptide consisting of the amino acid sequence of SEQ ID No.: 1. In another embodiment the disclosed antibody or antibody fragment is specific for human IL-17C encoded by the amino acid sequence of SEQ ID No.: 1 and is a monoclonal antibody or antibody fragment.

In one embodiment the disclosed antibody or antibody fragment specific for IL-17C is a monoclonal antibody or antibody fragment.

In one embodiment the disclosed antibody or antibody fragment specific for IL-17C is a human, humanized or chimeric antibody. In certain embodiments, said antibody or antibody fragment specific for IL-17C is an isolated antibody or antibody fragment. In another embodiment said antibody or antibody fragment is a recombinant antibody or antibody fragment. In a further embodiment said antibody or antibody fragment is a recombinant human antibody or antibody fragment. In a further embodiment said recombinant human antibody or antibody fragment is an isolated recombinant human antibody or antibody fragment. In a further embodiment said recombinant human antibody or antibody fragment or isolated recombinant human antibody or antibody fragment is monoclonal.

In another embodiment the disclosed antibody or antibody fragment comprises a heavy chain of SEQ ID No.: 17 and a light chain of SEQ ID No.: 16 or a heavy chain of SEQ ID No.: 30 and a light chain of SEQ ID No.: 29 or a heavy chain and a light chain that has at least 60%, at least 70 %, at least 80%, at least 90% or at least 95% identity to the a heavy chain of SEQ ID No.: 17 or 30 and to the light chain of SEQ ID No.: 16 or 29.

In one embodiment the disclosed antibody or antibody fragment comprises a human heavy chain constant region and a human light chain constant region. In a further embodiment said human heavy chain constant region comprises the amino acid sequences of SEQ ID No.: 17 and the human light chain constant region comprises the amino acid sequences of SEQ ID No.: 16 or said human heavy chain constant region comprises the amino acid sequences of SEQ ID No.: 30 and the human light chain constant region comprises the amino acid sequences of SEQ ID No.: 29.

In one embodiment the disclosed antibody or antibody fragment is of the IgG isotype. In another embodiment said antibody is IgG1.

In one embodiment said antibody fragment is a bivalent antibody fragment.

In another embodiment, the present disclosure refers to an antibody or antibody fragment that cross-competes with an antibody described in Table 1. In one embodiment the present disclosure refers to an antibody or antibody fragment, wherein said antibody or antibody fragment cross-competes with an antibody or antibody fragment comprising 6 CDRs defined by Kabat of one of the antibodies in Table 1. In another embodiment the present disclosure refers to an antibody or antibody fragment specific for human IL-17C wherein said antibody or antibody fragment bivalently binds to an IL-17C homodimer and forms a complex consisting of said antibody or antibody fragment and one IL-17C homodimer and wherein said antibody or antibody fragment cross-competes with an antibody or antibody fragment comprising 6 CDRs defined by Kabat of one of the antibodies in Table 1.

In another embodiment the present disclosure refers to an antibody or antibody fragment, wherein said antibody or antibody fragment cross-competes with an antibody or antibody fragment comprising 6 CDRs, wherein the HCDR1 is the amino acid sequence of SEQ ID No.: 7, the HCDR2 is the amino acid sequence of SEQ ID No.: 8, the HCDR3 is the amino acid sequence of SEQ ID No.: 9, the LCDR1 is the amino acid sequence of SEQ ID No.: 13, the LCDR2 is the amino acid sequence of SEQ ID No.: 14 and the LCDR3 is the amino acid sequence of SEQ ID No.: 15. In another embodiment the present disclosure refers to an

antibody or antibody fragment, wherein said antibody or antibody fragment cross-competes with an antibody or antibody fragment comprising the VH according to SEQ ID No.: 17 and the VL according to SEQ ID No.: 16.

In another embodiment the present disclosure refers to an antibody or antibody fragment, wherein said antibody or antibody fragment cross-competes with an antibody or antibody fragment comprising 6 CDRs, wherein the HCDR1 is the amino acid sequence of SEQ ID No.: 20, the HCDR2 is the amino acid sequence of SEQ ID No.: 21, the HCDR3 is the amino acid sequence of SEQ ID No.: 22, the LCDR1 is the amino acid sequence of SEQ ID No.: 26, the LCDR2 is the amino acid sequence of SEQ ID No.: 27 and the LCDR3 is the amino acid sequence of SEQ ID No.: 28. In another embodiment the present disclosure refers to an antibody or antibody fragment, wherein said antibody or antibody fragment cross-competes with an antibody or antibody fragment comprising the VH according to SEQ ID No.: 30 and the VL according to SEQ ID No.: 29.

In another embodiment, the present disclosure refers to an antibody or antibody fragment that cross-competes with an antibody described in Table 1. In one embodiment the present disclosure refers to an antibody or antibody fragment, wherein said antibody or antibody fragment cross-competes with an antibody or antibody fragment comprising 6 CDRs defined by Chothia of one of the antibodies in Table 1. In another embodiment the present disclosure refers to an antibody or antibody fragment specific for human IL-17C wherein said antibody or antibody fragment bivalently binds to an IL-17C homodimer and forms a complex consisting of said antibody or antibody fragment and one IL-17C homodimer and wherein said antibody or antibody fragment cross-competes with an antibody or antibody fragment comprising 6 CDRs defined by Chothia of one of the antibodies in Table 1.

In another embodiment the present disclosure refers to an antibody or antibody fragment, wherein said antibody or antibody fragment cross-competes with an antibody or antibody fragment comprising 6 CDRs, wherein the HCDR1 is the amino acid sequence of SEQ ID No.: 10, the HCDR2 is the amino acid sequence of SEQ ID No.: 11, the HCDR3 is the amino acid sequence of SEQ ID No.: 12, the LCDR1 is the amino acid sequence of SEQ ID No.: 13, the LCDR2 is the amino acid sequence of SEQ ID No.: 14 and the LCDR3 is the amino acid sequence of SEQ ID No.: 15. In another embodiment the present disclosure refers to an antibody or antibody fragment, wherein said antibody or antibody fragment cross-competes with an antibody or antibody fragment comprising the VH according to SEQ ID No.: 17 and the VL according to SEQ ID No.: 18.

In another embodiment the present disclosure refers to an antibody or antibody fragment, wherein said antibody or antibody fragment cross-competes with an antibody or antibody fragment comprising 6 CDRs, wherein the HCDR1 is the amino acid sequence of SEQ ID No.: 23, the HCDR2 is the amino acid sequence of SEQ ID No.: 24, the HCDR3 is the amino acid sequence of SEQ ID No.: 25, the LCDR1 is the amino acid sequence of SEQ ID No.: 26, the LCDR2 is the amino acid sequence of SEQ ID No.: 27 and the LCDR3 is the amino acid sequence of SEQ ID No.: 28. In another embodiment the present disclosure refers to an antibody or antibody fragment, wherein said antibody or antibody fragment cross-competes with an antibody or antibody fragment comprising the VH according to SEQ ID No.: 30 and the VL according to SEQ ID No.: 29.

In a certain embodiment, the disclosure refers to an antibody or antibody fragment that cross-competes with an antibody described in Table 1 and reduces the specific binding of one of the antibodies described in Table 1 by at least 70%, 80% or 90% in an ELISA-based cross-competition assay. In a certain embodiment, the present disclosure refers to a monoclonal antibody or antibody fragment that cross-competes with an antibody described in Table 1 and reduces the specific binding of one of the antibodies described in Table 1 to IL-17C by at least 70%, 80% or 90% in an ELISA-based cross-competition assay. A representative assay set-up is illustrated in Example 6 in the present disclosure.

In another embodiment, the present disclosure refers to an antibody or antibody fragment that binds to (e.g., by binding, stabilizing, spatial distribution) the same epitope as one of the antibodies in Table 1. In a further embodiment said antibody or antibody fragment binds to (e.g., by binding, stabilizing, spatial distribution) the same epitope as an antibody or antibody fragment comprising 6 CDRs defined by Kabat of one of the antibodies in Table 1. In yet another embodiment said antibody or antibody fragment binds to (e.g., by binding, stabilizing, spatial distribution) the same epitope of IL-17C as an antibody or antibody fragment comprising 6 CDRs defined by Kabat of one of the antibodies in Table 1. In yet another embodiment said antibody or antibody fragment binds to (e.g., by binding, stabilizing, spatial distribution) the same epitope of polypeptide comprising the amino acid sequence of SEQ ID No.: 1 as an antibody or antibody fragment comprising 6 CDRs defined by Kabat of one of the antibodies in Table 1.

In another embodiment the present disclosure refers to an antibody or antibody fragment, wherein said antibody or antibody fragment binds to the same epitope as an antibody or antibody fragment comprising 6 CDRs, wherein the HCDR1 is the amino acid sequence of SEQ ID No.: 10, the HCDR2 is the amino acid sequence of SEQ ID No.: 11, the HCDR3 is the

amino acid sequence of SEQ ID No.: 12, the LCDR1 is the amino acid sequence of SEQ ID No.: 13, the LCDR2 is the amino acid sequence of SEQ ID No.: 14 and the LCDR3 is the amino acid sequence of SEQ ID No.: 15. In another embodiment the present disclosure refers to an antibody or antibody fragment, wherein said antibody or antibody fragment binds to the same epitope as an antibody or antibody fragment comprising the VH according to SEQ ID No.: 17 and the VL according to SEQ ID No.: 18.

