

[4] MUC17 is aberrantly expressed in some cancers. MUC17 mRNA was shown to be expressed in one pancreatic cancer cell line and three colon cancer cell lines (Gum et al. 2002). Immunohistochemistry studies confirmed expression of the MUC17 protein in pancreatic cancer ((Moniaux et al. 2006). In colon cancer, however, MUC17 protein expression was shown to be decreased (Senapati et al., J. Clin. Pathol. 2010). Nevertheless, the expression patterns of MUC17 make it a potential target for the treatment of different forms of malignancy. Clinical trials using anti-MUC17 antibody constructs were initiated to test their suitability for treating gastrointestinal cancer and gastroesophageal junction cancer (clinicaltrials.gov; NCT04117958).

Summary

[5] In view of the conflicting implications in the literature about MUC17 as a potential target for which pathological condition, it is the object of the present ~~invention-disclosure~~ to clearly identify specific conditions associated with MUC17 upregulation and to provide binders (e.g. antibodies) that selectively bind MUC17 for use as diagnostic tool in a MUC17-associated condition, preferably for use in the detection/diagnosis of said specific conditions and/or in the monitoring of disease status prior to, concurrent with and subsequent to a therapeutic invention. Monitoring serves to determine the success of a given treatment and permits to the treating physician to determine as to whether the treatment is effective or is insufficient and needs to be modified.

[6] Ideally, the diagnostic antibody binds to a region that is like the region identified or targeted by therapeutic antibody constructs. As tumor antigens can present themselves in different splice forms or may have mutations affecting the three-dimensional structure of the target it is desirable to verify that the target of the therapeutic antibody exists in a given patient and that such patient qualifies as being eligible to such treatment. When the target regions of a tumor antigen are not present in a given patient, treatment with a selectively binding therapeutic antibody construct may not be favorable in view of potential adverse events associated with the treatment. Further, patients would not be subjected to an inappropriate and potentially disadvantageous, exhausting and cost-intensive treatment and could rather be treated with alternative treatment methods that shows more promise as being effective. It should be kept in mind that patients that are subjected to immunotherapy are generally critically ill patients. Often such patients are refractory to first line therapies or have experienced relapses and/or have metastases that do not respond to the initial therapy. It is not desirable to treat such patients without having a clear diagnostic basis that a treatment with an immunotherapeutic compound is reasonable and medically founded.

[7] Accordingly, the present ~~invention-disclosure~~ provides an antibody binding to MUC17. The antibody may be used in diagnostic methods on tissue samples obtained from an individual, particularly

from a patient suspected to have a neoplastic disease associated and/or identifiable by an aberrating MUC17 expression, e.g. a gastrointestinal cancer, pancreatic cancer, etc..

[8] The antibody may also serve as a diagnostic tool in the detection of MUC17 in laboratory animals, for example in previously sacrificed cancer-bearing animals.

[9] Moreover, the ~~disclosure~~~~invention~~ provides a polynucleotide encoding the antibody construct, a vector comprising this polynucleotide, and host cells expressing the construct as well as diagnostic compositions comprising the same and kits comprising the antibody of the present ~~disclosure~~~~invention~~ as diagnostic tool alongside further ingredients comprising, but not limited to, at least one of secondary antibodies, enzymes, buffers, instructions for use, tools for calibration, controls, and to forth.

[9a] In one aspect, the present disclosure provides an antibody that binds to human MUC17 as depicted in SEQ ID NO: 1, wherein said antibody binds cell surface-associated MUC17 protein, wherein said antibody comprises a variable heavy chain comprising a CDR3 region depicted in SEQ ID NO: 4, a heavy chain CDR1 and CDR2 regions as depicted in SEQ ID Nos: 2 and 3 and the light chain CDR1, CDR2 and CDR3 regions depicted in SEQ ID Nos: 6, 7, and 8. In another aspects of the present disclosure provide a polynucleotide encoding an antibody as described herein; a host cell transformed or transfected with the polynucleotide as described herein; a composition comprising an antibody as described herein; a detection system comprising the antibody as described herein.

[9b] Yet other aspects of the present disclosure provide use of an antibody as described herein in a diagnostic method; a method of detecting neoplastic growth using the antibody, the composition or the detection system as described herein.

[9c] Another aspect of the present disclosure provides a method for detecting and/or quantifying MUC17 expression in a sample, comprising the steps of: (a) using an antibody or using a detection system as described herein, for determining the expression quantity of MUC17 in a sample; and (b) comparing the expression quantity of MUC17 determined in step (a) to (i) a pre-defined value for the MUC17 expression quantity, (ii) the expression quantity of MUC17 determined in a control sample, or (iii) the expression quantity of MUC17 determined in a sample obtained from the same source or subject at a previous time point.

[9d] Another aspect of the present disclosure provides an *in vitro* method for diagnosing a neoplastic disease associated with expression quantity of MUC17 or increased expression quantity of MUC17, comprising the steps of: (a) using an antibody or a composition, or using a detection system as described herein, for determining the expression quantity of MUC17 in a sample; and (b) comparing the expression quantity of MUC17 determined in step (a) to

- (i) a pre-defined cut-off value for the expression quantity of MUC17, indicating absence of such disease, or
- (ii) the expression quantity of MUC17 determined in a negative control sample representing absence of such neoplastic disease,

wherein a higher expression quantity of MUC17 determined in step (a) as compared to the pre-defined cut-off value of (i) or the expression quantity of MUC17 determined in the negative control sample of (ii) indicates the presence of a disease associated with expression of MUC17 or increased expression quantity of MUC17.

[9e] Another aspect of the present disclosure provides an *in vitro* method for monitoring the progression of a disease associated with expression of MUC17 or with increased expression quantity of MUC17 or for monitoring the response to treatment of a disease associated with expression of MUC17 or with increased expression quantity of MUC17, comprising the steps of: (a) using an antibody, or using a detection system as described herein, for determining the expression quantity of MUC17 at a first time point in a sample obtained from a subject diagnosed with such disease; (b) using an antibody, or using a detection system as described herein, for determining the expression quantity of MUC17 at a second time point or after treatment in a sample obtained from the subject; and (c) comparing the expression quantity of MUC17 determined in step (a) to the expression quantity of MUC17 determined in step (b); wherein a higher expression quantity of MUC17 determined in step (a) as compared to the expression quantity of MUC17 determined in step (b) indicates that the disease is progressing, and/or wherein a lower expression quantity of MUC17 determined in step (a) as compared to the expression quantity of MUC17 determined in step (b) indicates that said disease is entering remission or that said disease is responding to the treatment.

[9f] Another aspect of the present disclosure provides use of a drug in the manufacture of a medicament for treating at least one cancer, wherein the cancer is selected from the group consisting of esophageal cancer, gastric cancer, gastrointestinal cancer, gastroesophageal cancer, including gastroesophageal junction cancer, and/or pancreas cancer, wherein said patient has an increased expression of MUC17 on a cancer cell, particularly a cell of a colorectal carcinoma, a gastric carcinoma, a pancreatic carcinoma, colon adenocarcinoma, esophageal carcinoma, pancreatic adenocarcinoma, rectum adenocarcinoma, and stomach adenocarcinoma, wherein said increased expression was determined in a method as described herein, or wherein the use as described herein is comprised; and wherein the drug is an antibody construct comprising at least two domains, wherein one domain binds selectively to MUC17.

[9g] Another aspect of the present disclosure provides a diagnostic kit comprising the antibody or the composition and/or detection system as described herein.

EmbodimentExamples of the disclosureinvention

[10] In a first embodimentexample, the present invention-disclosure relates to an antibody that binds to human MUC17 as depicted in SEQ ID NO: 1, wherein said antibody binds cell surface-associated MUC17 protein.

