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Antibody- and chemokine constructs and their use in the treatment of autoimmune diseases

The present invention relates to antibody- and chemokine constructs against chemokine-receptor expressing cells, in particular against monocytes/macrophages expressing the chemokine receptor CCR5, and $CCR5^+$ T-cells. Furthermore, the invention relates to the use of antibody- and chemokine constructs for the destruction of chemokine-receptor expressing cells for treating autoimmune diseases and allergic diseases, especially for treating chronic inflammatory joint diseases. The antibody- and chemokine constructs of the invention enable the directed depletion of chemokine-receptor expressing cells and thus a directed immunosuppressive therapy of autoimmune diseases.

In Germany, about 1 % of the population suffer from rheumatoid arthritis. In addition, there is a number of other rheumatoid diseases also leading to arthritis. Currently, three groups of drugs - non-steroidal antirheumatics, cortisone preparations and second-line agents - and TNFα blocking agents are used for treating inflammatory joint diseases. Up to now, the therapy has focused on the local injection of cortisone preparations in combination with a systemic administration of antiphlogistics or second-line agents.

Non-steroidal antirheumatics have a mild analgetic and anti-inflammatory effect, but they have many side effects when applied frequently (e.g. gastric ulcers, nephroses). In high dosages, cortisone preparations have a strong decongestant and analgetic effect, however leading to a quick relapse after discontinuation of the therapy. Moreover, cortisone preparations cannot stop the destruction process of the joint disease. A long-term therapy with cortisone usually entails severe side effects (infections, Cushing's phenomenon, osteoporosis, parchment-like skin, metabolic and hormonal disorders). The local injection of cortisone also has the essential disadvantage that the activity of the migrated white blood cells is only reduced but not destroyed, thus leading to a quick relapse after discontinuation of the therapy. As

mentioned above, the same applies to the systemic application. Rarely is an inflammation due to the irritative effect of cortisone crystals aggravated after injection of cortisone. The duration of effect of a cortisone injection varies tremendously and ranges from primary ineffectiveness to a duration of effect of several weeks.

In rheumatology, second-line agents are used to achieve a long-term suppression of the inflammation and a reduction in cortisone preparations. Due to the considerable toxicity (allergies, infections, malign diseases, renal insufficiency, blood pressure crises, pulmonary diseases) it is necessary for medical specialists to attend closely to the patients. After beginning treatment, no therapeutic effect may be apparent for the first three months. Currently, there are 4 or 5 of such second-line agents at disposal, which are used individually at first or are combined if the therapy is not effective. Mostly, there is hardly anything known about the mode of action of second-line agents. It is not yet entirely clear whether the application of second-line agents can diminish the destruction of the joint. In recent years, a new group of substances has been introduced into the treatment of rheumatoid arthritis, which is based on the blocking of cell signal substances (particularly TNFα) by means of monoclonal antibodies or soluble receptor constructs.

In addition, there are time and again patients that do not respond to currently available therapies. In other cases, the conventional therapy has to be stopped due to intolerable side effects.

Hence, there is a need for a new therapeutic concept for the treatment of chronic inflammatory joint diseases or rheumatic diseases in general and other autoimmune diseases.

Thus, the technical problem underlying the present invention is to provide new therapeutic agents for treating inflammatory joint diseases and other autoimmune diseases as well as allergic diseases, which overcome the disadvantages of the state of the art.

The features defined in the independent claims serve to solve this problem.

Advantageous embodiments have been defined in the respective dependent claims.

This technical problem has been solved by providing antibody- or chemokine constructs which are capable of binding to a chemokine receptor on the surface of a target cell, wherein the binding of the construct to the chemokine receptor results in

the destruction of the target cell. The antibody- and chemokine constructs of the invention cause target cells expressing chemokine receptors, in particular leukocytes, to be selectively destroyed. The constructs of the invention include bispecific antibodies, antibody constructs, chemokine constructs, murine, chimeric or humanized antibodies and either bind both to a chemokine-receptor expressing target cell and to an antigen on the surface of effector cells, in particular a CD3 antigen or contain a toxin. The effector cells are preferred to be leukocytes, especially monocytes/macrophages or T-cells or dendritic cells.

