have also resulted in fatal autoimmune diseases due to basal expression of the targeted antigen (targeted tumor antigen) in normal tissues (on-target/off-tumor-reaction; Morgan et al., (2010) Mol Ther., (18) 843-51).

An alternative approach, in which activation of the T cell occurs through a more physiological mechanism, was the provision of an analogous single chain-TCR (scTv)-fragment fused to the Cβ constant domain derived from the T cell receptor (TCR) and its co-expression with a TCR-derived Cα constant domain (Voss et al., (2010) Blood, (115) 5154-5163), the latter which recruits the essential endogenous CD3ζ homodimer (Call et al., (2002) Cell, (111) 967-79.). However, in order for these constructs to function as immune system activators, it was essential that the constant domains derived from the TCR be derived from mice TCRs or be murinized Cohen et al., (2006) Cancer Res., **(**66) 8878-86) to achieve chain pairing between the scTCR and Cα. The fact that these constructs must have xenogenic sequences for functionality heightens the risk that the immune system will react against them when administered and lessens or destroys their therapeutic effectiveness.

Thus, there is a need for the provision of alternate recombinant antigen receptors, in which, e.g., the receptor, upon antigen binding, is sufficiently able to activate the T cell in which it is expressed in a normal physiological manner through the endogenous CD3 complex and, optionally, with no requirement for the presence of any amino acid sequences not of human origin, at least in the signal transmission domain of the antigen receptor, that could induce an unwanted immune response against the recombinant antigen receptor itself.

DESCRIPTION OF INVENTION

Summary

The present disclosure relates to recombinant antigen receptors having at least two antigen binding sites. The antigen receptors comprise two peptide chains. In one aspect, the present disclosure refers to an antigen receptor, which receptor comprises a first peptide chain and a second peptide chain, wherein the first peptide chain comprises at least a first and a second domain, and an immunoreceptor signal transmission domain; the second peptide chain comprises at least a first and a second domain, and an immunoreceptor signal transmission domain; wherein the immunoreceptor signal transmission domain is preferably of human origin, wherein the first

domain from the first peptide chain forms together with one of the domains from the second peptide chain a first antigen binding site, and wherein the second domain from the first peptide chain forms together with the other domain from the second peptide chain a second antigen binding site.

In another aspect, the present disclosure refers to a peptide chain comprising a first and a second domain which each comprise a variable region of a heavy chain of an immunoglobulin or each comprise a variable region of a light chain of an immunoglobulin and wherein the peptide chain further comprises an immunoreceptor signal transmission domain. In yet another aspect, the present disclosure refers to a recombinant cell expressing both the first and second peptide chains as described herein. In yet another aspect, the present disclosure refers to a recombinant cell expressing the peptide chain as described herein. In yet another aspect, the present disclosure refers to an *ex vivo* method for producing a cell expressing an antigen receptor which receptor comprises a first peptide chain and a second peptide chain, the method comprising: (a) providing a cell, preferably a human cell; (b) providing a first genetic construct encoding the first peptide chain comprising at least a first and a second domain, and an immunoreceptor signal transmission domain; (c) providing a second genetic construct encoding the second peptide chain comprising at least a first and a second domain and an immunoreceptor signal transmission domain; (d) introducing the first and second genetic constructs into the cell; and (e) allowing the constructs to be expressed in the cell; wherein the cell is preferably a T cell, wherein the first domain from the first peptide chain is able to form together with one of the domains from the second peptide chain a first antigen binding site, and wherein the second domain from the first peptide chain is able to form together with the other domain from the second peptide chain a second antigen binding site, wherein the first peptide chain and the second peptide chain are preferably provided on a single genetic construct.