[11] In a second embodimentexample, the present disclosureinvention relates to an antibody that binds to human MUC17 as depicted in SEQ ID NO: 1, wherein said antibody binds cell surface-associated MUC17 protein, wherein said antibody comprises a variable heavy chain comprising a CDR3 region depicted in SEQ ID NO: 4.

[12] In a third embodimentexample, the present disclosureinvention relates to an antibody according to embodimentexamples 1 and 2, wherein said antibody further comprising the heavy chain CDR1 and CDR2 regions as depicted in SEQ ID Nos: 2 and 3 and/or the light chain CDR1, CDR2 and/or CDR3 regions depicted in SEQ ID Nos: 6, 7 and 8.

[13] In a fourth embodimentexample, the present disclosureinvention relates to an antibody according to any one of the preceding embodimentexamples, wherein the monoclonal antibody comprises a VH region and/or a VL region comprised by the sequences depicted in SEQ ID NOs: 5 and 9.

[14] In a fifth embodimentexample, the present disclosureinvention relates to an antibody according to any one of the preceding embodimentexamples, wherein the antibody is a monoclonal antibody.

[15] In a sixth embodimentexample, the present disclosureinvention relates to an antibody according to any one of the preceding embodimentexamples, wherein the antibody specifically binds to human and cynomolgus monkey MUC17 in immunohistochemistry assays, to MUC17 expressing cells in fluorescence activated cell sorting assays, and to MUC17 expressing fixed and permeabilized cells, optionally wherein the antibody does not bind to the secreted form of huMUC17.

[16] In a seventh embodimentexample, the present disclosureinvention relates to an antibody according to any one of the preceding embodimentexamples, wherein the antibody comprises a VH region comprised in SEQ ID NO: 5 and a VL region according to SEQ ID NO: 9.

[17] In an eighth embodimentexample, the present disclosureinvention relates to an antibody according to any one of the preceding embodimentexamples, which is an IgG, IgD, IgE, IgM or IgA antibody, preferably an IgG antibody, such as an IgG1, IgG2, IgG3 or IgG4 antibody.

[18] Within said embodimentexample, it is further envisaged in the context of the present disclosureinvention to provide an antibody construct, wherein the first domain of the antibody construct

binds to an epitope within MUC17 which corresponds to amino acids 4171 to 4296 according to uniprot Q685J3 numbering.

[19] Within said embodimentexample, it is also envisaged in the context of the present disclosureinvention to provide an antibody construct, wherein the first domain of the antibody construct binds to an epitope within MUC17 which corresponds to amino acids 4184 to 4291 according to uniprot Q685J3 numbering.

[20] Within said embodimentexample, it is further envisaged in the context of the present inventiondisclosure to provide an antibody construct, wherein the first domain of the antibody construct binds to an epitope within MUC17 which corresponds to amino acids 4131 to 4243 according to uniprot Q685J3 numbering.

[21] Within said embodimentexample, it is also envisaged in the context of the present inventiondisclosure to provide an antibody construct, wherein the first domain of the antibody construct binds to an epitope within MUC17 which corresponds to amino acids 4244 to 4389 according to uniprot Q685J3 numbering.

[22] Within said embodimentexample, it is further envisaged in the context of the present inventiondisclosure to provide an antibody construct, wherein the first domain of the antibody construct binds to an epitope within MUC17 which corresponds to amino acids 4131 to 4243 according to uniprot Q685J3 numbering, but not to an epitope within MUC17 which corresponds to amino acids 4244 to 4389 according to uniprot Q685J3 numbering.

[23] Within said embodimentexample, it is also envisaged in the context of the present inventiondisclosure to provide an antibody construct, wherein the first domain of the antibody construct binds to an epitope within MUC17 which corresponds to amino acids 4171 to 4390 according to uniprot Q685J3 numbering or amino acids 4184 to 4390 according to uniprot Q685J3 numbering but not to an epitope within MUC17 which corresponds to amino acids 4291 to 4390 according to uniprot Q685J3 numbering or to an epitope within MUC17 which corresponds to amino acids 4341 to 4390 according to uniprot Q685J3 numbering.

[24] In a ninth embodimentexample, the present inventiondisclosure relates to a polynucleotide encoding an antibody as defined in any one of the preceding embodimentexamples.

[25] In a tenth embodimentexample, the present inventiondisclosure relates to vector comprising the polynucleotide as defined in embodimentexample nine.

[26] In an 11th [embodimentexample](#), the present [inventiondisclosure](#) relates to host cells transformed or transfected with the polynucleotide as defined in the tenth [embodimentexample](#) or with the vector as defined in ninth [embodimentexample](#).

[27] In a 12th [embodimentexample](#), the present [inventiondisclosure](#) relates to a process for producing an antibody as defined in any one of [embodimentexamples](#) one to eight, said process comprising culturing a host cell as defined in [embodimentexample](#) ten under conditions allowing the expression of said antibody and recovering the produced antibody from the culture.

[28] In a 13th [embodimentexample](#), the present [inventiondisclosure](#) relates to hybridoma producing the antibody according to any one of the preceding [embodimentexamples](#) one through eight.

[29] In a 14th [embodimentexample](#), the present [inventiondisclosure](#) relates to a composition comprising an antibody as defined in any one of [embodimentexamples](#) one to eight, or as produced according to the process of the 12th [embodimentexample](#).

[30] In a 15th [embodimentexample](#), the present [inventiondisclosure](#) relates to a detection system comprising the antibody as defined in any one of [embodimentexamples](#) 1 to 8, or as produced according to the process of [embodimentexample](#) 12.

[31] In a 16th [embodimentexample](#), the present [inventiondisclosure](#) relates to a use of an antibody as defined in any one of [embodimentexample](#) 1-8 or as produced according to the process of [embodimentexample](#) 12 or of the detection system of [embodimentexample](#) 15 in a diagnostic method.

[32] In a 17th [embodimentexample](#), the present [inventiondisclosure](#) relates to an antibody as defined in any one of [embodimentexample](#) 1-8 or as produced according to the process of [embodimentexample](#) 12, the composition of [embodimentexample](#) 14, or of the detection system of [embodimentexample](#) 15 for use in a method of detecting neoplastic growth.

[33] In an 18th [embodimentexample](#), the present [inventiondisclosure](#) relates to the antibody or detection system for use according to [embodimentexample](#) 17 in a method of detecting neoplastic growth comprising determining the quantity of expression of MUC17 in a sample from a patient suspected to suffer from a cancer and in a negative control sample and, optionally, in a positive control sample.

[34] In a 19th [embodimentexample](#), the present [inventiondisclosure](#) relates to the antibody or detection system for use according to any one of [embodimentexample](#) 17 and 18 in a method of detecting neoplastic growth comprising determining the quantity of expression of MUC17 in a sample from a patient suspected to suffer from a cancer and in a negative control sample, further comprising comparing the expression quantities of MUC17 between the samples, optionally wherein the expression quantities

in the negative control and/or the positive control may be derived from stored data in at least one negative control sample and/or at least one positive control sample obtained in a method of detecting neoplastic growth comprising determining the quantity of expression of MUC17, further optionally, wherein the expression quantities in the negative control sample and/or the positive control sample may be derived from stored data comprising averaged expression quantities of more than one negative control sample and/or more than one positive control sample obtained in a method of detecting neoplastic growth comprising determining the quantity of expression of MUC17.

[35] In a 20th embodimentexample, the present inventiondisclosure relates to the antibody or detection system for use according to any one of embodimentexample 17 and 19 in a method of detecting neoplastic growth comprising determining the quantity of expression of MUC17 in a sample, wherein the sample is either a solid tissue sample or a liquid tissue sample.