In a study with more than 40 patients suffering from different joint diseases it was found that there is a very strong concentration of monocytes/macrophages expressing the chemokine receptor CCR5 and T-lymphocytes in the inflamed joint. In the joint, more than 90 % of the monocytes and T-lymphocytes express the chemokine receptor CCR5, while in the blood only 10 % or 20 % do so. Due to this expression pattern, the chemokine receptor CCR5 or chemokine receptors in general are a very suitable aim for a cell-depleting therapy. Thus, in a joint almost all monocytes and T-lymphocytes would be affected by a CCR5 depletion, while in the bloodstream only a very small number of these cells would be depleted. In the case of chronic arthritis, monocytes and T-lymphocytes are predominant cell types, with monocytes being mainly responsible for the joint destruction.

Surprisingly, it could be shown now that leukocytes expressing chemokine receptors, in particular CCR5, can be destroyed purposefully by means of newly developed antibody- and chemokine constructs.

While current treatment strategies essentially represent a symptomatic therapy and can influence the course of a joint disease and the joint destruction only to a limited extent and second-line agents, for instance, become effective only after several months and, in addition, like the other drugs used, have a considerable toxicity when applied over longer periods of time, the constructs of the invention trigger an almost complete depletion of monocytes/macrophages expressing chemokine receptors, especially $CCR5^+$, and lymphocytes in the joint within a few hours only. These cell types are responsible for chronic inflammation and joint destruction. Due to the depletion, a long-lasting effect can be achieved. Since monocytes are eliminated very effectively, the use of the antibody of the invention makes it possible for the joint destruction to be influenced in a positive way. The non-selective inhibition of the immune system by established second-line agents and TNFα-blocking agents is suspected to increase disposition for infections and tumour formation. In contrast, due to the distribution of chemokine-receptor expressing cells, in particular of CCR5

expressing leukocytes, the leukocytes involved in the inflammation process can be eliminated to a very great extent without considerably influencing the immune defence altogether. All in all, the antibody of the invention makes a therapy possible which has a small range of side effects, simultaneously improving the course of the joint disease and preventing joint destruction.

In a preferred embodiment, the construct is a bispecific antibody which is directed with one specificity against a chemokine receptor, preferably against a human chemokine receptor and most preferably against the human chemokine receptor CCR5, and with the other specificity against an antigen on the surface of an effector cell, preferably against CD3 on the surface of a T-cell. The invention also comprises antibody constructs having an identical or a similar epitope specificity.

In a particularly preferred embodiment, the bispecific antibody is a single-chain antibody.

In another preferred embodiment, the antibody construct is a bispecific antibody one specificity of which is directed against a chemokine receptor, preferably against a human chemokine receptor and most preferably against the human chemokine receptor 5 (CCR5) and the other specificity is directed against a toxin. In this case too, in a preferred embodiment the bispecific antibody is a single-chain antibody.

In another preferred embodiment of the invention, the construct is a chemokine construct in the form of a chemokine toxin resulting from the fusion of a modified or unmodified chemokine with a modified or unmodified toxin. Chemokines binding to CCR5, such as constructs with MIP 1β, MIP 1α, MCP-2, MCP-3 and RANTES are particularly preferred.

As regards the chemokine construct of the invention, the chemokine may be covalently bound to a toxin, however, the binding between the chemokin and the toxin may also take place in a different manner. Via a multimerisation domain the chemokine can also be bound to a an antibody which has, apart from a compatible multimerisation domain, a specificity against an antigen on the surface of an effector cell, preferably against CD3 on the surface of a T-cell, and/or against a toxin. It is also possible to bind the chemokine via a multimerisation domain to a toxin with a compatible multimerisation domain. In addition, the chemokine can be covalently bound to an antibody having a specificity against an antigen on the surface of an effector cell, preferably against CD3 on the surface of a T-cell, and/or against a toxin. Moreover, the chemokine can, via a multimerisation domain, be bound to a toxin via

a compatible multimerisation domaine linked to the toxin. Binding to the multimerisation domain can be carried out in vitro or **in vivo**.