In another embodiment the present disclosure refers to an antibody or antibody fragment, wherein said antibody or antibody fragment binds to the same epitope as an antibody or antibody fragment comprising 6 CDRs, wherein the HCDR1 is the amino acid sequence of SEQ ID No.: 23, the HCDR2 is the amino acid sequence of SEQ ID No.: 24, the HCDR3 is the amino acid sequence of SEQ ID No.: 25, the LCDR1 is the amino acid sequence of SEQ ID No.: 26, the LCDR2 is the amino acid sequence of SEQ ID No.: 27 and the LCDR3 is the amino acid sequence of SEQ ID No.: 28. In another embodiment the present disclosure refers to an antibody or antibody fragment, wherein said antibody or antibody fragment binds to the same epitope as an antibody or antibody fragment comprising the VH according to SEQ ID No.: 30 and the VL according to SEQ ID No.: 29.

Regions of a given polypeptide that include an epitope can be identified using any number of epitope mapping techniques, well known in the art. See, e.g., *Epitope Mapping Protocols in Methods in Molecular Biology*, Vol. 66 (Glenn E. Morris, Ed., 1996) Humana Press, Totowa, New Jersey. For example, epitopes may be determined by e.g., concurrently synthesizing large numbers of peptides on solid supports, the peptides corresponding to portions of the protein molecule, and reacting the peptides with antibodies while the peptides are still attached to the supports. Such techniques are known in the art and described in, e.g., U.S. Patent No. 4,708,871 ; Geysen et al., (1984) *Proc. Natl. Acad. Sci. USA* 8:3998-4002; Geysen et al., (1985) *Proc. Natl. Acad. Sci. USA* 82:78-182; Geysen et al., (1986) *Mol. Immunol.* 23:709-715. Similarly, epitopes are readily identified by determining spatial conformation of amino acids such as by, e.g., hydrogen/deuterium exchange, x-ray crystallography and two-dimensional nuclear magnetic resonance. See, e.g., *Epitope Mapping Protocols*, supra. Antigenic regions of proteins can also be identified using standard antigenicity and hydropathy plots, such as those calculated using, e.g., the Omega version 1.0 software program available from the Oxford Molecular Group. This computer program employs the Hopp/Woods method, Hopp et al., (1981) *Proc. Natl. Acad. Sci. USA* 78:3824-3828; for determining antigenicity profiles, and the Kyte-Doolittle technique, Kyte et al., (1982) *J. Mol. Biol.* 157:105-132; for hydropathy plots.

In one embodiment, the present disclosure refers to an antibody or antibody fragment comprising 6 CDRs defined by Kabat of any of the antibodies in Table 1. In another aspect, the disclosure pertains to an isolated monoclonal antibody or fragment thereof comprising 6 CDRs defined by Kabat of each of the antibodies in Table 1.

In another embodiment, the present disclosure refers to an antibody or antibody fragment comprising 6 CDRs defined by Chotia of any of the antibodies in Table 1. In another aspect, the disclosure pertains to an isolated monoclonal antibody or fragment thereof comprising 6 CDRs defined by Chotia of each of the antibodies in Table 1.

In certain embodiments, the present disclosure refers to the antibodies or antibody fragments disclosed in Table 1, wherein said antibodies or antibody fragments can bind to IL-17C with an affinity of about less than 100 nM, more preferably less than about 60 nM, and still more preferably less than about 30 nM. Further preferred are antibodies or antibody fragments that bind to IL-17C with an affinity of less than about 10 nM, and more preferably less than about 3 nM.

In certain embodiments, the present disclosure refers to the antibodies or antibody fragments disclosed in Table 1, wherein said antibodies or antibody fragments can bind to IL-17C with a monovalent affinity of about less than 100 nM, more preferably less than about 60 nM, and still more preferably less than about 30 nM. Further preferred are antibodies or antibody fragments that bind to IL-17C with a monovalent affinity of less than about 10 nM, and more preferably less than about 3 nM.

In another embodiment, the present disclosure refers to antibodies or antibody fragments specific for IL-17C, wherein said antibodies or antibody fragments have a monovalent affinity to IL-17C with a dissociation rate constant (K_D) of less than $5 \times 10^{-2} \text{M}$, less than 10^{-2}M , less than $5 \times 10^{-3} \text{M}$, less than 10^{-3}M , less than $5 \times 10^{-4} \text{M}$, less than 10^{-4}M , less than $5 \times 10^{-5} \text{M}$, less than 10^{-5}M , less than $5 \times 10^{-6} \text{M}$, less than 10^{-6}M , less than $5 \times 10^{-7} \text{M}$, less than 10^{-7}M , less than $5 \times 10^{-8} \text{M}$, less than 10^{-8}M , less than $5 \times 10^{-9} \text{M}$, less than 10^{-9}M , less than $5 \times 10^{-10} \text{M}$, less than 10^{-10}M , less than $5 \times 10^{-11} \text{M}$, less than 10^{-11}M , less than $5 \times 10^{-12} \text{M}$, less than 10^{-12}M , less than $5 \times 10^{-13} \text{M}$, less than 10^{-13}M , less than $5 \times 10^{-14} \text{M}$, less than 10^{-14}M , less than $5 \times 10^{-15} \text{M}$, or less than 10^{-15}M and wherein said antibodies or antibody fragments in a bivalent format have an affinity to IL-17C with a dissociation rate constant (K_D) which is at least 2-fold, 5-fold, 10-fold, 100-fold, 1000-fold, 10000-fold, 100000-fold lower than the dissociation rate constant (K_D) in a monovalent format. In a further embodiment the bivalent affinity of said

antibodies or antibody fragments is determined in IgG-format, wherein the monovalent affinity of said antibodies or antibody fragments is determined in Fab-format.

The compositions of the present disclosure are preferably pharmaceutical compositions comprising an antibody or antibody fragment specific for IL-17C as disclosed herein and a pharmaceutically acceptable carrier, diluent or excipient, for the treatment of an inflammatory disorder or cancer. Such carriers, diluents and excipients are well known in the art, and the skilled artisan will find a formulation and a route of administration best suited to treat a subject with the IL-17C antibodies or antibody fragments of the present disclosure.

In another embodiment the present disclosure refers to pharmaceutical compositions comprising an antibody or antibody fragment specific for IL-17C as disclosed herein for the use in the treatment of a disorder or condition associated with the undesired presence of IL-17C. In another embodiment said condition associated with the undesired presence of IL-17C is an inflammatory disorder or cancer. In another embodiment said inflammatory disorder is rheumatoid arthritis, psoriasis, pulmonary inflammation, COPD and/or atopic dermatitis (AD), including moderate-to-severe AD. In a preferred embodiment said inflammatory disorder is atopic dermatitis (AD) and/or moderate-to-severe AD.

In another embodiment the present disclosure refers to the use of said pharmaceutical compositions comprising an antibody or antibody fragment specific for IL-17C as disclosed herein in the preparation of a medicament for the treatment of a disorder or condition associated with the undesired presence of IL-17C. In another embodiment said condition associated with the undesired presence of IL-17C is an inflammatory disorder or cancer. In another embodiment said inflammatory disorder is rheumatoid arthritis, psoriasis, pulmonary inflammation, COPD and/or atopic dermatitis (AD), including moderate-to-severe AD. In a preferred embodiment said inflammatory disorder is atopic dermatitis (AD) and/or moderate-to-severe AD.

In another embodiment the present disclosure refers to the use of said pharmaceutical composition for the treatment of a disorder or condition associated with the undesired presence of IL-17C. In another embodiment said condition associated with the undesired presence of IL-17C is an inflammatory disorder or cancer. In another embodiment said inflammatory disorder is rheumatoid arthritis, psoriasis, pulmonary inflammation, COPD and/or atopic dermatitis (AD), including moderate-to-severe AD. In a preferred embodiment said inflammatory disorder is atopic dermatitis (AD) and/or moderate-to-severe AD.

In another aspect, provided herein is a method of treating atopic dermatitis (AD) and/or moderate-to-severe atopic dermatitis (AD) in a subject, the method comprising administering a pharmaceutical composition comprising a therapeutically effective amount of the IL-17C antibodies or antibody fragments of the present disclosure. In one embodiment said subject is resistant, non-responsive or inadequately responsive to treatment by either a topical corticosteroid (TCS) or a calcineurin inhibitor. In another embodiment the subject is a subject in need thereof. In a preferred embodiment said subject is a human. In alternative aspects said subject is a rodent, such as a rat or a mouse.

In another embodiment, the present disclosure refers to a method for the prophylaxis of an inflammatory disorder in a subject, said method comprising administering an IL-17C antagonist to said subject. "Prophylaxis" as used in this context refers to methods which aim to prevent the onset of a disease or which delay the onset of a disease. In some embodiments said subject is a human. In alternative aspects said subject is a rodent, such as a rat or a mouse.

In some embodiments, the antibodies or antibody fragments specific for IL-17C of the present disclosure are administered subcutaneously. In other aspects the antibodies or antibody fragments specific for IL-17C of the present disclosure are administered intravenously, intra-articularly or intra-spinally.

In one embodiment, the disclosure pertains to an isolated monoclonal antibody or fragment thereof comprising a VH and a VL of any of the antibodies in Table 1.