In a further aspect, the present disclosure refers to a nucleic acid encoding both the first and second peptide chains as described herein, wherein the nucleic acid is preferably DNA or RNA. In yet another aspect, the present disclosure refers to a nucleic acid encoding the peptide chain as described herein, wherein the nucleic acid is preferably DNA or RNA. In yet another aspect, the present disclosure refers to a pharmaceutical composition comprising (a) the antigen receptor as described herein, (b) the recombinant cell as described herein, (c) a nucleic acid as described herein, or (d) a nucleic acid encoding the first peptide chain *and* a nucleic acid encoding the

second peptide chain, said chains being defined herein; and a pharmaceutically acceptable carrier, for use as a medicament.

In yet another aspect, the present disclosure refers to the use of the antigen receptor as described herein, the recombinant cell as described herein, or the nucleic acid as described herein; and a pharmaceutically acceptable carrier in the manufacture of a pharmaceutical composition for treating cancer.

In one example, the peptide chains each comprise at least two domains, in addition to an immunoreceptor signal transmission domain, in which each of the two domains on one peptide chain forms an antigen binding site with one of the domains on the other peptide chain. In another example, one of the peptide chains has at least four domains, in addition to an immunoreceptor signal transmission domain, in which two of the four domains form two antigen binding sites with the two remaining domains on the same peptide chain.

In one example, the present disclosure relates to an antigen receptor, which receptor comprises a first peptide chain and a second peptide chain, wherein the first peptide chain comprises at least a first and a second domain, and an immunoreceptor signal transmission domain; the second peptide chain comprises at least a first and a second domain, and an immunoreceptor signal transmission domain; wherein the first domain from the first peptide chain forms together with one of the domains from the second peptide chain a first antigen binding site, and wherein the second domain from the first peptide chain forms together with the other domain from the second peptide chain a second antigen binding site. In the antigen receptor of this example, the domains forming the respective antigen binding sites are preferably located on different peptide chains. Consequently, antigen binding sites are formed by intermolecular interaction of domains.

In one example, the first and/or second domains each comprise a variable region of an immunoglobulin chain or a variable region of a T cell receptor chain or a portion of the variable region.

In one example, one of the domains forming the first antigen binding site comprises a variable region of a heavy chain of an immunoglobulin with a specificity for an antigen or a portion thereof and the other domain forming the first antigen binding site comprises a variable region of a light chain of an immunoglobulin with a specificity for the antigen or a portion thereof. In one

example, one of the domains forming the second antigen binding site comprises a variable region of a heavy chain of an immunoglobulin with a specificity for an antigen or a portion thereof and the other domain forming the second antigen binding site comprises a variable region of a light chain of an immunoglobulin with a specificity for the antigen or a portion thereof.

In one example, the first domain from the first peptide chain comprises a variable region of a heavy chain of an immunoglobulin with a specificity for an antigen or a portion thereof and the domain from the second peptide chain forming an antigen binding site with the first domain from the first peptide chain comprises a variable region of a light chain of an immunoglobulin with a specificity for the antigen or a portion thereof. In one example, the second domain from the first peptide chain comprises a variable region of a heavy chain of an immunoglobulin with a specificity for an antigen or a portion thereof and the domain from the second peptide chain forming an antigen binding site with the second domain from the first peptide chain comprises a variable region of a light chain of an immunoglobulin with a specificity for the antigen or a portion thereof.

In one example, the first and the second domains from the first peptide chain each comprise a variable region of a heavy chain of an immunoglobulin or a portion thereof; and the first and the second domains from the second peptide chain each comprise a variable region of a light chain of an immunoglobulin or a portion thereof.

In one example, the N-terminal domain from the first peptide chain forms together with the N-terminal domain from the second peptide chain an antigen binding site; and the C-terminal domain from the first peptide chain forms together with the C-terminal domain from the second peptide chain an antigen binding site.

In one example, the N-terminal domain from the first peptide chain forms together with the C-terminal domain from the second peptide chain an antigen binding site; and the C-terminal domain from the first peptide chain forms together with the N-terminal domain from the second peptide chain an antigen binding site.