In another embodiment of the invention, the antibody construct is an antibody against a chemokine receptor, preferably against CCR5, which is covalently bound to a toxin. In this case, these are so-called immunotoxins.

Suitable toxins include, in particular, truncated Pseudomonas toxin, truncated diphtheria toxin and similar toxins.

The invention also comprises antibody constructs comprising an antibody against a chemokine receptor, preferably against CCR5, which, via a multimerisation domain in homodimers/heterodimers, can be bound in vitro and/or in vivo to a second antibody directed against an antigen on an effector cell, preferably against CD3, and/or against a toxin.

In addition, the invention also comprises antibody constructs in which an antibody against a chemokine receptor, preferably against CCR5, can be bound in vitro and/or in vivo via a mulitmerisation domain to a toxin with a compatible multimerisation domain.

In general, according to the invention, the antibody constructs, chemokine constructs and murine, chimeric or humanized antibodies are substances that are capable of destroying chemokine-receptor expressing cells, especially leukocytes, with this selective destruction being used for treating inflammatory diseases (autoimmune diseases, allergic diseases and the like).

In connection with the invention, the term antibody or antibody constructs also includes antibody fragments having the specificity(-ies) of the antibody or antibody construct, so-called active fragments.

Bispecific antibodies can be constructed employing the methods described below or known methods; chemically coupled antibodies or antibody fragments, the construction by means of the hybrid-hybridoma technique, the construction as bispecific single-chain antibodies, diabodies and the construction by means of joining two antibodies via multimerisation domains are but a few examples thereof.

The bispecific antibodies are preferred to be single-chain antibodies. Different parts of these antibodies can be joined by means of conventional methods or constructed

as a contiguous protein by means of recombinant DNA techniques, e.g. in such a way that a nucleic acid molecule coding for a chimeric or humanized antibody chain is expressed in order to construct a contiguous protein (cf. for example Mack et al. (1995) Proc. Natl. Acad. Sci. USA, Vol. 92, pp. 7021-7025).

In a particularly preferred embodiment, it is a single-chain antibody with the following Fv fragments: sc-Fv fragment of a monoclonal antibody against the chemokine receptor, preferably against CCR5, and an sc-Fv fragment of a monoclonal antibody against CD3. In this case, both the Fv fragment directed against the chemokine receptor and the Fv fragment against CD3 may be located in N-terminal position. The Fv fragment against CCR5 is preferred to be in N-terminal position. The order of the VL and VH antibody domains can be variable in both constructs, preferably, the order of the Fv fragment against CCR5 is VL-VH and the one of the Fv fragment against CD3 is VH-VL. The linkers between the variable domains as well between the two Fv fragments consist of peptide linkers, preferably of a hydrophilic flexible glycine- and serine-containing linker of 0-25 amino acids. An additional histidine chain of 6 x His in C- or N-terminal position can be used to simplify purification and detection.

Compared to conventional bispecific antibodies, bispecific single-chain antibodies have the advantage that they consist of only one protein chain and thus their composition is exactly defined. They have a low molecular weight of normally < 60 kD and can be produced easily and on a large scale in suitable cell lines, e.g. in CHO cells, using recombinant techniques. The most essential advantage, however, is that they have no constant antibody domains and thus only activate T-lymphocytes to lysis when these are bound to their target cells, i.e. to the chemokine-receptor expressing cells. Therefore, single-chain antibodies are often superior to conventional bispecific antibodies as their clinical use entails fewer or less severe side effects.