[36] In a 21th embodimentexample, the present inventiondisclosure relates to a method for detecting and/or quantifying MUC17 expression in a sample, comprising the steps of:

- (a) using an antibody as defined in or produced according to any one of the preceding embodimentexamples, or using a detection system of embodimentexample 15, for determining the expression quantity of MUC17 in a sample; and
- (b) comparing the expression quantity of MUC17 determined in step (a) to
- (c) a pre-defined value for the MUC17 expression quantity,
- (d) the expression quantity of MUC17 determined in a control sample, or
- (e) the expression quantity of MUC17 determined in a sample obtained from the same source or subject at a previous time point.

[37] In a 22nd embodimentexample, the present inventiondisclosure relates to a method for diagnosing a neoplastic disease associated with expression quantity of MUC17 or increased expression quantity of MUC17, comprising the steps of:

- (a) using an antibody as defined in or produced according to any one of embodimentexample, or using a detection system of embodimentexample 15, for determining the expression quantity of MUC17 in a sample; and
- (b) comparing the expression quantity of MUC17 determined in step (a) to
- (c) a pre-defined cut-off value for the expression quantity of MUC17, indicating absence of such disease, or

(d) the expression quantity of MUC17 determined in a negative control sample representing absence of such neoplastic disease,

wherein a higher expression quantity of MUC17 determined in step (a) as compared to the pre-defined cut-off value of (i) or the expression quantity of MUC17 determined in the negative control sample of (ii) indicates the presence of a disease associated with expression of MUC17 or increased expression quantity of MUC17.

[38] In a 23rd embodimentexample, the present inventiondisclosure relates to a method for monitoring the progression of a disease associated with expression of MUC17 or with increased expression quantity of MUC17 or for monitoring the response to treatment of a disease associated with expression of MUC17 or with increased expression quantity of MUC17, comprising the steps of:

- (a) using an antibody as defined in any one of the preceding embodimentexamples, or using a detection system of embodimentexample 15, for determining the expression quantity of MUC17 at a first time point in a sample obtained from a subject diagnosed with such disease;
- (b) using an antibody as defined in any one of the preceding embodimentexamples, or using a detection system of embodimentexample 15, for determining the expression quantity of MUC17 at a second time point or after treatment in a sample obtained from the subject; and
- (c) comparing the expression quantity of MUC17 determined in step (a) to the expression quantity of MUC17 determined in step (b);

wherein a higher expression quantity of MUC17 determined in step (a) as compared to the expression quantity of MUC17 determined in step (b) indicates that the disease is progressing, and/or wherein a lower expression quantity of MUC17 determined in step (a) as compared to the expression quantity of MUC17 determined in step (b) indicates that said disease is entering remission or that said disease is responding to the treatment.

[39] In a 24th embodimentexample, the present inventiondisclosure relates to the use or the product for use of any one of embodimentexamples 16 to 20 or the method of any one of embodimentexample 21 to 23, wherein the sample is a biological sample, preferably a human biological sample, such as a tissue sample, or a sample comprising cultured cells.

[40] In a 25th embodimentexample, the present inventiondisclosure relates to the use or the product for use of any one of embodimentexample 16 to 20 or the method of any one of embodimentexample 21 to 24, wherein the sample is obtained from a human subject, preferably a human subject suspected of having or having a disease associated with expression of MUC17 or increased expression quantity of

MUC17, or a subject having received treatment for a disease associated with expression of MUC17 or increased expression quantity of MUC17.

[41] In a 26th embodimentexample, the present inventiondisclosure relates to the use or the product for use of any one of embodimentexample 16 to 20 or the method of any one of embodimentexample 21 to 25, wherein the disease is selected from the group comprising esophageal cancer, gastric cancer, gastroesophageal cancer (including gastroesophageal junction cancer, GJC) gastrointestinal cancer, and pancreas cancer.

[42] In a 27th embodimentexample, the present inventiondisclosure relates to the use of the any of the products as defined herein above for the detection of MUC17 expression in a immunohistochemical method (IHC method) comprising the steps of providing a sample of a tissue (including a liquid biopsy material, e.g. cells obtained from an individual or animal or from cell culture). The sample material is generally provided on a support, e.g. a carrier such as a glass or plastic slide. The tissue may be fixed using fixation media known in the art such as paraffin, ethanol, or acetone, or any other suitable medium that ensure fixation of a tissue or cells on a support. The sample are subsequently prepared, e.g. deparaffinated, incubated with media permitting access of the herein described antibodies to the target of interest, here MUC17. The tissues are subsequently incubated with a medium comprising a sufficient amount of the antibodies disclosed herein to allow these antibodies to bind to MUC17 that is present in the tissue sample. After a commonly known and reasonable amount of time the incubation of the tissue with the antibody is stopped, generally by washing the support and tissue in a medium such as PBS. Both, incubation steps and washing steps may be performed at room temperature, but elevated temperatures or lower temperatures, e.g. from 2 – 50°C are possible. Generally, the incubation temperature depends on the duration of the incubation time. For example, it is possible to stain tissues overnight at 4°C, but it is equally possible to shorten the incubation time to only a few minutes at higher temperatures, e.g., at about 30 to 40°C, e.g. at 37 °C. To check the influence of the incubation media, fixation medium, the incubation time and temperature, tests are usually performed with positive control material that are known to express the target (here MUC17), and with negative controls of sample that are known as not expressing MUC17. A negative control may also (optionally, additionally) be performed using the antibody product of the present inventiondisclosure, and blocking epitopes, i.e. epitopes that correspond to those that are recognized or bound specifically / selectively by the herein described antibodies. These blocking epitopes are added in a titration assay to a positive control material. A concentration of the epitopes that prevent the antibody of the present inventiondisclosure to specifically and/or selectively detect MUC17 may thus be determined. This way, a positive control – in the presence of the blocking epitope – no longer serves as positive control, because the amount of antibody binding MUC17 is blocked by a sufficient amount of blocking epitopes that saturate the antibodies. Determining the correct amount of blocking epitopes and antibodies to conduct appropriate positive and negative controls is a matter known to a person skilled in the technique of immunocytochemistry and particularly immunohistochemistry. Once the appropriate

Claims

1. An antibody that binds to human MUC17 as depicted in SEQ ID NO: 1, wherein said antibody binds cell surface-associated MUC17 protein._a
- ~~2. The antibody according to claim 1,~~ wherein said antibody comprises a variable heavy chain comprising a CDR3 region depicted in SEQ ID NO: 4._a
- ~~3. The antibody according to claim 1 or 2, wherein said antibody further comprises the a~~ heavy chain CDR1 and CDR2 regions as depicted in SEQ ID Nos: 2 and 3 and~~for~~ the light chain CDR1, CDR2 and~~for~~ CDR3 regions depicted in SEQ ID Nos: 6, 7, and 8.
42. The antibody according to any one of the preceding claims, wherein the antibody comprises a VH region and/or a VL region as comprised in SEQ ID Nos: 5 and/or 9.
- ~~5. The antibody according to any one of the preceding claims, wherein the antibody is a monoclonal antibody.~~
- ~~6. The antibody according to any one of the preceding claims, wherein the antibody specifically binds to human and cynomolgus monkey MUC17 when used in vitro in immunohistochemistry assays, to MUC17-expressing cells in fluorescence-activated cell sorting assays, and to MUC17-expressing fixed and permeabilized cells, optionally wherein the antibody does not bind to the secreted form of huMUC17.~~
- ~~7. The antibody according to any one of the preceding claims, which is an IgG, IgD, IgE, IgM or IgA antibody, preferably an IgG antibody, such as an IgG1, IgG2, IgG3 or IgG4 antibody.~~
83. A polynucleotide encoding an antibody as defined in any one of the preceding claims.
- ~~9. A vector comprising the polynucleotide as defined in claim 8.~~
104. A host cell transformed or transfected with the polynucleotide as defined in claim ~~8~~₃~~or with the vector as defined in claim 9.~~
- ~~11. A process for producing an antibody as defined in any one of claims 1 to 7, said process comprising the steps of culturing a host cell as defined in claim 10 under conditions allowing the expression of said antibody and recovering the produced antibody from the culture.~~
- ~~12. A hybridoma producing the antibody according to any one of the preceding claims.~~