In one example, the present disclosure relates to an antigen receptor, which receptor comprises a first peptide chain and a second peptide chain, wherein the first peptide chain comprises at least four domains, and an immunoreceptor signal transmission domain; the second peptide chain

comprises an immunoreceptor signal transmission domain; wherein two of the domains from the first peptide chain form a first antigen binding site, and wherein the other two domains from the first peptide chain form a second antigen binding site. In the antigen receptor of this example, the domains forming the respective antigen binding sites are preferably located on the same peptide chain. Consequently, antigen binding sites are formed by intramolecular interaction of domains.

In one example, the four domains each comprise a variable region of an immunoglobulin chain or a variable region of a T cell receptor chain or a portion of the variable region.

In one example, one of the domains forming the first antigen binding site comprises a variable region of a heavy chain of an immunoglobulin with a specificity for an antigen or a portion thereof and the other domain forming the first antigen binding site comprises a variable region of a light chain of an immunoglobulin with a specificity for the antigen or a portion thereof. In one example, one of the domains forming the second antigen binding site comprises a variable region of a heavy chain of an immunoglobulin with a specificity for an antigen or a portion thereof and the other domain forming the second antigen binding site comprises a variable region of a light chain of an immunoglobulin with a specificity for the antigen or a portion thereof.

In one example, the two N-terminal domains of the four domains form together an antigen binding site; and the two C-terminal domains of the four domains form together an antigen binding site.

In one example, one of the two N-terminal domains of the four domains comprises a variable region of a heavy chain of an immunoglobulin or a portion thereof and the other of the two N-terminal domains of the four domains comprises a variable region of a light chain of an immunoglobulin or a portion thereof; and one of the two C-terminal domains of the four domains comprises a variable region of a heavy chain of an immunoglobulin or a portion thereof and the other of the two C-terminal domains of the four domains comprises a variable region of a light chain of an immunoglobulin or a portion thereof.

In one example of the antigen receptors of the disclosure, the immunoreceptor signal transmission domain comprises a constant or invariant region of a T cell receptor chain or a constant or invariant region of an immune cell Fc receptor chain or a portion of the constant or invariant region. In one example of the antigen receptors of the disclosure, (i) the first peptide

chain comprises a constant region of a T cell receptor alpha chain or a portion thereof and the second peptide chain comprises a constant region of a T cell receptor beta chain or a portion thereof, or (ii) the first peptide chain comprises a constant region of a T cell receptor beta chain or a portion thereof and the second peptide chain comprises a constant region of a T cell receptor alpha chain or a portion thereof.

In one example of the antigen receptors of the disclosure, the immunoreceptor signal transmission domain is of human origin.

In one example, an antigen receptor of the disclosure comprises (a) linker(s) connecting domains of the antigen receptor. In one example, an antigen receptor of the disclosure comprises one or more linkers between the domains forming the antigen binding sites and/or between the domains forming the antigen binding sites and the immunoreceptor signal transmission domains. The linker can be an arbitrary amino acid sequence of any length so long as it does not interfere with the functions of the antigen receptor, such as the ability of the antigen receptor to bind antigen or to associate with the endogenous CD3 complex, or interfere with the ability of the antigen receptor to induce an immune response upon antigen binding.

In one example of the antigen receptors of the disclosure, the first and second antigen binding sites bind to the same antigen or different antigens. In one example of the antigen receptors of the disclosure, the first and second antigen binding sites bind to different epitopes on the same antigen. Consequently, while the domains forming the first antigen binding site are preferably derived from the same immunoglobulin and the domains forming the second antigen binding site are preferably derived from the same immunoglobulin, the domains forming the first antigen binding site and the domains forming the second antigen binding site are derived from the same or different immunoglobulins, said different immunoglobulins binding to the same or different antigens.

In one example, the antigen is a disease-specific antigen, preferably a tumor antigen. In one example, the antigen is expressed on the surface of a cell.