In another embodiment, the disclosure pertains to an isolated monoclonal antibody or fragment thereof comprising a Heavy chain (IgG1) and a Light chain of any of the antibodies in Table 1.

In another embodiment, the disclosure refers to an isolated nucleic acid encoding a heavy chain sequence and/or light chain sequence of an antibody that binds to IL-17C the nucleic acid comprising

a HCDR1 region of SEQ ID No.: 58, the HCDR2 region of SEQ ID No.: 59, the HCDR3 region of SEQ ID No.: 60, the LCDR1 region of SEQ ID No.: 64, the LCDR2 region of SEQ ID No.: 65 and the LCDR3 region of SEQ ID No.: 66, or

a HCDR1 region of SEQ ID No.: 61, the HCDR2 region of SEQ ID No.: 62, the HCDR3 region of SEQ ID No.: 63, the LCDR1 region of SEQ ID No.: 64, the LCDR2 region of SEQ ID No.: 65 and the LCDR3 region of SEQ ID No.: 66, or

a HCDR1 region of SEQ ID No.: 33, the HCDR2 region of SEQ ID No.: 34, the HCDR3 region of SEQ ID No.: 35, the LCDR1 region of SEQ ID No.: 39, the LCDR2 region of SEQ ID No.: 40 and the LCDR3 region of SEQ ID No.: 41, or

a HCDR1 region of SEQ ID No.: 36, the HCDR2 region of SEQ ID No.: 37, the HCDR3 region of SEQ ID No.: 38, the LCDR1 region of SEQ ID No.: 39, the LCDR2 region of SEQ ID No.: 40 and the LCDR3 region of SEQ ID No.: 41, or

a HCDR1 region of SEQ ID No.: 46, the HCDR2 region of SEQ ID No.: 47, the HCDR3 region of SEQ ID No.: 48, the LCDR1 region of SEQ ID No.: 52, the LCDR2 region of SEQ ID No.: 53 and the LCDR3 region of SEQ ID No.: 54, or

a HCDR1 region of SEQ ID No.: 49, the HCDR2 region of SEQ ID No.: 50, the HCDR3 region of SEQ ID No.: 51, the LCDR1 region of SEQ ID No.: 52, the LCDR2 region of SEQ ID No.: 53 and the LCDR3 region of SEQ ID No.: 54.

In another embodiment, the disclosure refers to a nucleic acid encoding an isolated monoclonal antibody or fragment thereof wherein the nucleic acid comprises a VH region of SEQ ID No.: 19 and a VL region of SEQ ID No.: 18, or a VH region and a VL region that has at least 60%, at least 70 %, at least 80%, at least 90% or at least 95% identity to the VH region of SEQ ID No.: 19 and/or the VL region of SEQ ID No.: 18.

In another embodiment, the disclosure refers to a nucleic acid encoding an isolated monoclonal antibody or fragment thereof wherein the nucleic acid comprises a VH region of SEQ ID No.: 68 and a VL region of SEQ ID No.: 67, or a VH region and a VL region that has at least 60%, at least 70 %, at least 80%, at least 90% or at least 95% identity to the VH region of SEQ ID No.: 68 and/or the VL region of SEQ ID No.: 67.

In another embodiment, the disclosure refers to a nucleic acid encoding an isolated monoclonal antibody or fragment thereof wherein the nucleic acid comprises a VH region of SEQ ID No.: 32 and a VL region of SEQ ID No.: 31, or a VH region and a VL region that has at least 60%, at least 70 %, at least 80%, at least 90% or at least 95% identity to the VH region of SEQ ID No.: 32 and/or the VL region of SEQ ID No.: 31.

In another embodiment, the disclosure refers to a nucleic acid encoding an isolated monoclonal antibody or fragment thereof wherein the nucleic acid comprises a Heavy chain (IgG1) of SEQ ID No.: 45 and a Light chain of SEQ ID No.: 44.

In another embodiment, the disclosure refers to a nucleic acid encoding an isolated monoclonal antibody or fragment thereof wherein the nucleic acid comprises a Heavy chain (IgG1) of SEQ ID No.: 70 and a Light chain of SEQ ID No.: 69.

In another embodiment, the disclosure refers to a nucleic acid encoding an isolated monoclonal antibody or fragment thereof wherein the nucleic acid comprises a Heavy chain (IgG1) of SEQ ID No.: 71 and a Light chain of SEQ ID No.: 57.

In another embodiment, the disclosure refers to a nucleic acid encoding an isolated monoclonal antibody or fragment thereof wherein the nucleic acid comprises a VH and a VL of any of the antibodies in Table 1.

In another embodiment, the disclosure refers to a nucleic acid encoding an isolated monoclonal antibody or fragment thereof wherein the nucleic acid comprises a Heavy chain (IgG1) and a Light chain of any of the antibodies in Table 1.

In another embodiment, the disclosure refers to a method of producing an isolated monoclonal antibody or fragment thereof of any of the antibodies in Table 1.

Table 1: Antibody sequences

Antibody #		SEQ ID No.:	[aa] / DNA
MAB#1	HCDR1(Kabat)	SEQ ID No.:7	DYAMH
	HCDR2(Kabat)	SEQ ID No.:8	YIGGVGEGTQYAESVKG
	HCDR3(Kabat)	SEQ ID No.:9	GFAIRYYGFDY
	HCDR1 (Chothia)	SEQ ID No.:10	GFTVSDY
	HCDR2 (Chothia)	SEQ ID No.:11	GGVGEG
	HCDR3 (Chothia)	SEQ ID No.:12	GFAIRYYGFDY
	LCDR1(Kabat & Chothia)	SEQ ID No.:13	SGDKLGDKYAY
	LCDR2(Kabat & Chothia)	SEQ ID No.:14	QDSKRPS
	LCDR3(Kabat & Chothia)	SEQ ID No.:15	QVFTFPLVTT

Antibody #		SEQ ID No.:	[aa] / DNA
	VL	SEQ ID No.:16	SYELTQPPSVSVSPGQTASITCSGDKLGDKYAYW YQQKPGQSPVLVIYQDSKRPSGIPERFSGSNSGN TATLTISGTQAEDEADYYCQVFTFPLVTTVFGGGT KLTVLGQ
	VH	SEQ ID No.:17	EVQLLES GGGLVQP GGSLRLSCAASGFTVSDYAM HWVRQAPGKGLEWVSYIGGVGEGTQYAESVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYYCARGFAI RYYGFDYWGGQGLTVTVSS
	VL (DNA)	SEQ ID No.:18	agctatgaactgaccagccgagcggttagcgtagccaggcca gaccgcccagcattacgttagcggcgacaaactggcgacaaatc gcctactggtatcagcagaaaccgggcccagagcccggtgctggtatc tatcaggatagcaaacgcccagcggcattccagaacgcttagcgg cagcaacagcggcaacaccgcccaccctgaccattagcggcaccca ggccgaagacgaagccgatttactgccaggtttcactttcccgctgg ttactactgtgttggcgggcggtaccaagctgaccgtgctgggcccag
	VH (DNA)	SEQ ID No.:19	gaagtgcagctgctggaagcgggtggcggtctggtgcagccagggtg tagcctgcgcctgagctgtgcccgaagcggcttcacagtgccgacta cgcaatgcattgggtgcgccaagcaccaggcaaaaggcctggaatgg gtgagttacataggtggcggtgggtgaggggacacaatatgcagagag cgtgaaaggctcgcttaccattagtcgcgataacagcaaaaacaccct gtatctgcaaatgaacagcctgcgggcagaagataccgcagtttattat tgccgcgtgggttcgcaatccgttattatggatttgatttggggccagg gcaccctggttactgtctcgagc
	HCDR1 (Kabat)	SEQ ID No.:33	gactacgcaatgcat
	HCDR2 (Kabat)	SEQ ID No.:34	tacataggtggcggtgggtgaggggacacaatatgcagagagcgtga aaggt
	HCDR3 (Kabat)	SEQ ID No.:35	ggtttcgcaatccgttattatggatttgattat
	HCDR1 (Chothia)	SEQ ID No.:36	ggcttcacagtgccgactac
	HCDR2 (Chothia)	SEQ ID No.:37	ggtggcgtgggtgagggg
	HCDR3 (Chothia)	SEQ ID No.:38	ggtttcgcaatccgttattatggatttgattat
	LCDR1 (Kabat & Chothia)	SEQ ID No.:39	agcggcgacaaactggcgacaaatcgcctac
	LCDR2 (Kabat & Chothia)	SEQ ID No.:40	caggatagcaaacgcccagc
	LCDR3 (Kabat & Chothia)	SEQ ID No.:41	cagggtttcactttcccgctggttactact
	Light chain	SEQ ID No.:42	SYELTQPPSVSVSPGQTASITCSGDKLGDKYAYW YQQKPGQSPVLVIYQDSKRPSGIPERFSGSNSGN TATLTISGTQAEDEADYYCQVFTFPLVTTVFGGGT KLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLIS DFYPGAVTVAWKADSSPVKAGVETTTPSKQSNK YAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKT VAPTECS