- ~~135.~~ A composition comprising an antibody as defined in any one of claims 1 ~~to 7~~ and 2, ~~or as produced according to the process of claim 11.~~
- ~~146.~~ A detection system comprising the antibody as defined in any one of claims 1 ~~to 7~~ and 2, ~~or as produced according to the process of claim 11,~~ or a composition according to claim ~~135.~~
- ~~157.~~ Use of an antibody as defined in any one of claims 1 and 2-7 ~~or as produced according to the process of claim 11 or of the detection system of claim 14~~ in a diagnostic method.
- ~~168.~~ A method of detecting neoplastic growth using the antibody as defined in any one of claims 1 to 2, the composition of claim 5 or the detection system of claim 6~~An antibody as defined in any one of claims 1-7 or as produced according to the process of claim 11, the composition of claim 13, or of the detection system of claim 14 for use in a method of detecting neoplastic growth.~~
- ~~179.~~ The ~~antibody or detection system for use~~method according to claim ~~16-8~~ in a method of detecting ~~neoplastic growth further~~ comprising determining the quantity of expression of MUC17 in a sample from a patient suspected to suffer from a cancer and, optionally, in a negative control sample and, further optionally, in a positive control sample.
- ~~1810.~~ The ~~antibody or detection system for use~~method according to any one of claims ~~16-8~~ and ~~17-9~~ in a method of detecting neoplastic growth further comprising determining the quantity of expression of MUC17 in a sample from a patient suspected to suffer from a cancer and in a negative control sample, further comprising comparing the expression quantities of MUC17 between the samples, optionally wherein the expression quantities in the negative control and/or the positive control may be derived from stored data in at least one negative control sample and/or at least one positive control sample obtained in a method of detecting neoplastic growth comprising determining the quantity of expression of MUC17, further optionally, wherein the expression quantities in the negative control sample and/or the positive control sample may be derived from stored data comprising averaged expression quantities of more than one negative control sample and/or more than one positive control sample obtained in a method of detecting neoplastic growth comprising determining the quantity of expression of MUC17.
- ~~1911.~~ The ~~antibody or detection system for use~~method according to any one of claims ~~17-9~~ and ~~18-10~~ in a method of detecting neoplastic growth further comprising determining the quantity of expression of MUC17 in a sample, wherein the sample is either a solid tissue sample or a liquid tissue sample.
- ~~2012.~~ A method for detecting and/or quantifying MUC17 expression in a sample, comprising the steps of:

- (a) using an antibody as defined in ~~or produced according to~~ any one of the preceding claims, or using a detection system of claim ~~146~~, for determining the expression quantity of MUC17 in a sample; and
- (b) comparing the expression quantity of MUC17 determined in step (a) to
 - (i) a pre-defined value for the MUC17 expression quantity,
 - (ii) the expression quantity of MUC17 determined in a control sample, or
 - (iii) the expression quantity of MUC17 determined in a sample obtained from the same source or subject at a previous time point.

~~21~~13. An *in vitro* method for diagnosing a neoplastic disease associated with expression quantity of MUC17 or increased expression quantity of MUC17, comprising the steps of:

- (a) using an antibody or a composition as defined in ~~or produced according to~~ the preceding claims, or using a detection system of claim ~~146~~, for determining the expression quantity of MUC17 in a sample; and
- (b) comparing the expression quantity of MUC17 determined in step (a) to
 - (i) a pre-defined cut-off value for the expression quantity of MUC17, indicating absence of such disease, or
 - (ii) the expression quantity of MUC17 determined in a negative control sample representing absence of such neoplastic disease,

wherein a higher expression quantity of MUC17 determined in step (a) as compared to the pre-defined cut-off value of (i) or the expression quantity of MUC17 determined in the negative control sample of (ii) indicates the presence of a disease associated with expression of MUC17 or increased expression quantity of MUC17.

~~22~~14. An *in vitro* method for monitoring the progression of a disease associated with expression of MUC17 or with increased expression quantity of MUC17 or for monitoring the response to treatment of a disease associated with expression of MUC17 or with increased expression quantity of MUC17, comprising the steps of:

- (a) using an antibody as defined in any one of the preceding claims, or using a detection system of claim ~~146~~, for determining the expression quantity of MUC17 at a first time point in a sample obtained from a subject diagnosed with such disease;
- (b) using an antibody as defined in any one of the preceding claims, or using a detection system of claim ~~146~~, for determining the expression quantity of MUC17 at a second time point or after treatment in a sample obtained from the subject; and
- (c) comparing the expression quantity of MUC17 determined in step (a) to the expression quantity of MUC17 determined in step (b);

wherein a higher expression quantity of MUC17 determined in step (a) as compared to the expression quantity of MUC17 determined in step (b) indicates that the disease is progressing, and/or wherein a lower expression quantity of MUC17 determined in step (a) as compared to the expression quantity of MUC17 determined in step (b) indicates that said disease is entering remission or that said disease is responding to the treatment.

~~23. The use or the product for use of any one of claims 15 to 19 or the method of any one of claims 20 to 22, wherein the sample is a biological sample, preferably a human biological sample, such as a tissue sample, or a sample comprising cultured cells.~~

~~24. The use or the product for use of any one of claims 15 to 19 or the method of any one of claims 20 to 23, wherein the sample is obtained from a human subject, preferably a human subject suspected of having or having a disease associated with expression of MUC17 or increased expression quantity of MUC17, or a subject having received treatment for a disease associated with expression of MUC17 or increased expression quantity of MUC17.~~

~~25~~15. The use ~~or the product for use~~ of any one of claims ~~7 15 to 19~~ or the method of any one of claims ~~20-8~~ to ~~24~~14, wherein the disease is selected from the group comprising esophageal cancer, gastric cancer, gastrointestinal cancer, gastroesophageal cancer, including gastroesophageal junction cancer, and pancreas cancer.

~~26~~16. ~~Use of a drug in the manufacture of a medicament for~~A method of treatment of a patient, ~~preferably a human patient, having treating~~ at least one cancer, ~~wherein the cancer is~~ selected from the group ~~comprising~~ consisting of esophageal cancer, gastric cancer, gastrointestinal cancer, gastroesophageal cancer, including gastroesophageal junction cancer, and/or pancreas cancer, wherein said patient has an increased expression of MUC17 on a cancer cell, particularly a cell of a colorectal carcinoma, a gastric carcinoma, a pancreatic carcinoma, colon adenocarcinoma, esophageal carcinoma, pancreatic adenocarcinoma, rectum adenocarcinoma, and stomach adenocarcinoma-.

~~27. The method of treatment according to claim 26,~~ wherein said increased expression was determined in a method according to any one of claims ~~20-8~~ to ~~22~~14, or wherein the use ~~or the product for use of any one of claims 15 to 19, 23, and/or 24~~ is comprised; and wherein the drug is an antibody construct comprising at least two domains, wherein one domain binds selectively to MUC17.