Furthermore, the invention relates to a cell of eukaryotic or prokaryotic origin producing an antibody construct of the invention, in particular a bispecific antibody of the invention, or an in vitro technique for the protein production.

The chemokine toxins of the invention resulting from binding a chemokine to a toxin can be constructed by chemical coupling, producing a fusion protein from a chemokine and a modified or unmodified prokaryotic or eukaryotic toxin and by joining a chemokine and a toxin via additional multimerisation domains.

In a particularly preferred embodiment, it is a recombinantly produced fusion protein of a chemokine which binds to the human chemokine receptor CCR5 (MIP 1β, MIP 1α, RANTES, MCP-2, MCP-3) and a truncated version of Pseudomonas exotoxin A (e.g. PE38, PE40). In this case, the chemokine is bound to the Pseudomonas toxin by means of a short peptide linker. The linker preferably consists of a flexible and hydrophilic amino acid sequence, in particular of glycines and serines and has a length of 0 to 20 amino acids.

In addition, the technical problem of the invention is solved by providing a pharmaceutical composition comprising at least one antibody- or chemokine construct of the invention, comprising especially at least one bispecific antibody in a quantity sufficient to destroy chemokine-receptor expressing cells, and optionally a pharmaceutically acceptable carrier.

Pharmaceutical compositions comprising the bispecific antibody of the invention are suitable for parenteral administration, i.e. subcutaneous, intramuscular, intravenous, intra-articular, intraperitoneal, wherein the compositions for parenteral administration usually include a solution of the antibody or a cocktail thereof, dissolved in an acceptable carrier, preferably an aqueous carrier. Suitable aqueous carriers are, for instance, water, NaCl solution and glycine. In addition, the compositions can contain conventional pharmaceutically acceptable adjuvants as are used, for instance, for adjusting the pH value, as a buffer substance or the like.

The concentration of the bispecific antibody in the composition can vary considerably, i.e. from less than approximately 10^{-7} % w/v to 1 % w/v. The concentration is preferred to be between 10^{-4} % w/v and 10^{-1} % w/v. In the case of intra-articular application, the dose of the bispecific antibody should be 1 mg to 0.001 mg and particularly about 0.02 mg of the bispecific single-chain antibody.

Thus, for an intra-articular application in a knee joint, for instance, a suitable composition would comprise about 20 µg of the bispecific antibody or chemokine toxin of the invention, dissolved in approximately 2-5 ml sterile NaCl solution, e.g. buffered with phosphate or Tris. An intravenous injection would also be a suitable form of application.

A further objective of the invention is to provide new possibilities for the application of the antibody of the invention.

This objective is achieved by using at least one of the antibodies or chemokine toxins of the invention for depleting chemokine-receptor expressing cells. In a preferred embodiment, the antibody of the invention or the chemokine toxin of the invention are used for the preparation of a pharmaceutical composition for treating chronic arthritis and other autoimmune diseases or allergic diseases.

The selective chemokine-receptor depletion, in particular the CCR5 depletion, has two essential advantages when compared to previous immunosuppressive therapies (e.g. cortisone, methotrexate, cytokine blocking): Firstly, previous therapies do not aim at depleting the infiltrating leukocytes, but only lead to a suppression of the activity. This leads to a quick relapse after termination of the therapy and requires permanent immunosuppression. In contrast thereto, in the case of the depletion of the responsible leukocytes in the joint, there is hope that a long-lasting remission may already be achieved after one or few treatments. The second advantage of a chemokine-receptor depletion is that, due to the distribution of cells expressing chemokine-receptors, especially CCR5, only cells are depleted that are involved in the inflammation process the other cells, however, remain intact to a large extent.