Antibody #		SEQ ID No.:	[aa] / DNA
	Heavy chain (IgG1)	SEQ ID No.:43	EVQLLES GGG LVQP GGS LRLSCAAS GFTVSDYAM HWVRQAPGKGLEWVSYIGGVGEGTQYAESVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYYCARGFAI RYYGFDYWGGTLVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNV NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLG GPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPVLDSDGSFFLYS KLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSL SLSPGK
	Light chain (DNA)	SEQ ID No.:44	agctatgaactgacccagccgagcggttagcgtagccaggcca gaccgccagcattacctgtagcgcgacaaactggcgacaaatac gcctactggtatcagcagaaaccgggagagcccggtgctggtatc tatcaggatagcaaacgcccagcgcgattccagaacgcttagcgg cagcaacagcggaacaccgccaccctgaccattagcggcaccga ggccgaagacgaagccgattattactgccagggtttcactttcccgctgg ttactactgtgttgccgcggtaccaagctgaccgtgctgggccagcc caaagccgcccctagcgtgaccctgtcccccaagcagcaggaa ctccaggccaacaaggccaccctgctgtgcctgatcagcgactctac cctggcgccgtgaccgtggcctggaaggccgatagcagccctgtgaa ggccggcggtggaaccaccaccccccagcaagcagagcaacaaca aatacgccgcccagcagctacctgagcctgacccccgagcagtgga gtcccacagatcctacagctgccaggtcacacacgagggcagcacc gtggaaaagaccgtggccccaccgagtgacgc

[illegible]

[illegible]

Antibody #		SEQ ID No.:	[aa] / DNA
MAB#2	HCDR1 (Kabat)	SEQ ID No.:20	SDHYIS
	HCDR2 (Kabat)	SEQ ID No.:21	YISSSGSTTYAESVKG
	HCDR3 (Kabat)	SEQ ID No.:22	QSYFLPYFDV
	HCDR1 (Chothia)	SEQ ID No.:23	GFTFSDH
	HCDR2 (Chothia)	SEQ ID No.:24	SSSGST
	HCDR3 (Chothia)	SEQ ID No.:25	QSYFLPYFDV
	LCDR1 (Kabat & Chothia)	SEQ ID No.:26	TGTSSDVGSYNLVS
	LCDR2 (Kabat & Chothia)	SEQ ID No.:27	EGSKRPS
	LCDR3 (Kabat & Chothia)	SEQ ID No.:28	ASRGSRRVLYV
	VL	SEQ ID No.:29	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLV SWYQQHPGKAPKLMIYEGSKRPSGVSNRFGSK SGNTASLTISGLQAEDEADYYCASRGSRRVLYVFG GGTKLTVLGQ
	VH	SEQ ID No.:30	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDHYI SWIRQAPGKGLEWVSYISSSGSTTYAESVKG TISRDNANKNSLYLQMNSLRAEDTAVYYCARQSYFL LPYFDVWGQGLTVTVSS
	VL (DNA)	SEQ ID No.:31	cagagcgccctgaccagccagccagcgtagcggtagccaggcc agagcattaccattagctgcaccggcaccagcagcgagtgggcag ctataacctggttagctggtatcagcagcatccgggcaaagcccgaa actgatgatctatgaaggcagcaaacgccgagcggttagcaac cgcttagtgccagcaaaagcggaacaccgagcctgaccattag cgccctgcaagccgaagacgaagccgattactactgcgcaagtcgg ggaagccgctggtgctgtatgttttggcggcggtaccaagctgaccgt gctgggccag
	VH (DNA)	SEQ ID No.:32	caggtgcagctggtggaagcggcggtggcctggtgaaaccaggcg gtagcctgcgctgagctgcgcgcagcggtttaccttagcgatca ttacattagctggtatcgccaggccccaggcaaaaggcctggaatgggt tagctatattagcagcagtgccagcaccacattacgcgagagcgt gaaaggccgcttaccattagccgcgataacgcgcaaaaacagcctgt atctgcaaatgaacagcctgcgggcccgaagataccgctgtattatt gcgcgcgacaatctactatttctgccttatttcgacgtttggggccagg gcacctggttactgtctcgagc
	HCDR1 (Kabat)	SEQ ID No.:46	agcgatcattacattagc
	HCDR2 (Kabat)	SEQ ID No.:47	tatattagcagcagtgccagcaccacattacgccgagagcgtgaa aggc
	HCDR3 (Kabat)	SEQ ID No.:48	caatcctactatttctgccttatttcgacgtt
	HCDR1 (Chothia)	SEQ ID No.:49	ggctttaccttagcgatcat
	HCDR2 (Chothia)	SEQ ID No.:50	agcagcagtgccagcacc
	HCDR3 (Chothia)	SEQ ID No.:51	caatcctactatttctgccttatttcgacgtt
	LCDR1 (Kabat & Chothia)	SEQ ID No.:52	accggcaccagcagcgacgtgggcagctataacctggttagc

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Working Examples

ANOVA	analysis of variance
BSA	bovine serum albumin
BW	body weight
CDR	Complementarity determining region
DLS	Dynamic Light Scattering
DMEM	Dulbecco's Modified Eagle Medium
EC ₅₀	50% effective concentration

ECD	extracellular domain
ECL	electrochemiluminescence
ELISA	enzyme-linked immunosorbent assay
EtOH	Ethanol
Fab	antigen-binding fragment
FBS	Foetal Bovine Serum
Fc	constant fragment
HPLC	High Performance Liquid Chromatography
i.p.	intraperitoneal(ly)
i.v.	intravenous(ly)
IC ₅₀	50% inhibitory concentration
IFN- γ	Interferon-gamma
Ig	immunoglobulin
IHC	immunohistochemistry
IL-17R	interleukin 17 receptor
IL-xx	interleukin xx
K _D	dissociation constant
MC903	calcipotriol
MPEK	mouse primary keratinocytes
mRNA	messenger ribonucleic acid
NF- κ B	nuclear factor kappa B
<i>p.o.</i>	<i>per os</i> , oral(ly)
PBS	phosphate buffered saline
qPCR	quantitative polymerase chain reaction
qRT-PCR	quantitative real-time polymerase chain reaction
SEM	standard error of the mean
Th2	Type 2 helper T cells

Example 1: Generation of Antigen, Fab fragments and antibodies

1.1 Antigen Generation and Quality control

Amino acid sequences of IL-17C from human, cynomolgus monkey and mouse, were aligned.

Without leader sequence, homology of 79% is shared among all three species.

	Human	Cynomolgus	Mouse
Human	100%	95%	79%
Cynomolgus		100%	79%
Mouse			100%

IL-17C from different species was purchased from different providers or produced in-house and solubilised, if necessary. Per 100 µg protein 4 µl biotinylation reagent of the ECL™ biotinylation module were added and incubated for 60 min at room temperature in the dark with gentle agitation. Subsequently biotinylated protein was purified using Zeba™ Desalt spin columns and OD280nm was determined.

Antigens were biotinylated by using the ECL™ biotinylation module (GE Healthcare; #1061918). After biotinylation the product was purified using Zeba™ Desalt spin columns (Pierce; #89889).

Biotinylated and non-biotinylated mouse, cynomolgus and human IL-17C were subjected to a quality control comprising analyses under denaturing, reducing and denaturing, non-reducing conditions in SDS-PAGE and in native state by High Pressure-Size Exclusion Chromatography (HP-SEC) and Dynamic Light Scattering (DLS).

HP-SEC was performed on a Dionex UltiMate 3000 Titanium HPLC system (Dionex Corporation, Germering, Germany) in combination with Wyatt miniDAWN Treos and Wyatt Optilab rEX (Wyatt Technology Europe, Dernbach, Germany). For separation a Tosoh TSK-Gel G3000SWxl column was used (Tosoh Bioscience, Stuttgart, Germany). For each sample 15 µg of protein was loaded onto the column, separation was performed at a flow rate of 0.5 ml/min and recorded analyzing the UV absorption at 280 nm. The running buffer was composed of 49 mM NaH₂PO₄, 51 mM Na₂HPO₄, 100 mM K₂SO₄, 0.0005% Tween-80 at pH 6.8.

All DLS experiments were performed using a DynaPro Titan cuvette system (Wyatt Technology Europe, Dernbach, Germany) with protein concentrations between 0.2 and 1.0 mg/ml. In case of precipitation or particle formation, the sample was centrifuged at 10.000 g for 5 minutes prior to the experiment.

The extracellular domain (ECD) of mouse IL-17 receptor E (UniProt Q8BH06, isoform 1) and human IL-17 receptor E (UniProt Q8NFR9) were cloned in the expression vector pMAX_vk_Fc2_His using KpnI and EcoRV resulting in C-terminal Fc2_H fusion constructs. Beside the natural leader (AG00158) a second construct with a Vk-Leader was generated (AG00159).

Both constructs were transiently expressed in HKB11 cells. The cell suspension was scaled up three days post transfection and the cell culture supernatant was harvested 6 days post transfection. After sterile filtration, the solution was subjected to protein A affinity chromatography. Buffer exchange was performed to PBS and samples were sterile filtered (0.2 µm pore size). Protein concentrations were determined by UV-spectrophotometry. Purity of the products was analysed under denaturing, reducing and denaturing, non-reducing conditions in SDS-PAGE and in native state by HP-SEC and DLS.