In one example, the present disclosure relates to a peptide chain of any of the antigen receptors of the disclosure. In one example, the present disclosure relates to a peptide chain comprising a first and a second domain which each comprise a variable region of a heavy chain of an

immunoglobulin or a portion thereof or each comprise a variable region of a light chain of an immunoglobulin or a portion thereof and wherein the peptide chain further comprises an immunoreceptor signal transmission domain. In one example, the present disclosure relates to a peptide chain which comprises at least four domains, and an immunoreceptor signal transmission domain, wherein two of the domains from the peptide chain form a first antigen binding site, and the other two domains from the peptide chain form a second antigen binding site. Further example s of the peptide chains of the disclosure are as described herein for the antigen receptors of the disclosure.

In one example, the present disclosure relates to a cell, in particular an immune effector cell such as a T cell, genetically modified to express an antigen receptor of the disclosure. In one example, the present disclosure relates to a recombinant cell, in particular an immune effector cell such as a T cell, expressing the first peptide chain, the second peptide chain or both the first and second peptide chains of an antigen receptor of the disclosure or expressing a peptide chain of the disclosure. Further example s of the cell or recombinant cell of the disclosure are as described herein for the antigen receptors of the disclosure or the peptide chains of the disclosure.

In one example, the present disclosure relates to a method for producing a cell expressing an antigen receptor of the disclosure, the method comprising: (a) providing a cell; (b) providing a first genetic construct encoding the first peptide chain of an antigen receptor of the disclosure; (c) providing a second genetic construct encoding the second peptide chain of an antigen receptor of the disclosure; (d) introducing the first and second genetic constructs into the cell; and (e) allowing the constructs to be expressed in the cell. In one example, the present disclosure relates to a method for producing a cell expressing an antigen receptor which receptor comprises a first peptide chain and a second peptide chain, the method comprising: (a) providing a cell; (b) providing a first genetic construct encoding the first peptide chain comprising at least a first and a second domain, and an immunoreceptor signal transmission domain; (c) providing a second genetic construct encoding the second peptide chain comprising at least a first and a second domain and an immunoreceptor signal transmission domain; (d) introducing the first and second genetic constructs into the cell; and (e) allowing the constructs to be expressed in the cell; wherein the first domain from the first peptide chain is able to form together with one of the domains from the second peptide chain a first antigen binding site, and wherein the second domain from the first peptide chain is able to form together with the other domain from the second peptide chain a second antigen binding site. In one example, the present disclosure relates

to a method for producing a cell expressing an antigen receptor which receptor comprises a first peptide chain and a second peptide chain, the method comprising: (a) providing a cell; (b) providing a first genetic construct encoding the first peptide chain comprising at least four domains, and an immunoreceptor signal transmission domain; (c) providing a second genetic construct encoding the second peptide chain comprising an immunoreceptor signal transmission domain; (d) introducing the first and second genetic constructs into the cell; and (e) allowing the constructs to be expressed in the cell; wherein two of the domains from the first peptide chain are able to form a first antigen binding site, and wherein the other two domains from the first peptide chain are able to form a second antigen binding site. In one example of the methods of the disclosure, expression of the antigen receptor is at the cell surface. In one example of the methods of the disclosure, the first peptide chain and the second peptide chain are provided on a single genetic construct. In one example of the methods of the disclosure, the cell is a human cell. In one example of the methods of the disclosure, the cell is an immune effector cell such as a T cell. In one example of the methods of the disclosure, the genetic constructs comprise DNA and/or RNA. Further example s of the methods of the disclosure are as described herein for the antigen receptors of the disclosure.

In one example, the present disclosure relates to a recombinant cell, in particular an immune effector cell such as a T cell, produced by the methods of the disclosure for producing a cell expressing an antigen receptor. Further example s of the recombinant cell of the disclosure are as described herein for the antigen receptors of the disclosure or the methods of the disclosure for producing a cell expressing an antigen receptor.