~~28. The method of treatment according to claim 26 and 27 comprising the administration of a drug to said patient, wherein the drug is selected from the group comprising small molecules, peptidic drugs, antibodies and derivatives thereof, toxins, radiation therapy, and surgery.~~

~~29. The method of treatment according to any one of claims 26 to 28, wherein the drug is an antibody construct comprising at least two domains, wherein one domain binds selectively to MUC17.~~

~~30. The method of treatment according to any one of claims 26 to 29, wherein the drug is an antibody construct comprising at least two domains, wherein another domain binds selectively to CD3, to human CD3, particularly to the human CD3 Epsilon chain.~~

~~31. The method of treatment according to any one of claims 26 to 30, wherein the drug is an antibody construct further comprising a third domain which comprises two polypeptide monomers, each comprising a hinge, a CH2 domain and a CH3 domain, wherein said two polypeptide monomers are fused to each other via a peptide linker.~~

~~32. The method of treatment according to any one of claims 26 to 31, wherein the drug is a single chain antibody construct.~~

~~33. The method of treatment according to any one of claims 26 to 32, wherein the drug is an antibody construct, wherein said third domain comprises in an amino to carboxyl order:~~

~~hinge-CH2-CH3-linker-hinge-CH2-CH3.~~

~~34. The method of treatment according to any one of claims 26 to 33, wherein the drug is an antibody construct, wherein each of said polypeptide monomers in the third domain has an amino acid sequence that is at least 90% identical to a sequence selected from the group from the group consisting of: SEQ ID NO: 22-29.~~

~~35. — The method of treatment according to any one of claims 26 to 34, wherein the drug is an antibody construct, wherein each of said polypeptide monomers has an amino acid sequence selected from SEQ ID NO: 22-29.~~

~~36. The method of treatment according to any one of claims 26 to 35, wherein the drug is an antibody construct, wherein the CH2 domain comprises an intra domain cysteine disulfide bridge.~~

~~37. — The method of treatment according to any one of claims 26 to 36, wherein the drug is an antibody construct, wherein~~

~~(i) — the first domain comprises two antibody variable domains and the second domain comprises two antibody variable domains;~~

~~(ii) — the first domain comprises one antibody variable domain and the second domain comprises two antibody variable domains;~~

~~(iii) — the first domain comprises two antibody variable domains and the second domain comprises one antibody variable domain; or~~

- (iv) ~~the first domain comprises one antibody variable domain and the second domain comprises one antibody variable domain.~~
38. ~~The method of treatment according to any one of claims 26 to 37, wherein the drug is an antibody construct, wherein the first and second domain are fused to the third domain via a peptide linker.~~
39. ~~The method of treatment according to any one of claims 26 to 38, wherein the drug is an antibody construct, wherein the antibody construct comprises in an amino to carboxyl order:~~
- ~~(a) the first domain;~~
- ~~(b) a peptide linker preferably having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10-12;~~
- ~~(c) the second domain.~~
40. ~~The method of treatment according to any one of claims 26 to 39, wherein the drug is an antibody construct, wherein the antibody construct further comprises in an amino to carboxyl order:~~
- ~~(d) a peptide linker having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 11, 12, 17, 18, 19 and 20.~~
- ~~(e) the first polypeptide monomer of the third domain;~~
- ~~(f) a peptide linker having an amino acid sequence selected from the group consisting of SEQ ID NOs: 13, 14, 15 and 16; and~~
- ~~(g) the second polypeptide monomer of the third domain.~~
41. ~~The method of treatment according to any one of claims 26 to 40, wherein the drug is an antibody construct, wherein the first domain of the antibody construct binds to an epitope within MUC17 which corresponds to SEQ ID NO. 526 (aa 4171 to 4296 according to uniprot Q685J3 numbering).~~
42. ~~The method of treatment according to any one of claims 26 to 41, wherein the drug is an antibody construct, wherein the first domain of the antibody construct binds to an epitope within MUC17 which corresponds to SEQ ID NO. 527 (aa 4184 to 4291 according to uniprot Q685J3 numbering).~~
43. ~~The method of treatment according to any one of claims 26 to 42, wherein the drug is an antibody construct, wherein the first domain of the antibody construct binds to an epitope within MUC17 which corresponds to SEQ ID NO. 528 (aa 4131 to 4243 according to uniprot Q685J3 numbering).~~

44. ~~The method of treatment according to any one of claims 26 to 43, wherein the drug is an antibody construct, wherein the first domain of the antibody construct binds to an epitope within MUC17 which corresponds to SEQ ID NO. 529 (aa 4244 to 4389 according to uniprot Q685J3 numbering).~~
45. ~~The method of treatment according to any one of claims 26 to 44, wherein the drug is an antibody construct, wherein the first domain of the antibody construct binds to an epitope within MUC17 which corresponds to SEQ ID NO. 528 (aa 4131 to 4243 according to uniprot Q685J3 numbering) but not to an epitope within MUC17 which corresponds to SEQ ID NO. 529 (aa 4244 to 4389 according to uniprot Q685J3 numbering).~~
46. ~~The method of treatment according to any one of claims 26 to 45, wherein the drug is an antibody construct, wherein the first domain of the antibody construct binds to an epitope within MUC17 which corresponds to SEQ ID NO. 530 (aa 4171 to 4390 according to uniprot Q685J3 numbering) or SEQ ID NO. 531 (aa 4184 to 4390 according to uniprot Q685J3 numbering) but not to an epitope within MUC17 which corresponds to SEQ ID NO. 532 (aa 4291 to 4390 according to uniprot Q685J3 numbering) or to an epitope within MUC17 which corresponds to SEQ ID NO. 533 (aa 4341 to 4390 according to uniprot Q685J3 numbering).~~
47. ~~The method of treatment according to any one of claims 26 to 46, wherein the drug is an antibody construct, wherein the ratio between cytotoxicity and binding affinity (EC_{50}/K_D)*1000 is below 250, wherein the cytotoxicity is determined in NUGC 4 cells as target cells and huPBMC as effector cells, and wherein the binding affinity is determined by a surface plasmon resonance-based assay.~~
48. ~~The method of treatment according to any one of claims 26 to 47, wherein the drug is an antibody construct, wherein the ratio between cytotoxicity and binding affinity (EC_{50}/K_D)*1000 is below 125, wherein the cytotoxicity is determined in NUGC 4 cells as target cells and huPBMC as effector cells, and wherein the binding affinity is determined by a surface plasmon resonance-based assay.~~
49. ~~The method of treatment according to any one of claims 26 to 48, wherein the drug is an antibody construct, wherein the ratio between cytotoxicity and binding affinity (EC_{50}/K_D)*1000 is below 21, wherein the cytotoxicity is determined in NUGC 4 cells as target cells and huPBMC as effector cells, and wherein the binding affinity is determined by a surface plasmon resonance-based assay.~~
50. ~~The method of treatment according to any one of claims 26 to 49, wherein the drug is an antibody construct, wherein the first binding domain comprises a VH region comprising CDR H1, CDR H2 and CDR H3 selected from:~~