1.2. Pannings and Fab / Antibody generation

For the antibody generation the MorphoSys Ylanthia® library was used to select Fab fragments against human IL-17C. The MorphoSys Ylanthia® library (Tiller *et al.* mAbs 5:3, 1–26; May/June (2013) and U.S. Patent No. 8,728,981) is a commercially available phagemid library and employs the CysDisplay® technology for displaying the Fab on the phage surface (Lohning *et al.*, WO2001/05950).

To identify IL-17C - specific antibodies different panning strategies were used. Each panning strategy comprised at least 3 individual rounds of panning against the respective antigens including human IL-17C (SEQ ID NO.: 1) and mouse IL-17C.

The isolated clones identified were matured, engineered and/or germlined in order to increase affinity and/or functionality. Thereafter several hundred clones were screened and functionality was rigorously tested in *in vitro* assays comprising e.g. the evaluation of binding to human, cynomolgus monkey and mouse IL-17C via SET, inhibition of binding of human, cynomolgus monkey and mouse IL-17C to its respective IL-17RE and functional inhibition of IL-17C (IL-17RE-driven NF-κB reporter assay in mouse NIH3T3 cells and IL-17C mediated CSF3 expression in mouse primary keratinocytes (MPEK)).

Finally two preferred lead molecules (MAB#1 and MAB#2) were selected and are further described in the working examples as outlined below.

Example 2: Affinity determination in monovalent Fab and bivalent IgG format

Monovalent Fab and bivalent IgG affinity was determined by SET. Therefore purified Fabs were titrated on human, cynomolgus or mouse IL-17C for determination of KD. Respectively purified IgGs were titrated on human, cynomolgus or mouse IL-17C for EC₅₀ determination.

Solution equilibrium titration (SET) was basically performed as described in the literature (Friquet *et al.*, (1985) J. Immunol. Meth. 77: 305-19). In order to improve the sensitivity and accuracy of the SET method, it was transferred from classical ELISA to ECL based technology (Haenel *et al.* (2005) Anal Biochem. 339.1: 182-84).

Respective results for MAB#1 and MAB#2 are shown in Table 2 and Table 3 respectively.

Example 3: Characterization of IL-17C specific Fabs or IgGs for receptor inhibition activity

Purified IL-17C specific Fabs or IgGs, respectively were tested for its capacity to inhibit the binding of IL-17C to its specific receptor IL-17RE. Therefore MA6000 384-well plates (Meso Scale Discovery, MSD) were coated with 30 µl of mouse IL17RE/Fc chimeric protein at 75 ng/ml in PBS at 4°C overnight. The next day a serial antibody dilution (concentrations from 0.001 to 100 nM) were pre-incubated for 30 min at RT with an equal volume of biotinylated human/cynomolgus or mouse IL-17C to determine an IC₅₀ concentration for receptor binding inhibition. After blocking of plates for 1h with 2.5% BSA in PBST, previously formed antibody-ligand complexes were added for 1h to coated IL17RE/Fc and receptor binding was detected via Streptavidin-ECL using MSD Sector Imager.

Both antibodies (MAB#1 and MAB#2) equally inhibited interaction of human/cynomolgus or mouse IL-17C with IL-17RE in Fab and in IgG format. IC₅₀ concentrations in the double-digit pM-range were observed for both antibodies in IgG format throughout all three clinically relevant species. Results are shown in rows 3 and 4 in Table 2 and Table 3 respectively.

Example 4: Functional testing in IL-17C-driven NF- κ B reporter assay

Purified IL-17C specific IgGs were further tested for their ability to inhibit the biological activity of human, mouse and cynomolgus IL-17C in a functional cell based assay that monitors the IL-17C driven activation of a NF- κ B reporter gene in NIH3T3 cells overexpressing the murine IL-17RE.

NIH3T3 cells were cultured in DMEM supplemented with 10% FBS and 1% Pen/Strep at 37°C, 5% CO₂. For the assay, NIH3T3 cells were transfected in suspension with total amount of 100ng DNA (20 ng mouse IL-17RE expression construct, 50ng NF- κ B luciferase reporter construct and 30ng pBluescript) using the Polyplus jet-PEI transfection agent. In brief, the DNA was diluted in 5 μ l 150 mM NaCl (per well) and 0.2 μ l jet-PEI in 8 μ l 150 mM NaCl (per well) was prepared. After 5 minutes incubation at room temperature, the JetPEI[®] solution was added to the DNA solution and further incubated for 20-30 minutes at room temperature. NIH3T3 cells were diluted to have ~40,000 cells in 87 μ l medium. The cells were added to the DNA-JetPEI I[®] mix (87 μ l cells and 13 μ l DNA-JetPEI I[®] mix/well) and the final volume was transferred into 96 well plates.

After an overnight incubation at 37°C in a humidified 5% CO₂ incubator, the medium was removed and replaced jetPEI[®] with 90 μ l medium containing 5% FBS and 1% Pen/Strep. 10 μ l of a serial antibody dilution made in DPBS that was pre-incubated for 30 minutes at room temperature with an equal volume of purified recombinant IL-17C (either human IL-17C (Novus #NBP1-42910), mouse mIL-17C (R&D Systems #2306-mI-025) or cynomolgus IL-17C (produced in house)), was added to the cells. The final concentration of IL-17C was 0.5 ng/ml.

After incubating the plates at 37°C in CO₂ incubator, 100 μ l SteadyLite Plus (Perkin Elmer) is added followed by readout of the luminescence on the Envision (Perkin Elmer).

Both antibodies effectively reduced NF- κ B reporter gene activation mediated by IL-17RE in the presence of human, mouse and cynomolgus IL-17C. Respective results can be found in row 5 of Table 2 and Table 3 respectively.

Example 5: IL-17C-driven gene expression in primary human keratinocytes

Keratinocytes endogenously express the IL-17RE and IL-17RA receptors, both of which are needed for functional signaling of IL-17C. Human primary keratinocytes derived from

healthy individuals and mouse primary keratinocytes derived from C57BL/6 mice were therefore used to determine the capacity of MAB#1 IgG1 and MAB#2 IgG1 to inhibit the biological activity of respectively human and mouse IL-17C in a more physiological context.

NHEK (normal human epidermal keratinocytes) were obtained from Lonza and cultured in Keratinocyte Growth Medium with supplements (KGM-Gold™ Bullet kit, Lonza) following manufacturer's protocol. NHEKs that were sub-cultured to and cryopreserved at passage 3 were thawed and immediately seeded in KGM cell culture medium at 30,000 cells/well in a 96 well cell culture plate. After 2 days, the medium was removed and changed to KGM-Gold w/o hydrocortisone prior to addition of hIL-17C (Novus #NBP1-42910) and hTNF α (Peprotech #300-01A) to final concentrations of 10 ng/ml each.

For testing antibodies, the human IL-17C was first pre-incubated for 30 minutes at room temperature with an equal volume of a serial dilution of antibody made in DPBS. Cells were stimulated with recombinant IL-17C (pre-incubated with or without a dilution of antibody) in presence of TNF α . Co stimulation with IL-17C and TNF α is known to result in synergistic induction of various genes and was shown to be necessary as IL-17C alone has limited effect on the expression of investigated genes .

Cells were cultured for 48 hours and then total RNA was extracted using RNeasy 96 Kit (Qiagen), reverse transcribed using Taqman® Reverse Transcription Reagents (Applied Biosystems) and the expression of beta-defensin 2 DEFB4A (human) or CSF3 (mouse) genes was determined by quantitative polymerase chain reaction (qPCR). In brief, 10 μ l PCR reactions were prepared using Taqman® universal PCR master mix/No AmpErase® UNG and predesigned Assay-on-demand Gene expression primer/probe sets for DEFB4B or CSF3 (#Hs00823638_m1, all Applied Biosystems). qPCR was performed on the ViiA7™ Real-Time PCR instrument (Applied Biosystems). Gene expression was normalized to a housekeeping gene either β -actin (Taqman primer set #4310881E) or GAPDH (Taqman primer set #4310893E).

Both antibodies (MAB#1 and MAB#2) were shown to effectively reduce 2 DEFB4A (human) or CSF3 (mouse) gene expression respectively and confirmed their ability to neutralize the biological activity of human IL-17C and also mouse IL-17C (Table 2 and Table 3).

Overview of functional *in vitro* characterization:

Respective results from *in vitro* testing are summarized in Table 2 for MAB#1 and in Table 3 for MAB#2. The amino acid and the nucleic acid sequences of the variable regions and the CDRs of those two antibodies are shown in Table 1. Both antibodies fulfilled respective criteria and were considered as potential molecules for clinical development.

Table 2: Summary *in vitro* characterization MAB#1

MAB#1	Human IL-17C	Mouse IL-17C	Cynomolgus IL-17C
SET monovalent affinity (Fab)	$K_D = 3950 \pm 50 \text{ pM}$ (n=2)	$K_D = 28000 \pm 4000 \text{ pM}$ (n=2)	$K_D = 22000 \pm 100 \text{ pM}$ (n=2)
SET apparent affinity (IgG)	$EC_{50} = 19 \pm 6.9 \text{ pM}$ (n=3)	$EC_{50} = 387 \pm 63 \text{ pM}$ (n=3)	$EC_{50} = 257 \pm 59 \text{ pM}$
Receptor inhibition assay – Fab format	$IC_{50} = 2900 \text{ pM}$	$IC_{50} = 6000 \text{ pM}$	$IC_{50} = 2700 \text{ pM}$
Receptor inhibition assay – IgG format	$IC_{50} = 59 \text{ pM}$	$IC_{50} = 55 \text{ pM}$	$IC_{50} = 44 \text{ pM}$
NF- κ B reporter assay	$IC_{50} = 31.3 \pm 12.1 \text{ pM}$ (n=3)	$IC_{50} = 47.6 \pm 9.4 \text{ pM}$ (n=3)	$IC_{50} = 12.8 \pm 1.9 \text{ pM}$ (n=3)
Keratinocyte assay	$IC_{50} = 319.2 \pm 86.3 \text{ pM}$ (n=3)	$IC_{50} = 112.1 \pm 26.7 \text{ pM}$ (n=3)	n.d.