In one example, the present disclosure relates to a nucleic acid such as DNA or RNA encoding the first peptide chain, the second peptide chain or both the first and second peptide chains of an antigen receptor of the disclosure or encoding a peptide chain of the disclosure. Further example s of the nucleic acid of the disclosure are as described herein for the antigen receptors of the disclosure or the peptide chains of the disclosure.

The present disclosure generally embraces the treatment of diseases by targeting cells expressing one or more antigens on the cell surface such as diseased cells expressing one or more disease-specific antigens on the cell surface, in particular cancer cells expressing one or more tumor antigens on the cell surface using antigen receptors of the disclosure. The methods provide for the selective eradication of cells that express on their surface one or more antigens, thereby

minimizing adverse effects to normal cells not expressing the antigen(s). In one example, T cells genetically modified to express an antigen receptor of the disclosure targeting the cells through binding to the antigen(s) are administered. T cells are able to recognize diseased cells expressing the antigen(s) on the cell surface, resulting in the eradication of diseased cells. In one example, the target cell population or target tissue is tumor cells or tumor tissue.

In one example, the present disclosure relates to a pharmaceutical composition comprising the antigen receptor of the disclosure, the recombinant cell of the disclosure, or the nucleic acid of the disclosure; and a pharmaceutically acceptable carrier. The pharmaceutical composition of the disclosure may be used as a medicament, in particular in the treatment of a disease such as cancer characterized by expression of one or more antigens which are bound by the antigen receptor of the disclosure such as one or more tumor antigens.

In one example, the present disclosure relates to a method of treating a disease such as cancer comprising administering to a subject a therapeutically effective amount of the pharmaceutical composition of the disclosure, wherein the disease is characterized by expression of at least one antigen such as a tumor antigen which is bound by the antigen receptor.

In one example, the present disclosure relates to a method of treating a subject having a disease, disorder or condition associated with expression or elevated expression of at least one antigen, the method comprising administering to the subject T cells genetically modified to express an antigen receptor of the disclosure targeted to the at least one antigen. In one example, the disease, disorder or condition is cancer. In one example, the T cells may be autologous, allogeneic or syngeneic to the subject.

In one example of the disclosure, the antigen receptor binds to only one antigen (e.g. by being monospecific and recognizing the same epitope or by being bispecific or multispecific and recognizing different epitopes on the same antigen) or binds to different antigens, in particular two different antigens.

Further described in the disclosure is the method of treating further comprises obtaining a sample of cells from a subject, the sample comprising T cells or T cell progenitors, and transfecting the cells with a nucleic acid encoding the antigen receptor of the disclosure to provide T cells genetically modified to express the antigen receptor. Further described in the disclosure is the T

cells genetically modified to express the antigen receptor are stably or transiently transfected with nucleic acid encoding the antigen receptor. Thus, the nucleic acid encoding the antigen receptor is integrated or not integrated into the genome of the T cells. Further described in the disclosure is the T cells and/or the sample of cells are from the subject to which the T cells genetically modified to express the antigen receptor are administered. Further described in the disclosure is the T cells and/or the sample of cells are from a mammal which is different to the mammal to which the T cells genetically modified to express the antigen receptor are administered.

Also described in the disclosure is the T cells genetically modified to express the antigen receptor are inactivated for expression of an endogenous T cell receptor and/or endogenous HLA.