- (a) — ~~CDR H1 as depicted in SEQ ID NO. 31, CDR H2 as depicted in SEQ ID NO. 32 and CDR H3 as depicted in SEQ ID NO. 33;~~
- (b) — ~~CDR H1 as depicted in SEQ ID NO. 42, CDR H2 as depicted in SEQ ID NO. 43 and CDR H3 as depicted in SEQ ID NO. 44;~~
- (c) — ~~CDR H1 as depicted in SEQ ID NO. 53, CDR H2 as depicted in SEQ ID NO. 54 and CDR H3 as depicted in SEQ ID NO. 55;~~
- (d) — ~~CDR H1 as depicted in SEQ ID NO. 64, CDR H2 as depicted in SEQ ID NO. 65 and CDR H3 as depicted in SEQ ID NO. 66;~~
- (e) — ~~CDR H1 as depicted in SEQ ID NO. 75, CDR H2 as depicted in SEQ ID NO. 76 and CDR H3 as depicted in SEQ ID NO. 77;~~
- (f) — ~~CDR H1 as depicted in SEQ ID NO. 86, CDR H2 as depicted in SEQ ID NO. 87 and CDR H3 as depicted in SEQ ID NO. 88;~~
- (g) — ~~CDR H1 as depicted in SEQ ID NO. 97, CDR H2 as depicted in SEQ ID NO. 98 and CDR H3 as depicted in SEQ ID NO. 99;~~
- (h) — ~~CDR H1 as depicted in SEQ ID NO. 108, CDR H2 as depicted in SEQ ID NO. 109 and CDR H3 as depicted in SEQ ID NO. 110;~~
- (i) — ~~CDR H1 as depicted in SEQ ID NO. 119, CDR H2 as depicted in SEQ ID NO. 120 and CDR H3 as depicted in SEQ ID NO. 121;~~
- (j) — ~~CDR H1 as depicted in SEQ ID NO. 130, CDR H2 as depicted in SEQ ID NO. 131 and CDR H3 as depicted in SEQ ID NO. 132;~~
- (k) — ~~CDR H1 as depicted in SEQ ID NO. 141, CDR H2 as depicted in SEQ ID NO. 142 and CDR H3 as depicted in SEQ ID NO. 143;~~
- (l) — ~~CDR H1 as depicted in SEQ ID NO. 152, CDR H2 as depicted in SEQ ID NO. 153 and CDR H3 as depicted in SEQ ID NO. 154;~~
- (m) — ~~CDR H1 as depicted in SEQ ID NO. 163, CDR H2 as depicted in SEQ ID NO. 164 and CDR H3 as depicted in SEQ ID NO. 165;~~
- (n) — ~~CDR H1 as depicted in SEQ ID NO. 174, CDR H2 as depicted in SEQ ID NO. 175 and CDR H3 as depicted in SEQ ID NO. 176;~~

- (o) — ~~CDR H1 as depicted in SEQ ID NO. 185, CDR H2 as depicted in SEQ ID NO. 186 and CDR H3 as depicted in SEQ ID NO. 187;~~
- (p) — ~~CDR H1 as depicted in SEQ ID NO. 196, CDR H2 as depicted in SEQ ID NO. 197 and CDR H3 as depicted in SEQ ID NO. 198;~~
- (q) — ~~CDR H1 as depicted in SEQ ID NO. 207, CDR H2 as depicted in SEQ ID NO. 208 and CDR H3 as depicted in SEQ ID NO. 209;~~
- (r) — ~~CDR H1 as depicted in SEQ ID NO. 218, CDR H2 as depicted in SEQ ID NO. 219 and CDR H3 as depicted in SEQ ID NO. 220;~~
- (s) — ~~CDR H1 as depicted in SEQ ID NO. 229, CDR H2 as depicted in SEQ ID NO. 230 and CDR H3 as depicted in SEQ ID NO. 231;~~
- (t) — ~~CDR H1 as depicted in SEQ ID NO. 240, CDR H2 as depicted in SEQ ID NO. 241 and CDR H3 as depicted in SEQ ID NO. 242;~~
- (u) — ~~CDR H1 as depicted in SEQ ID NO. 251, CDR H2 as depicted in SEQ ID NO. 252 and CDR H3 as depicted in SEQ ID NO. 253;~~
- (v) — ~~CDR H1 as depicted in SEQ ID NO. 262, CDR H2 as depicted in SEQ ID NO. 263 and CDR H3 as depicted in SEQ ID NO. 264;~~
- (w) — ~~CDR H1 as depicted in SEQ ID NO. 273, CDR H2 as depicted in SEQ ID NO. 274 and CDR H3 as depicted in SEQ ID NO. 275;~~
- (x) — ~~CDR H1 as depicted in SEQ ID NO. 284, CDR H2 as depicted in SEQ ID NO. 285 and CDR H3 as depicted in SEQ ID NO. 286;~~
- (y) — ~~CDR H1 as depicted in SEQ ID NO. 295, CDR H2 as depicted in SEQ ID NO. 296 and CDR H3 as depicted in SEQ ID NO. 297;~~
- (z) — ~~CDR H1 as depicted in SEQ ID NO. 306, CDR H2 as depicted in SEQ ID NO. 307 and CDR H3 as depicted in SEQ ID NO. 308;~~
- (aa) — ~~CDR H1 as depicted in SEQ ID NO. 317, CDR H2 as depicted in SEQ ID NO. 318 and CDR H3 as depicted in SEQ ID NO. 319;~~
- (ab) — ~~CDR H1 as depicted in SEQ ID NO. 328, CDR H2 as depicted in SEQ ID NO. 329 and CDR H3 as depicted in SEQ ID NO. 330;~~

~~(ac) — CDR H1 as depicted in SEQ ID NO. 339, CDR H2 as depicted in SEQ ID NO. 340 and CDR H3 as depicted in SEQ ID NO. 341;~~

~~(ad) — CDR H1 as depicted in SEQ ID NO. 350, CDR H2 as depicted in SEQ ID NO. 351 and CDR H3 as depicted in SEQ ID NO. 352;~~

~~(ae) — CDR H1 as depicted in SEQ ID NO. 361, CDR H2 as depicted in SEQ ID NO. 362 and CDR H3 as depicted in SEQ ID NO. 363;~~

~~(af) — CDR H1 as depicted in SEQ ID NO. 372, CDR H2 as depicted in SEQ ID NO. 373 and CDR H3 as depicted in SEQ ID NO. 374;~~

~~(ag) — CDR H1 as depicted in SEQ ID NO. 383, CDR H2 as depicted in SEQ ID NO. 384 and CDR H3 as depicted in SEQ ID NO. 385;~~

~~(ah) — CDR H1 as depicted in SEQ ID NO. 394, CDR H2 as depicted in SEQ ID NO. 395 and CDR H3 as depicted in SEQ ID NO. 396;~~

~~(ai) — CDR H1 as depicted in SEQ ID NO. 405, CDR H2 as depicted in SEQ ID NO. 406 and CDR H3 as depicted in SEQ ID NO. 407;~~

~~(aj) — CDR H1 as depicted in SEQ ID NO. 416, CDR H2 as depicted in SEQ ID NO. 417 and CDR H3 as depicted in SEQ ID NO. 418;~~

~~(ak) — CDR H1 as depicted in SEQ ID NO. 427, CDR H2 as depicted in SEQ ID NO. 428 and CDR H3 as depicted in SEQ ID NO. 429;~~

~~(al) — CDR H1 as depicted in SEQ ID NO. 438, CDR H2 as depicted in SEQ ID NO. 439 and CDR H3 as depicted in SEQ ID NO. 440;~~

~~(am) — CDR H1 as depicted in SEQ ID NO. 449, CDR H2 as depicted in SEQ ID NO. 450 and CDR H3 as depicted in SEQ ID NO. 451;~~

~~(an) — CDR H1 as depicted in SEQ ID NO. 460, CDR H2 as depicted in SEQ ID NO. 461 and CDR H3 as depicted in SEQ ID NO. 462;~~

~~(ao) — CDR H1 as depicted in SEQ ID NO. 471, CDR H2 as depicted in SEQ ID NO. 472 and CDR H3 as depicted in SEQ ID NO. 473;~~

~~(ap) — CDR H1 as depicted in SEQ ID NO. 482, CDR H2 as depicted in SEQ ID NO. 483 and CDR H3 as depicted in SEQ ID NO. 484;~~