Table 3: Summary *in vitro* characterization MAB#2

MAB#2	Human IL-17C	Mouse IL-17C	Cynomolgus IL-17C
SET monovalent affinity (Fab)	$K_D = 37 \pm 17 \text{ pM}$ (n=2)	$K_D = 460 \pm 90 \text{ pM}$ (n=2)	$K_D = 63 \pm 20 \text{ pM}$ (n=2)
SET apparent affinity (IgG)	$EC_{50} = 16 \pm 4 \text{ pM}$ (n=3)	$EC_{50} = 323 \pm 12 \text{ pM}$ (n=3)	NT
Receptor inhibition assay – Fab format	$IC_{50} = 76 \text{ pM}$	$IC_{50} = 150 \text{ pM}$	$IC_{50} = 50 \text{ pM}$
Receptor inhibition assay – IgG format	$IC_{50} = 58 \text{ pM}$	$IC_{50} = 48 \text{ pM}$	$IC_{50} = 57 \text{ pM}$
NF- κ B reporter assay	$IC_{50} = 18.5 \pm 2.2 \text{ pM}$ (n=3)	$IC_{50} = 64.8 \pm 8.6 \text{ pM}$ (n=3)	$IC_{50} = 12.9 \pm 4.5 \text{ pM}$ (n=3)
Keratinocyte assay	$IC_{50} = 279.9 \pm 161.7 \text{ pM}$ (n=3)	$IC_{50} = 51.0 \pm 9.0 \text{ pM}$ (n=3)	n.d.

Example 6: ELISA-based cross-competition assay

Cross-competition of an anti-IL-17C antibody or another IL-17C binding agent may be detected by using an ELISA assay according to the following standard procedure.

The general principle of the ELISA-assay involves coating of an anti-IL-17C antibody (such as MAB#1 or MAB#2) onto the wells of an ELISA plate. An excess amount of a second, potentially cross-competitive, anti-IL-17C antibody is then added in solution (i.e. not bound to the ELISA plate). Subsequently a limited amount of IL-17C-Fc is then added to the wells.

The antibody which is coated onto the wells and the antibody in solution will compete for binding of the limited number of IL-17C molecules. The plate is then washed to remove IL-17C molecules that has not bound to the coated antibody and to also remove the second, solution phase antibody as well as any complexes formed between the second, solution phase antibody and IL-17C. The amount of bound IL-17C is then measured using an appropriate IL-17C detection reagent. Therefore, IL-17C may be fused with a tag, e.g. Fc, Flag, etc. which can be detected via an appropriate tag-specific agent.

An antibody in solution that is cross-competitive to the coated antibody will be able to cause a decrease in the number of IL-17C molecules that the coated antibody can bind relative to the number of IL-17C molecules that the coated antibody can bind in the absence of the second, solution phase antibody.

This assay is described in more detail further below for two antibodies termed Ab-X and Ab-Y. In the instance where Ab-X is chosen to be the immobilized antibody, it is coated onto the wells of the ELISA plate, after which the plates are blocked with a suitable blocking solution to minimize non-specific binding of reagents that are subsequently added. An excess amount of Ab-Y is then added to the ELISA plate such that the moles of Ab-Y IL-17C binding sites per well are at least 10 fold higher than the moles of Ab-X IL-17C binding sites that are used, per well, during the coating of the ELISA plate. IL-17C is added such that the moles of IL-17C added per well were at least 25-fold lower than the moles of Ab-X IL-17C binding sites that are used for coating each well. Following a suitable incubation period, the ELISA plate is washed and a detection reagent specific for the IL-17C antigen is added to measure the amount of IL-17C molecules specifically bound by the coated anti-IL-17C antibody (in this case Ab-X). The background signal for the assay is defined as the signal obtained in wells with the coated antibody (in this case Ab-X), second solution phase antibody (in this case Ab-Y), buffer only (i.e. no IL-17C) and detection reagents. The positive control signal for the assay is defined as

the signal obtained in wells with the coated antibody (in this case Ab-X), second solution phase antibody buffer only (i.e. no second solution phase antibody), IL-17C detection reagents. The ELISA assay needs to be run in such a manner so as to have the positive control signal be at least 6 times the background signal.

To avoid any artifacts (e.g. significantly different affinities between Ab-X and Ab-Y for IL-17C) resulting from the choice of which antibody to use as the coating antibody and which to use as the second (competitor) antibody, the cross-blocking assay needs to be run in two formats: 1) format 1 is where Ab-X is the antibody that is coated onto the ELISA plate and Ab-Y is the competitor antibody that is in solution and 2) format 2 is where Ab-Y is the antibody that is coated onto the ELISA plate and Ab-X is the competitor antibody that is in solution.

Example 7: IL-23 induced psoriasis-model in mice

To examine *in vivo* efficacy and therapeutic potential, both candidate antibodies were further evaluated in an IL-23 induced psoriasis-model in mice.

The IL-23 induced psoriasis-model in mice was essentially carried out as described by Rizzo H *et al.* J Immunol (2011) Vol. 186(3) pp. 1495-1502.

In brief, skin lesions were induced in Balb/C mice by intradermal injection of IL-23 into the ears (1 µg) for 4 consecutive days (day1 to day4). Measurement of gross ear thickness was done daily up to day 5 on which the mice were sacrificed. At sacrifice, the pinna ears were sampled and cut longitudinally in 2 halves. One half was fixed in formalin for in depth histological analysis of epidermal/dermal thickness of ear skin. The second half was immersed in RNAlater for quantitative reverse-transcription polymerase chain reaction (qRT-PCR) analysis of mRNA expression levels of disease-relevant IL-17A, IL-22 and IL-1β pro-inflammatory cytokines and LCN2, S100A8 and S100A9 anti-microbial proteins. Groups (n=10) of IL-23 injected mice were treated with the MAB#1 or MAB#2 antibodies which were administered twice *i.p.* at a dose of 10 mg/kg (once 3 days before and once just before the first IL-23 intradermal injection).

Each antibody was tested in 2 independent experiments divided over 3 different studies. In each study the following control groups (each n=10) were included:

A control group of mice did not receive daily injections of IL-23 but instead received daily intradermal injection of the same volume of a BSA/PBS solution. This group was treated with a negative control isotype antibody MOR03207 (2x 10 mg/kg, i.p.).

For each of the studies the gross ear thickness and epidermal thickness was followed over time and individual data points per animal were used to determine the % prevention of the IL-23 mediated thickening. qPCR expression data were expressed using the Rq (relative quantity) equation ($Rq=2^{-\Delta Ct}$ where $\Delta Ct = Ct(\text{gene of interest}) - Ct(\text{housekeeping gene})$) after normalization to cyclophilin A expression levels used as housekeeping gene. For all measurements, mean $\pm$ SEM data of groups were compared with a one-way analysis of variance (ANOVA) and Dunnett multiple comparison post hoc test using PRISM software. A “p” value of < 0.05 was considered to be statistically significant (*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$; ns: not significant)

In summary, the administration of both candidates IgGs MAB#1 and MAB#2 (2x10 mg/kg) ameliorated the IL-23 induced skin inflammation, demonstrating the *in vivo* efficacy and therapeutic potential of both antibodies. Both antibodies had similar effects at level of IL-23 induced epidermal thickening and a similar impact at level of IL-23 induced gene expression. (see Table 4).

Table 4: Summary *In vivo* efficacy in IL-23 model

	MAB#1	MAB#2
% prevention of Gross ear thickness (mean and significance in 2-3 studies)	-34 Significant in 2 out of 2 studies	-6 Not significant in 2 out of 2 studies
% prevention of epidermal thickness (mean and significance in 2-3 studies)	-62 Significant in 2 out of 2 studies	-50 Significant in 2 out of 2 studies
Number of disease related genes significantly reduced (in each of the 3 studies performed)	nt / 3 / 6	1 / 6 / nt

Example 8: MC903 mouse model of atopic dermatitis

The efficacy of the MAB#1 antibody in atopic dermatitis was examined in a non-infectious cutaneous inflammation mouse model of atopic dermatitis where topical application of the low-calcemic vitamin D3 analogue MC903 (calcipotriol) induces atopic dermatitis like

skin lesion characterized by a red and scaly skin, accompanied by an epidermal hyperplasia and dermal infiltration of various cell types as well as an increase of Th2 cytokine in skin and elevated serum IgE (Li M *et al.* Proc Natl Acad Sci USA (2006) Vol. 103(31) pp. 11736-11741; Li M *et al.* J Invest Dermatol. (2009) Vol. 129(2). pp. 498-502).