Also described in the disclosure is an antigen is expressed in a diseased cell such as a cancer cell. In one example, an antigen is expressed on the surface of a diseased cell such as a cancer cell. In one example, an antigen receptor binds to an extracellular domain or to an epitope in an extracellular domain of an antigen. In one example, an antigen receptor binds to native epitopes of an antigen present on the surface of living cells. Also described in the disclosure is the antigen is a tumor antigen. Also described in the disclosure is the antigen is selected from the group consisting of claudins, such as claudin 6 and claudin 18.2, CD19, CD20, CD22, CD33, CD123, mesothelin, CEA, c-Met, PSMA, GD-2, and NY-ESO-1. Also described in the disclosure is the antigen is a pathogen antigen. The pathogen may be a fungal, viral, or bacterial pathogen. Further described in the disclosure is expression of the antigen is at the cell surface. In one example an antigen is a claudin, in particular claudin 6 or claudin 18.2, and said antigen receptor binds to the first extracellular loop of said claudin. In one example, binding of said antigen receptor when expressed by T cells and/or present on T cells to an antigen present on cells results in immune effector functions of said T cells such as the release of cytokines. In one example, binding of said antigen receptor when expressed by T cells and/or present on T cells to an antigen present on cells such as antigen presenting cells results in stimulation, priming and/or expansion of said T cells. In one example, binding of said antigen receptor when expressed by T cells and/or present on T cells to an antigen present on diseased cells such as cancer cells results in cytolysis and/or apoptosis of the diseased cells, wherein said T cells preferably release cytotoxic factors, e.g. perforins and granzymes.

Also described in the disclosure is the domains of an antigen receptor forming antigen binding sites are comprised by an exodomain of the antigen receptor. Also described in the disclosure is an antigen receptor of the disclosure comprises a transmembrane domain. In one example, the transmembrane domain is a hydrophobic alpha helix that spans the membrane.

Also described in the disclosure is an antigen receptor of the disclosure comprises a signal peptide which directs the nascent protein into the endoplasmic reticulum. In one example, the signal peptide precedes the domains forming antigen binding sites.

Also described in the disclosure is an antigen receptor of the disclosure is preferably specific for the antigen to which it is targeted, in particular when present on the surface of a cell such as a diseased cell or an antigen-presenting cell.

Also described in the disclosure is an antigen receptor of the disclosure may be expressed by and/or present on the surface of a T cell, preferably a cytotoxic T cell. In one example, the T cell is reactive with the antigen(s) to which the an antigen receptor of the disclosure is targeted.

In a further example, the disclosure provides the agents and compositions described herein for use in the methods described herein.

Other features and advantages of the instant disclosure will be apparent from the following detailed description and claims.

Detailed description of the invention

Although the present invention is described in detail below, it is to be understood that this invention is not limited to the particular methodologies, protocols and reagents described herein as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art.

In the following, the elements of the present invention will be described. These elements are listed with specific embodiments, however, it should be understood that they may be combined in any manner and in any number to create additional embodiments. The variously described examples and preferred embodiments should not be construed to limit the present invention to only the explicitly described embodiments. This description should be understood to support and

WE CLAIM:

1. An antigen receptor, which receptor comprises a first peptide chain and a second peptide chain, wherein

the first peptide chain comprises at least a first and a second domain, and an immunoreceptor signal transmission domain;

the second peptide chain comprises at least a first and a second domain, and an immunoreceptor signal transmission domain;

wherein the immunoreceptor signal transmission domain is preferably of human origin,

wherein the first domain from the first peptide chain forms together with one of the domains from the second peptide chain a first antigen binding site, and

wherein the second domain from the first peptide chain forms together with the other domain from the second peptide chain a second antigen binding site.

2. The receptor of claim 1, wherein the immunoreceptor signal transmission domain comprises a constant or invariant region of a T cell receptor chain or a constant or invariant region of an immune cell Fc receptor chain or a portion of the constant or invariant region.

3. The receptor of claim 1 or 2, wherein the first and/or second peptide chains further comprise a linker between the first and second domains and/or between the first and second domains and the immunoreceptor signal transmission domain.

4. The receptor of any one of claims 1 to 3, wherein the first and/or second domains each comprise a variable region of an immunoglobulin chain or a variable region of a T cell receptor chain or a portion of the variable region.