The mode of action of the bispecific antibody of the invention one specificity of which is directed against a chemokine receptor and the other specificity against an antigen on the surface of T-cells as effector cells is illustrated in Figure 1 (top) and Figure 2 by means of a preferred embodiment of the invention. As is demonstrated in Figure 1 (top), a bispecific antibody binds with its two arms to two different antigens. In a preferred embodiment, these are the chemokine receptor CCR5 and the surface molecule CD3 on T-lymphocytes. As is shown in Figure 2, the bispecific antibody leads to a cross-linking of T-lymphocytes and CCR5-expressing cells. Due to the cross-linking the T-lymphocytes are activated to lysis and the $CCR5^+$ cells bound thereto are destroyed. As a consequence, a lysis of $CCR5^+$ cells only takes place in the presence of T-lymphocytes. These are present in large amounts with all forms of chronic arthritis. In this way, it is particularly possible to purposefully eliminate the cells responsible for the inflammation by injecting the bispecific antibody into the inflamed joint.

Further embodiments of the invention and their mode of action are illustrated in the enclosed Figures 1 to 9.

Due to the possibility of purposefully depleting chemokine-receptor expressing cells, the concept of the invention is not only suitable for chronic arthritis but also for rheumatic diseases and other autoimmune diseases which were found to have a

similarly strong concentration of cells expressing chemokine receptors, especially CCR5.

While there have already been reports on various possibilities for using bispecific antibodies in the treatment of tumours (e.g. Kroesen, B. J. et al. (1993) Cancer Immunol. Immunother. 37:400-7; Nitta, T. et al. (1990) Lancet 335:368-71; Bolhuis, R. L. et al. (1992) Int J Cancer Suppl, 7:78-81; Canevari, S. et al. (1995) J. Natl. Cancer Inst. 87:1463-9; De Gast, G. et al. (1995) J. Hematother. 4:433-437; Kroesen, B. J. et al. (1994) Br. J. Cancer, 70:652-61; Tibben, J. G. et al. (1993) J. Natl. Cancer Inst. 85:1003-4), the application of bispecific antibodies for immunosuppression has not been described so far.

Description of the Figures:

Figure 1 illustrates antibody- and chemokine constructs of the invention causing the cross-linking of target cells, in this case CCR5-expressing cells, and effector cells, in this case T-cells with CD3 on the surface. Top: bispecific antibody with specificities both against CCR5 and CD3, middle: chemokine construct consisting of a chemokine and an antibody against CD3, bottom: chemokine construct in which a chemokine with multimerisation domain can be bound to an antibody directed against CD3 via a compatible multimerisation domain.

As illustrated schematically in Figure 2, the cross-linking leads to the activation of T-lymphocytes to lysis and to the destruction of the CCR5 positive cells cross-linked thereto.

Figure 3 shows antibody- and chemokine constructs of the invention leading to a linkage between target cells, in this case CCR5-expressing cells, and a toxin. Top: bispecific antibody having specificities against both CCR5 and a toxin, bottom: chemokine construct consisting of a chemokine and an antibody against a toxin.

The cross-linking of a target cell and a toxin, as illustrated in Figure 4, leads to the cell death of the CCR5 positive target cell.

Figure 5 shows, similarly to Figure 3, antibody- and chemokine constructs leading to a linkage between a target cell and a toxin, wherein, however, the toxin is not bound via the specificity of an antibody directed against the toxin, but is either covalently bound to an antibody directed against the chemokine receptor, preferably against CCR5 (Figure 5, top) or to a chemokine (Figure 5, middle), or can, via a multimerisation domain, be bound to an antibody with a compatible multimerisation domain directed against a chemokine receptor (Figure 5, bottom).

As has been demonstrated in Figure 6, the cross-linking of a target cell and a toxin also lead to the cell death of the target cell.

Figure 7 shows the result of an FACS analysis (carried out as described in Mack et al. (1998) J. Exp. Med. 187, pp. 1215-1224), explaining the depletion of CCR5 positive T-cells and monocytes from the inflamed synovial joint fluid of a patient with chronic polyarthritis or from cultivated peripheral blood leukocytes (PBMC).