- ~~(aq) — CDR H1 as depicted in SEQ ID NO. 493, CDR H2 as depicted in SEQ ID NO. 494 and CDR H3 as depicted in SEQ ID NO. 495;~~
- ~~(ar) — CDR H1 as depicted in SEQ ID NO. 504, CDR H2 as depicted in SEQ ID NO. 505 and CDR H3 as depicted in SEQ ID NO. 506; and~~
- ~~(as) — CDR H1 as depicted in SEQ ID NO. 515, CDR H2 as depicted in SEQ ID NO. 516 and CDR H3 as depicted in SEQ ID NO. 517; wherein preferred are~~
- ~~(c) — CDR H1 as depicted in SEQ ID NO. 53, CDR H2 as depicted in SEQ ID NO. 54 and CDR H3 as depicted in SEQ ID NO. 55;~~
- ~~(n) — CDR H1 as depicted in SEQ ID NO. 174, CDR H2 as depicted in SEQ ID NO. 175 and CDR H3 as depicted in SEQ ID NO. 176;~~
- ~~(ae) — CDR H1 as depicted in SEQ ID NO. 339, CDR H2 as depicted in SEQ ID NO. 340 and CDR H3 as depicted in SEQ ID NO. 341; and~~
- ~~(aj) — CDR H1 as depicted in SEQ ID NO. 416, CDR H2 as depicted in SEQ ID NO. 417 and CDR H3 as depicted in SEQ ID NO. 418.~~
- ~~51. The method of treatment according to any one of claims 26 to 50, wherein the drug is an antibody construct, wherein the first binding domain comprises a VL region comprising CDR H1, CDR L2 and CDR L3 selected from:~~
- ~~(a) — CDR L1 as depicted in SEQ ID NO. 34, CDR L2 as depicted in SEQ ID NO. 35 and CDR L3 as depicted in SEQ ID NO. 36;~~
- ~~(b) — CDR L1 as depicted in SEQ ID NO. 45, CDR L2 as depicted in SEQ ID NO. 46 and CDR L3 as depicted in SEQ ID NO. 47;~~
- ~~(c) — CDR L1 as depicted in SEQ ID NO. 56, CDR L2 as depicted in SEQ ID NO. 57 and CDR L3 as depicted in SEQ ID NO. 58;~~
- ~~(d) — CDR L1 as depicted in SEQ ID NO. 67, CDR L2 as depicted in SEQ ID NO. 68 and CDR L3 as depicted in SEQ ID NO. 69;~~
- ~~(e) — CDR L1 as depicted in SEQ ID NO. 78, CDR L2 as depicted in SEQ ID NO. 79 and CDR L3 as depicted in SEQ ID NO. 80;~~
- ~~(f) — CDR L1 as depicted in SEQ ID NO. 89, CDR L2 as depicted in SEQ ID NO. 90 and CDR L3 as depicted in SEQ ID NO. 91;~~

- (g) — CDR L1 as depicted in SEQ ID NO. 100, CDR L2 as depicted in SEQ ID NO. 101 and CDR L3 as depicted in SEQ ID NO. 102;
- (h) — CDR L1 as depicted in SEQ ID NO. 111, CDR L2 as depicted in SEQ ID NO. 112 and CDR L3 as depicted in SEQ ID NO. 113;
- (i) — CDR L1 as depicted in SEQ ID NO. 122, CDR L2 as depicted in SEQ ID NO. 123 and CDR L3 as depicted in SEQ ID NO. 124;
- (j) — CDR L1 as depicted in SEQ ID NO. 133, CDR L2 as depicted in SEQ ID NO. 134 and CDR L3 as depicted in SEQ ID NO. 135;
- (k) — CDR L1 as depicted in SEQ ID NO. 144, CDR L2 as depicted in SEQ ID NO. 145 and CDR L3 as depicted in SEQ ID NO. 146;
- (l) — CDR L1 as depicted in SEQ ID NO. 155, CDR L2 as depicted in SEQ ID NO. 156 and CDR L3 as depicted in SEQ ID NO. 157;
- (m) — CDR L1 as depicted in SEQ ID NO. 166, CDR L2 as depicted in SEQ ID NO. 167 and CDR L3 as depicted in SEQ ID NO. 168;
- (n) — CDR L1 as depicted in SEQ ID NO. 177, CDR L2 as depicted in SEQ ID NO. 178 and CDR L3 as depicted in SEQ ID NO. 179;
- (o) — CDR L1 as depicted in SEQ ID NO. 188, CDR L2 as depicted in SEQ ID NO. 189 and CDR L3 as depicted in SEQ ID NO. 190;
- (p) — CDR L1 as depicted in SEQ ID NO. 199, CDR L2 as depicted in SEQ ID NO. 200 and CDR L3 as depicted in SEQ ID NO. 201;
- (q) — CDR L1 as depicted in SEQ ID NO. 210, CDR L2 as depicted in SEQ ID NO. 211 and CDR L3 as depicted in SEQ ID NO. 212;
- (r) — CDR L1 as depicted in SEQ ID NO. 221, CDR L2 as depicted in SEQ ID NO. 222 and CDR L3 as depicted in SEQ ID NO. 223;
- (s) — CDR L1 as depicted in SEQ ID NO. 232, CDR L2 as depicted in SEQ ID NO. 233 and CDR L3 as depicted in SEQ ID NO. 234;
- (t) — CDR L1 as depicted in SEQ ID NO. 243, CDR L2 as depicted in SEQ ID NO. 244 and CDR L3 as depicted in SEQ ID NO. 245;

- (u) — CDR L1 as depicted in SEQ ID NO. 254, CDR L2 as depicted in SEQ ID NO. 255 and CDR L3 as depicted in SEQ ID NO. 256;
- (v) — CDR L1 as depicted in SEQ ID NO. 265, CDR L2 as depicted in SEQ ID NO. 266 and CDR L3 as depicted in SEQ ID NO. 267;
- (w) — CDR L1 as depicted in SEQ ID NO. 276, CDR L2 as depicted in SEQ ID NO. 277 and CDR L3 as depicted in SEQ ID NO. 278;
- (x) — CDR L1 as depicted in SEQ ID NO. 287, CDR L2 as depicted in SEQ ID NO. 288 and CDR L3 as depicted in SEQ ID NO. 289;
- (y) — CDR L1 as depicted in SEQ ID NO. 298, CDR L2 as depicted in SEQ ID NO. 299 and CDR L3 as depicted in SEQ ID NO. 300;
- (z) — CDR L1 as depicted in SEQ ID NO. 309, CDR L2 as depicted in SEQ ID NO. 310 and CDR L3 as depicted in SEQ ID NO. 311;
- (aa) — CDR L1 as depicted in SEQ ID NO. 320, CDR L2 as depicted in SEQ ID NO. 321 and CDR L3 as depicted in SEQ ID NO. 322;
- (ab) — CDR L1 as depicted in SEQ ID NO. 331, CDR L2 as depicted in SEQ ID NO. 332 and CDR L3 as depicted in SEQ ID NO. 333;
- (ac) — CDR L1 as depicted in SEQ ID NO. 342, CDR L2 as depicted in SEQ ID NO. 343 and CDR L3 as depicted in SEQ ID NO. 344;
- (ad) — CDR L1 as depicted in SEQ ID NO. 353, CDR L2 as depicted in SEQ ID NO. 354 and CDR L3 as depicted in SEQ ID NO. 355;
- (ae) — CDR L1 as depicted in SEQ ID NO. 364, CDR L2 as depicted in SEQ ID NO. 365 and CDR L3 as depicted in SEQ ID NO. 366;
- (af) — CDR L1 as depicted in SEQ ID NO. 375, CDR L2 as depicted in SEQ ID NO. 376 and CDR L3 as depicted in SEQ ID NO. 377;
- (ag) — CDR L1 as depicted in SEQ ID NO. 386, CDR L2 as depicted in SEQ ID NO. 387 and CDR L3 as depicted in SEQ ID NO. 388;
- (ah) — CDR L1 as depicted in SEQ ID NO. 397, CDR L2 as depicted in SEQ ID NO. 398 and CDR L3 as depicted in SEQ ID NO. 399;