8.1 Animals

BALB/c mice (female, 8-week old) were obtained from Janvier Labs (France). Mice were kept on a 12 hours light/dark cycle (0700-1900). Temperature was maintained at 22°C, and food and water were provided *ad libitum*.

8.2. Experimental procedures

In order to induce an AD-like response, 2 nmol MC903 (Tocris, dissolved in ethanol) was topical applied in a volume of 20 µL on both ears of mice for 5 consecutive days. A non-disease control group received the same quantity of ethanol (EtOH).

The severity of skin inflammation (erythema and thickening) was observed daily. Ear thickness was measured with an electronic caliper (Mitutoyo). Inflammation was further assessed using an *in vivo* imaging technique. To that end, Prosense 680 probe (1.6 nmol, Perkin Elmer) was administered by intraperitoneal route 24 hours before imaging. Imaging was performed with the Bruker In-vivo Xtreme Imaging System. Images were captured by a deeply cooled 4MP CCD camera (f-stop 1.1, binning 2x2, 5 sec acquisition time, Ex 630 nm, Em 700 nm). For anatomical co-registration, a reflectance image was taken (f-stop 2.8, 0.175 sec acquisition time). All images were taken with a 190x190 field of view and images were analysed using Molecular Imaging Software version 7.1 (Bruker Biospin, Billerica, MA, USA). For each group, the mean values and standard error of mean (sem) was calculated using for each mouse the mean value of left and right ear.

At sacrifice, samples from ear skin were collected and fixed in 4% formaldehyde before embedding in paraffin. 4 µm-thick slices were stained with hematoxylin and eosin (H&E stain) for histomorphometric evaluation of epidermal thickness by image analysis with Sisn'Com software (France). Five fields per ear (high power field x20) covering the whole ear from top to bottom were measured, and the 5 values were averaged per ear and per mice (left/right ear). An additional set of tissue slices were prepared for IHC staining of IL-17C using the anti-IL-17C

biotinylated MAB antibody (and biotinylated MOR03207 isotype negative control antibody). Processing and staining was essentially done as described above.

Ear skin samples were also taken for analysis of cytokine expression using qPCR or ELISA. Ear tissue pieces for qPCR gene analysis were submerged in RNALater® stabilisation solution (Ambion) and stored at -20°C. Ear skin samples for quantification at protein level were immediately snap frozen in liquid N₂ and stored at -80°C. For gene expression analysis, tissue was disrupted and lysed in RNA lysis solution using Precellys homogenisator (microtubes filled with 1.4 mm ceramide beads, 3 times 3 cycles of 15 sec at 6000 rpm). Total RNA was further extracted using NucleoSpin® RNA Kit according to manufactures guidelines (Macherey-Nagel) and 300 ng was reverse-transcribed using Applied Biosystems™ High-Capacity cDNA Reverse Transcription Kit. 5 µL of 10-fold diluted cDNA was used in real-time quantitative PCR reactions using SYBR Green technology with gene-specific primers from Qiagen. qPCR was performed on the ViiA™ 7 Real-Time PCR System (Applied Biosystems). Gene expression was normalized to the expression of 3 different house-keeping genes (cyclophilin, b-actin and GAPDH) and expressed as relative mRNA level of specific gene expression as obtained using the $2^{-\Delta Ct}$ method, with $\Delta Ct = Ct_{\text{gene}} - \text{Geomean } Ct\text{-value (housekeeping genes)}$. For quantification of expression at protein level, tissues were first disrupted and lysed in 250 µL lysis buffer (T-PER™ Tissue Protein Extraction Reagent (Pierce) supplemented with Protease Inhibitor Cocktail (Roche) and Halt™ Phosphatase Inhibitor Cocktail (Pierce)) using Precellys homogenisator (microtubes filled with 2.8 mm metal beads, 10 min 14000 rpm at 4°C). The amount of TSLP in ears was determined using a TSLP mouse DuoSet ELISA kits from R&D System. The amount was normalized to total protein content in lysate which was determined using Coomassie Protein Assay Reagent (Thermo Fisher) in reference to BSA protein standard. Data were expressed as amount of cytokine in ear which was calculated using the formula: concentration cytokine in sample / concentration of protein in sample x total ear protein content.

The significance of effect of a treatment on each of the readouts was assessed with Prism® Software using one-way ANOVA followed by a Dunnett's multiple comparison post-hoc test versus the MC903 + MOR03207 control group with *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

8.3. Efficacy of MAB#1 in a Mouse Model of Atopic Dermatitis (Prophylactic)

The efficacy of various doses of MAB#1 in the MC903 atopic dermatitis model was assessed in a prophylactic setting. In brief, skin lesions were induced in BALB/c mice by topical

administration of 2 nmol MC903 (dissolved in ethanol) on both ears for 5 consecutive days; mice were sacrificed at Day 8. MAB#1 was administered i.p. 3 times, i.e. 3 days before, at start of and 4 days after the first MC903 application. Effects on ear swelling, ear inflammation, epidermal hyperplasia, dermal thickness and gene expression were evaluated. A group of mice which received an isotype negative control antibody (MOR03207) served as comparator. Dexamethasone (5 mg/kg in 0.5% methyl cellulose, administered daily by oral route (p.o.) as of the first day of MC903 application) was used as active comparator. Mice were randomly divided into equal groups (n=10).

The severity of skin inflammation (erythema and thickening) was followed during the course of the experiment. The gross ear thickness was measured using a Mitutoyo thickness gage during the course of the experiment. Inflammation was further assessed at Day 5 using an in vivo imaging technique as described in 8.2).

Ethanol (as vehicle control) had no effect on ears. In contrast, MC903-treated ears became red and swollen. Treatment with MAB#1 at doses of 2 mg/kg or higher significantly prevented ear thickening. The effect of MAB#1 was maximal at a dose of 10 mg/kg and was comparable to the effect of dexamethasone (Figure 1). In line with these observations, ear inflammation (assessed by in vivo imaging at Day 5) was clearly increased in MC903-treated animals and reduced by MAB#1 with significant and near maximal effect observed at a dose of 10 mg/kg (Figure 2).

To confirm the reduction of ear thickness by MAB#1, histological sections of ears collected at Day 8 were stained with hematoxylin and eosin for histomorphometric evaluation of epidermal and dermal thickness. Values of five fields per ear covering the whole ear from top to bottom were captured, and averaged per mouse. MAB#1 at doses of 10 mg/kg and higher significantly prevented the increase in thickness of both epidermal and dermal layer (Figure 3).

8.3.1 Effect of MAB#1 on Gene Expression

To further characterize the effect of MAB#1 in the MC903 atopic dermatitis-like skin inflammation model, the expression of various atopic dermatitis-relevant genes was analysed at mRNA level by qPCR or at protein level by enzyme-linked immunosorbent assay (ELISA). TSLP and IL-33 protein expression in ears and TARC level in plasma were increased by MC903 application and significantly inhibited upon treatment with MAB#1 at doses of 10 mg/kg

or higher (Figure 4). A similar inhibitory effect was observed with MAB#1 on several other genes that were upregulated in MC903-treated ears, like IL-31 (a cytokine linked with itch in atopic dermatitis), the Th2-cytokine IL-4, and other genes that have been shown to be upregulated in human atopic dermatitis, like S100A8/9 and IFN- γ . Vice versa, MAB#1 was shown to prevent the downregulation of FLG2 in MC903-treated ears, which might suggest a potential role of MAB#1 in restoring barrier function.

8.4 Efficacy of MAB#1 in a Mouse Model of Atopic Dermatitis (Therapeutic)

The efficacy of various doses of MAB#1 in the MC903 atopic dermatitis model was assessed in a more disease-relevant therapeutic setting. In brief, skin lesions were induced in BALB/c mice before the start of any treatment by topical administration of 2 nmol MC903 (dissolved in ethanol) on both ears for 5 consecutive days. MAB#1 was administered i.p. 4 times, with the first administration at the last day of MC903 skin application (Day 5) and following ones at Day 8, 12 and 15. Mice were sacrificed at Day 16. Effects on ear swelling, ear inflammation, epidermal hyperplasia, dermal thickness and gene expression were evaluated. In addition, effect on influx of immune cells (eosinophils, T cells and mast cells) was also evaluated. A group of mice which received an isotype negative control antibody (MOR03207) served as comparator. Dexamethasone (1 mg/kg in 0.5% methyl cellulose, administered p.o. starting as of the last day of MC903 application at Day 5 and subsequently from Day 8 to 12 and from Day 15 to 16) was used as active comparator.

8.4.1 Effect of MAB#1 on Gross Ear Thickness and Inflammation

The gross ear thickness was measured using a Mitutoyo thickness gage during the course of the experiment. Topical application of MC903 on ears elicited a marked increase in ear thickness as of Day 3 as compared to ears treated with ethanol (as vehicle control for MC903). Disease activity was well induced at Day 5 (i.e. day of first treatment) and continued to evolve after (even though MC903 application was stopped) as evident from a continued increase in ear swelling in the group treated with the negative control antibody MOR03207 (Figure 5). Treatment with MAB#1 at doses of 0.4 mg/kg or higher significantly reduced ear thickening as of Day 12, with the higher doses of MAB#1 having a stronger effect and significantly reducing ear thickness even at earlier time points (as of Day 8 for MAB#1 at 50 mg/kg and as of Day 10 for doses of 10 and 2 mg/kg). In line with these observations, ear inflammation as assessed by *in vivo* imaging (as described in 8.2) at Day 12, was still increased

in animals treated with negative control antibody and significantly reduced by MAB#1 at all doses, with maximal effect observed at dose of 2 mg/kg (Figure 6).