Figure 8 shows the cytotoxicity of the chemokine toxin Rä-PE38, or more precisely the destruction of CCR5-expressing CHO cells by the chemokine toxin Ra-PE38 (10 ng/ml) after a 24-hour incubation (right, bottom). CHO cells that express the chemokine receptor CXCR4 instead of CCR5 are not destroyed by Ra-PE38 (top) since RANTES does not bind to CXCR4. Incubation with medium does not kill CHO cells. Ra-PE38 – a fusion protein of RANTES and a truncated Pseudomonas exotoxin with a molecular weight of 38 kD[1].

Thus, Figure 8 explains the approach outlined in Figure 5, middle.

Figure 9 displays the 48-hour incubation of synovial fluid with CD3-CCR5 bispecific antibodies. Therefore, Figure 9 is to been seen in connection with Figure 7, top. There is a concentration-dependent depletion of the T-lymphocytes and monocytes. With an antibody concentration of 125 ng/ml, the monocytes and T-lymphocytes were reduced by 96 % and 97.5 %, respectively.

The following examples are to illustrate the invention and are no limitation to particular embodiments or fields of application. One can rather imagine a plurality of further possibilities of applying the present invention.

Examples

Example 1: Construction of a bispecific antibody

For the construction of bispecific antibodies, for example the single-chain technique may be used (Mack et al. (1995) Proc. Natl. Acad. Sci. U S A, 92:7021-7025; Mack et al. (1997) J. Immunol. 158:3965-3970). In this case, as shown schematically in Figures 1 (top) and 3 (top), the variable domains of the light (VL) and the heavy (VH) immunoglobulin chains of two different antibodies are fused in a particular order, optionally a histidine chain of 6 x His is attached in addition. The fusion is effected on a DNA basis so that a protein chain with four different variable domains is formed after expression (cf. Figures 1 (top) and 3 (top)). The attached histidine chain enables a simple and efficient purification via immobilized Ni ions in one step. Figure 1 (top) shows a preferred embodiment of the bispecific antibody binding to the CD3 antigen on the surface of the effector cell and the human CCR5 on the surface of leukocytes as target cells.

[1] Translator's note: sentence incomplete

By means of RT-PCR the variable antibody domains from the hybridoma cells generating the desired antibody are amplified. The PCR fragments obtained in this way are cloned into a vector and sequenced. Subsequently, a single-chain antibody with a specificity is generated by means of fusion PCR by inserting a linker of $(Gly_4Ser_1)_3$ between the two variable antibody domains. In a further fusion PCR, the antibody fragment against CCR5 is fused to the already published antibody fragment against CD3, with a linker consisting of Gly_4Ser_1 is inserted (cf. Mack et al. supra). The following order of the domains is chosen: VL(1)-VH(1)-VH(2)-VL(2), with (1) being the specificity against CCR5 and (2) the specificity against CD3.

Example 2: Expression and purification of the bispecific antibody of Example 1

In order to express the bispecific antibody, the corresponding DNA sequence is subcloned in a eukaryotic expression vector (e.g. PEF-DHFR, Mack et al. (1995) PNAS, supra) and transfected in DHFR-deficient CHO cells by means of electroporation. The bispecific antibody is purified from the supernatant of stably transfected CHO cells by means of affinity chromatography at Ni-NTA, with elution taking place by lowering the pH value. Subsequently, the pH is adjusted and the protein is adjusted to a suitable concentration.

Example 3: In vitro tests at blood leukocytes and leukocytes at inflamed joints

For the in vitro tests, joint effusion fluid including the cells contained is incubated with the bispecific antibodies for one or several days. After 24 hours, the CCR5 positive lymphocytes and monocytes have already almost disappeared. When the medium is controlled after longer incubation, the monocytes have differentiated into macrophages which are visible at the bottom of the culture flask. After an appropriate incubation with the bispecific antibody, no macrophages are visible.