5. The receptor of any one of claims 1 to 4, wherein

(i) the first peptide chain comprises a constant region of a T cell receptor alpha chain or a portion thereof and the second peptide chain comprises a constant region of a T cell receptor beta chain or a portion thereof, or

(ii) the first peptide chain comprises a constant region of a T cell receptor beta chain or a portion thereof and the second peptide chain comprises a constant region of a T cell receptor alpha chain or a portion thereof.

6. The receptor of any one of claims 1 to 5, wherein the first domain from the first peptide chain comprises a variable region of a heavy chain of an immunoglobulin with a specificity for an antigen or a portion thereof and the domain from the second peptide chain forming an antigen binding site with the first domain from the first peptide chain comprises a variable region of a light chain of an immunoglobulin with a specificity for the antigen or a portion thereof.

7. The receptor of any one of claims 1 to 6, wherein the second domain from the first peptide chain comprises a variable region of a heavy chain of an immunoglobulin with a specificity for an antigen or a portion thereof and the domain from the second peptide chain forming an antigen binding site with the second domain from the first peptide chain comprises a variable region of a light chain of an immunoglobulin with a specificity for the antigen or a portion thereof.

8. The receptor of any one of claims 1 to 7, wherein the first and second antigen binding sites bind to the same antigen or different antigens.

9. The receptor of any one of claims 1 to 8, wherein

the first and the second domains from the first peptide chain each comprise a variable region of a heavy chain of an immunoglobulin or a portion thereof; and

the first and the second domains from the second peptide chain each comprise a variable region of a light chain of an immunoglobulin or a portion thereof.

10. The receptor of any one of claims 1 to 9, wherein

the N-terminal domain from the first peptide chain forms together with the N-terminal domain from the second peptide chain an antigen binding site; and

the C-terminal domain from the first peptide chain forms together with the C-terminal domain from the second peptide chain an antigen binding site.

11. A peptide chain comprising a first and a second domain which each comprise a variable region of a heavy chain of an immunoglobulin or each comprise a variable region of a light chain of an immunoglobulin and wherein the peptide chain further comprises an immunoreceptor signal transmission domain.

12. A recombinant cell expressing both the first and second peptide chains defined in any one of claims 1 to 10.

13. A recombinant cell expressing the peptide chain of claim 11.

14. An *ex vivo* method for producing a cell expressing an antigen receptor which receptor comprises a first peptide chain and a second peptide chain, the method comprising:

(a) providing a cell, preferably a human cell;

(b) providing a first genetic construct encoding the first peptide chain comprising at least a first and a second domain, and an immunoreceptor signal transmission domain;

(c) providing a second genetic construct encoding the second peptide chain comprising at least a first and a second domain and an immunoreceptor signal transmission domain;

(d) introducing the first and second genetic constructs into the cell; and

(e) allowing the constructs to be expressed in the cell;

wherein the cell is preferably a T cell,

wherein the first domain from the first peptide chain is able to form together with one of the domains from the second peptide chain a first antigen binding site, and

wherein the second domain from the first peptide chain is able to form together with the other domain from the second peptide chain a second antigen binding site,
wherein the first peptide chain and the second peptide chain are preferably provided on a single genetic construct.

15. A nucleic acid encoding both the first and second peptide chains defined in any one of claims 1 to 10, wherein the nucleic acid is preferably DNA or RNA.

16. A nucleic acid encoding the peptide chain of claim 11, wherein the nucleic acid is preferably DNA or RNA.

17. A pharmaceutical composition comprising
(a) the antigen receptor of any one of claims 1 to 10,
(b) the recombinant cell of claim 12,
(c) a nucleic acid of claim 15, or
(d) a nucleic acid encoding the first peptide chain *and* a nucleic acid encoding the second peptide chain, said chains being defined as in any one of claims 1 to 10;

and a pharmaceutically acceptable carrier, for use as a medicament.

18. Use of the antigen receptor of any one of claims 1 to 10, the recombinant cell of claim 12, or the nucleic acid of claim 15; and a pharmaceutically acceptable carrier in the manufacture of a pharmaceutical composition for treating cancer.