8.4.2 Effect of MAB#1 on Ear Epidermal/dermal Thickness

To confirm the reduction of ear thickness by MAB#1, histological sections of ears collected at Day 16 were stained with hematoxylin and eosin for histomorphometric evaluation of epidermal and dermal thickness. MAB#1 at doses of 2 mg/kg and higher strongly reduced the increase in thickness of both epidermal and dermal layer, in line with the measurements of gross ear thickness (Figure 7).

8.4.3 Effect of MAB#1 on dermal cell infiltration

To further characterize the effect of MAB#1 on disease processes in the MC903 atopic dermatitis model, we evaluated the effect on cell infiltrations. More specifically, we assessed the effect on eosinophils, T-lymphocytes and mast cells by immunohistochemistry (IHC) and subsequent quantification of the area that stained with respectively antibodies detecting eosinophil peroxidase, T cell marker CD3 and mast cell tryptases (for details see (Marsais, 2016)). In line with the increased inflammation and ear thickness, infiltration of eosinophils, T cells and to lesser extent mast cells was still prominent at Day 16 in ears of mice in which disease activity was induced by MC903. Treatment of MAB#1 reduced the dermal infiltration of all three cell types examined (Figure 8). A significant reduction in number of infiltrated eosinophils and T cells was observed at all MAB#1 doses tested with the higher dose of 50 mg/kg having the more stronger effect reducing the influx of these cell types to levels comparable to the effect of dexamethasone. The effect on mast cell infiltration was in general weaker but still significant: influx was significantly reduced by MAB#1 at the higher doses of 50 and 10 mg/kg.

8.4.4 Effect of MAB#1 on Gene Expression

Expression was analysed on ear skin samples or plasma collected at Day 16 either by qPCR for eight disease-relevant genes or by ELISA for TSLP and IL-33 produced in ears and TARC in plasma as described in 8.2.

No significant differential expression could be observed for most of the analysed genes between EtOH-treated non-disease control mice and mice in which disease was induced by application of MC903 for the first 5 days. Only levels of IL-33 protein and IL-4, S100A9 and

IFN- γ mRNA expression levels were still increased. Increased expression levels for those genes (except IFN- γ) were reduced by MAB#1 treatment as shown in Figure 9 at all dose levels.

8.5. Results

MAB#1 prevented the generation of an atopic dermatitis-like skin inflammation in the MC903 model, with a significant impact on epidermal and dermal thickening, inflammation and type 2 T helper cell (Th2)-like gene expression when dosed prophylactically at 3x10 mg/kg intraperitoneally (i.p.). Significant effects on gross ear thickness were already observed in this model at doses of 3x2 mg/kg (i.p.). Also in the therapeutic MC903 model MAB#1 improved skin inflammation. Significant therapeutic effects on gross ear thickness, epidermal thickening, inflammation and influx of eosinophils and T cells were observed at doses of 4x0.4 mg/kg (i.p.), up to doses of 4x2 to 10 mg/kg (i.p.).

Example 9: Flaky tail mouse model of Atopic Dermatitis

The efficacy of the MAB#1 antibody was evaluated in the Flaky Tail model. Flaky Tail mice have a mutation in the Flg and Matt (Matt^{ma/ma}Flg^{fl/fl}) genes resulting in skin barrier dysfunction. These mice spontaneously develop atopy and progressive dermatitis characterised by a mixed Th2/Th17 inflammatory phenotype and reproduce cardinal features of AD in man.

9.1. Animals & experimental procedures

Flaky tail (Matt^{ma/ma}Flg^{fl/fl}) mice on a congenic C57BL/6J background were used as described in Fallon et al (2009) Nat Genet. 41(5): 602–608 and Saunders et al (2013) J Allergy Clin Immunol 132(5): 1121-1129. Female Flaky tail mice, 9-10 weeks old, were randomized into four groups (8 mice per group) and treated for 6 weeks as follows:

- Group I: Isotype negative control antibody (MOR03207) (30 mg/kg, ip twice weekly x 6 weeks)
- Group II: MAB#1 (3mg/kg, ip twice weekly x 6 weeks)
- Group III: MAB#1(30mg/kg, ip twice weekly x 6 weeks)

- Group IV: Dexamethasone 2mg/kg (ip twice per week x 6 weeks) as active comparator

The severity of AD-like skin inflammation was scored using the macroscopic diagnostic criteria adapted from assessment of skin inflammation in the NC/Nga mouse model as described in Saunders et al (2013) J Allergy Clin Immunol 132(5): 1121-1129. In brief, a scoring system (0: none; 1: mild; 2: moderate; 3: marked) was applied to the signs of erythema, excoriation and scaling. The total scores for each mouse (with the maximum of 9) were calculated from the sum of the individual scores for each of the three parameters.

The occurrence of eczematous lesions in eyelid skin was monitored at end of the study and blepharitis was scored separately for its severity (0: normal, 1: eyelid erythema and/or edema, 2: eyelid erythema, edema and scaling, 3: eyelid erythema, edema, scaling, erosion). The maximum blepharitis score (mean of both eyes) for each mouse is 3.

9.2. Efficacy of MAB#1 in spontaneous & chronic Flaky tail mouse model of AD

Clinical scoring of skin inflammation shows that Flaky Tail mice had already signs of spontaneous eczematous-like dermatitis at start of treatment which further progressed during the 6-week follow up period into an overt dermatitis, in non-treated animals. Treatment with MAB#1 reduces progression with significant effect comparable to the effect of dexamethasone observed at the highest tested dose of 30 mg/kg (Figure 10). A similar effect of the MAB#1 antibody is observed at the level of blepharitis at the end of the treatment (Figure 11).

Claims

1. An antibody or antibody fragment specific for IL-17C wherein said antibody or antibody fragment comprises
 - (a) a HCDR1 region comprising the amino acid sequence of SEQ ID NO: 7, a HCDR2 region comprising the amino acid sequence of SEQ ID NO: 8, a HCDR3 region comprising the amino acid sequence of SEQ ID NO: 9, a LCDR1 region comprising the amino acid sequence of SEQ ID NO: 13, a LCDR2 region comprising the amino acid sequence of SEQ ID NO: 14 and a LCDR3 region comprising the amino acid sequence of SEQ ID NO: 15, or
 - (b) a HCDR1 region comprising the amino acid sequence of SEQ ID NO: 20, a HCDR2 region comprising the amino acid sequence of SEQ ID NO: 21, a HCDR3 region comprising the amino acid sequence of SEQ ID NO: 22, a LCDR1 region comprising the amino acid sequence of SEQ ID NO: 26, a LCDR2 region comprising the amino acid sequence of SEQ ID NO: 27 and a LCDR3 region comprising the amino acid sequence of SEQ ID NO: 28.
2. The antibody or antibody fragment according to claim 1, wherein said antibody or antibody fragment is specific for human IL-17C.
3. The isolated antibody or antibody fragment according to claim 2, wherein said antibody or antibody fragment is specific for human IL-17C, cynomolgus IL-17C and mouse IL-17C.
4. The antibody or antibody fragment according to claim 1, wherein said antibody or antibody fragment is a human, humanized or chimeric antibody or antibody fragment.
5. The antibody or antibody fragment according to claim 1, wherein said antibody or antibody fragment comprises the heavy chain amino acid sequence of SEQ ID NO: 17 and the light chain amino acid sequence of SEQ ID NO: 16.
6. The antibody or antibody fragment according to claim 1, wherein said antibody or antibody fragment comprises the heavy chain amino acid sequence of SEQ ID NO: 30 and the light chain amino acid sequence of SEQ ID NO: 29.
7. The antibody or antibody fragment according to claim 1, wherein said antibody or antibody fragment is an isolated antibody or antibody fragment.
8. The antibody or antibody fragment according to claim 1, wherein said antibody or antibody fragment is a recombinant antibody or antibody fragment.

9. A pharmaceutical composition comprising the antibody or antibody fragment according to claim 1 and a pharmaceutically acceptable carrier or excipient.
10. An antibody or antibody fragment specific for IL-17C wherein said antibody or antibody fragment comprises a HCDR1 region comprising the amino acid sequence of SEQ ID NO: 7, a HCDR2 region comprising the amino acid sequence of SEQ ID NO: 8, a HCDR3 region comprising the amino acid sequence of SEQ ID NO: 9, a LCDR1 region comprising the amino acid sequence of SEQ ID NO: 13, a LCDR2 region comprising the amino acid sequence of SEQ ID NO: 14 and a LCDR3 region comprising the amino acid sequence of SEQ ID NO: 15.
11. An antibody or antibody fragment specific for IL-17C wherein said antibody or antibody fragment comprises a HCDR1 region comprising the amino acid sequence of SEQ ID NO: 20, a HCDR2 region comprising the amino acid sequence of SEQ ID NO: 21, a HCDR3 region comprising the amino acid sequence of SEQ ID NO: 22, a LCDR1 region comprising the amino acid sequence of SEQ ID NO: 26, a LCDR2 region comprising the amino acid sequence of SEQ ID NO: 27 and a LCDR3 region comprising the amino acid sequence of SEQ ID NO: 28.