A corresponding result can be obtained when cultivated PBMC are incubated with the bispecific antibody. In this case, there is a complete depletion of CCR5 positive monocytes and an almost complete depletion of CCR5 positive T-lymphocytes. The depletion of CCR5 positive T-cells and monocytes is shown in Figure 7.

The results show that, according to Example 1, the construct of the invention is capable of completely destroying CCR5 positive monocytes. This applies to both

monocytes from the joint aspirate and blood monocytes which express CC55 when being differentiated into macrophages. Depletion of the monocytes/macrophages takes place within a few hours (< 24 hrs). In particular the depletion of monocytes/macrophages in the joint is of great advantage in therapy since it is these cells that are mainly responsible for the joint destruction. Moreover, for the activation of T-lymphocytes an interaction with macrophages is also required so that, at the same time, the function of the T-lymphocytes is suppressed.

In addition to the depletion of monocytes/macrophages, a considerable reduction in the number of CCR5 positive T-lymphocytes could be observed.

Claims

1. An antibody- or chemokine construct which is able to bind to a chemokine receptor on the surface of a target cell, wherein the binding of the construct to the chemokine receptor results in the destruction of the target cell, and active fragments of said constructs.

2. The antibody and chemokine construct according to claim 1, wherein the chemokine receptor is a human receptor.

3. The antibody- or chemokine construct according to claim 1 or 2, wherein the chemokine receptor is the chemokine receptor 5 (CCR5).

4. The antibody construct according to any one of the aforementioned claims, wherein the construct is a bispecific antibody which is able to bind to a chemokine receptor as a first antigen and a CD3 antigen on the surface of an effector cell as a second antigen.

5. The antibody construct according to any one of claims 1 to 3, wherein the construct is a bispecific antibody which is capable of binding to a chemokine receptor as a first antigen and a toxin as a second antigen.

6. The antibody construct according to any one of claims 1 to 3 which is covalently bound to a toxin.

7. The antibody construct according to any one of claims 1 to 3 which can, via a multimerisation domain, be bound in vitro and/or in vivo to a second antibody construct that is able to bind to a CD3 antigen on the surface of an effector cell and/or a toxin, or, via a compatible multimerisation domain, to a toxin.

8. Chemokine construct according to any one of claims 1 to 3, wherein said chemokine construct is the fusion construct of a modified or an unmodified chemokine with a modified or an unmodified toxin.

9. The chemokine construct of any one of claims 1 to 3, wherein the chemokine construct can, via a multimerisation domain, be bound in vitro and/or in vivo to an antibody construct that is able to bind to a CD3 antigen on the surface of an

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effector cell and/or a toxin, or, via a compatible multimerisation domain, to a toxin.

10. The chemokine construct according to any one of claims 1 to 3, wherein the chemokine is covalently bound to an antibody construct which is capable of binding to a CD3 antigen on the surface of an effector cell and/or a toxin.

11. The chemokine- or antibody construct according to any one of claims 4, 7, 9 or 10, wherein the effector cell is a leukocyte, in particular a monocyte/macrophage or a T-cell, or a dendritic cell.

12. The antibody construct according to any one of claims 1 to 7 or 9 to 11, which is a single-chain construct.

13. Cell of eukaryotic or prokaryotic origin which produces an antibody- or chemokine construct according to any one of the aforementioned claims.

14. Pharmaceutical composition comprising at least one antibody- or chemokine construct according to any one of claims 1 to 12 in a quantity sufficient to destroy chemokine-receptor expressing cells, and optionally an pharmaceutically acceptable carrier.

15. Use of at least one antibody- or chemokine construct according to any one of claims 1 to 12 for the depletion of chemokine-receptor expressing cells.

16. Use of at least one antibody- or chemokine construct according to any one of claims 1 to 12 for the treatment of chronic arthritis and other autoimmune diseases and allergic diseases.

17. Use of at least one antibody- or chemokine construct according to any one of claims 1 to 12 for the preparation of a pharmaceutical composition for treating chronic arthritis and other autoimmune diseases and allergic diseases.

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