- (ai) ~~CDR L1 as depicted in SEQ ID NO. 408, CDR L2 as depicted in SEQ ID NO. 409 and CDR L3 as depicted in SEQ ID NO. 410;~~
- (aj) ~~CDR L1 as depicted in SEQ ID NO. 419, CDR L2 as depicted in SEQ ID NO. 420 and CDR L3 as depicted in SEQ ID NO. 421;~~
- (ak) ~~CDR L1 as depicted in SEQ ID NO. 430, CDR L2 as depicted in SEQ ID NO. 431 and CDR L3 as depicted in SEQ ID NO. 432;~~
- (al) ~~CDR L1 as depicted in SEQ ID NO. 441, CDR L2 as depicted in SEQ ID NO. 442 and CDR L3 as depicted in SEQ ID NO. 443;~~
- (am) ~~CDR L1 as depicted in SEQ ID NO. 452, CDR L2 as depicted in SEQ ID NO. 453 and CDR L3 as depicted in SEQ ID NO. 454;~~
- (an) ~~CDR L1 as depicted in SEQ ID NO. 463, CDR L2 as depicted in SEQ ID NO. 464 and CDR L3 as depicted in SEQ ID NO. 465;~~
- (ao) ~~CDR L1 as depicted in SEQ ID NO. 474, CDR L2 as depicted in SEQ ID NO. 475 and CDR L3 as depicted in SEQ ID NO. 476;~~
- (ap) ~~CDR L1 as depicted in SEQ ID NO. 485, CDR L2 as depicted in SEQ ID NO. 486 and CDR L3 as depicted in SEQ ID NO. 487;~~
- (aq) ~~CDR L1 as depicted in SEQ ID NO. 496, CDR L2 as depicted in SEQ ID NO. 497 and CDR L3 as depicted in SEQ ID NO. 498;~~
- (ar) ~~CDR L1 as depicted in SEQ ID NO. 507, CDR L2 as depicted in SEQ ID NO. 508 and CDR L3 as depicted in SEQ ID NO. 509; and~~
- (as) ~~CDR L1 as depicted in SEQ ID NO. 518, CDR L2 as depicted in SEQ ID NO. 519 and CDR L3 as depicted in SEQ ID NO. 520; wherein preferred are~~
- (e) ~~CDR L1 as depicted in SEQ ID NO. 56, CDR L2 as depicted in SEQ ID NO. 57 and CDR L3 as depicted in SEQ ID NO. 58;~~
- (n) ~~CDR L1 as depicted in SEQ ID NO. 177, CDR L2 as depicted in SEQ ID NO. 178 and CDR L3 as depicted in SEQ ID NO. 179;~~
- (ac) ~~CDR L1 as depicted in SEQ ID NO. 342, CDR L2 as depicted in SEQ ID NO. 343 and CDR L3 as depicted in SEQ ID NO. 344; and~~

(aj) — CDR-L1 as depicted in SEQ ID NO. 419, CDR-L2 as depicted in SEQ ID NO. 420 and CDR-L3 as depicted in SEQ ID NO. 421.

52. — The method of treatment according to any one of claims 26 to 51, wherein the drug is an antibody construct, wherein the first binding domain comprises a VL region and a VH region selected from the group consisting of:

- (a) — a VL region as depicted in SEQ ID NO. 38 and a VH region as depicted in SEQ ID NO. 37;
- (b) — a VL region as depicted in SEQ ID NO. 49 and a VH region as depicted in SEQ ID NO. 48;
- (c) — a VL region as depicted in SEQ ID NO. 60 and a VH region as depicted in SEQ ID NO. 59;
- (d) — a VL region as depicted in SEQ ID NO. 71 and a VH region as depicted in SEQ ID NO. 70;
- (e) — a VL region as depicted in SEQ ID NO. 82 and a VH region as depicted in SEQ ID NO. 81;
- (f) — a VL region as depicted in SEQ ID NO. 93 and a VH region as depicted in SEQ ID NO. 92;
- (g) — a VL region as depicted in SEQ ID NO. 104 and a VH region as depicted in SEQ ID NO. 103;
- (h) — a VL region as depicted in SEQ ID NO. 115 and a VH region as depicted in SEQ ID NO. 114;
- (i) — a VL region as depicted in SEQ ID NO. 126 and a VH region as depicted in SEQ ID NO. 125;
- (j) — a VL region as depicted in SEQ ID NO. 137 and a VH region as depicted in SEQ ID NO. 136;
- (k) — a VL region as depicted in SEQ ID NO. 148 and a VH region as depicted in SEQ ID NO. 147;
- (l) — a VL region as depicted in SEQ ID NO. 159 and a VH region as depicted in SEQ ID NO. 158;
- (m) — a VL region as depicted in SEQ ID NO. 170 and a VH region as depicted in SEQ ID NO. 169;
- (n) — a VL region as depicted in SEQ ID NO. 181 and a VH region as depicted in SEQ ID NO. 180;
- (o) — a VL region as depicted in SEQ ID NO. 192 and a VH region as depicted in SEQ ID NO. 191;
- (p) — a VL region as depicted in SEQ ID NO. 203 and a VH region as depicted in SEQ ID NO. 202;
- (q) — a VL region as depicted in SEQ ID NO. 214 and a VH region as depicted in SEQ ID NO. 213;
- (r) — a VL region as depicted in SEQ ID NO. 226 and a VH region as depicted in SEQ ID NO. 225;
- (s) — a VL region as depicted in SEQ ID NO. 236 and a VH region as depicted in SEQ ID NO. 235;

(t) — a VL region as depicted in SEQ ID NO. 247 and a VH region as depicted in SEQ ID NO. 246;

(u) — a VL region as depicted in SEQ ID NO. 258 and a VH region as depicted in SEQ ID NO. 257;

(v) — a VL region as depicted in SEQ ID NO. 269 and a VH region as depicted in SEQ ID NO. 268;

(w) — a VL region as depicted in SEQ ID NO. 280 and a VH region as depicted in SEQ ID NO. 279;

(x) — a VL region as depicted in SEQ ID NO. 292 and a VH region as depicted in SEQ ID NO. 290;

(y) — a VL region as depicted in SEQ ID NO. 302 and a VH region as depicted in SEQ ID NO. 301;

(z) — a VL region as depicted in SEQ ID NO. 313 and a VH region as depicted in SEQ ID NO. 312;

(aa) — a VL region as depicted in SEQ ID NO. 324 and a VH region as depicted in SEQ ID NO. 323;

(ab) — a VL region as depicted in SEQ ID NO. 335 and a VH region as depicted in SEQ ID NO. 334;

(ac) — a VL region as depicted in SEQ ID NO. 346 and a VH region as depicted in SEQ ID NO. 345;

(ad) — a VL region as depicted in SEQ ID NO. 357 and a VH region as depicted in SEQ ID NO. 356;

(ae) — a VL region as depicted in SEQ ID NO. 368 and a VH region as depicted in SEQ ID NO. 367;

(af) — a VL region as depicted in SEQ ID NO. 379 and a VH region as depicted in SEQ ID NO. 378;

(ag) — a VL region as depicted in SEQ ID NO. 390 and a VH region as depicted in SEQ ID NO. 389;

(ah) — a VL region as depicted in SEQ ID NO. 401 and a VH region as depicted in SEQ ID NO. 400;

(ai) — a VL region as depicted in SEQ ID NO. 412 and a VH region as depicted in SEQ ID NO. 411;

(aj) — a VL region as depicted in SEQ ID NO. 423 and a VH region as depicted in SEQ ID NO. 422;

(ak) — a VL region as depicted in SEQ ID NO. 434 and a VH region as depicted in SEQ ID NO. 433;

(al) — a VL region as depicted in SEQ ID NO. 445 and a VH region as depicted in SEQ ID NO. 444;

(am) — a VL region as depicted in SEQ ID NO. 456 and a VH region as depicted in SEQ ID NO. 455;

(an) — a VL region as depicted in SEQ ID NO. 467 and a VH region as depicted in SEQ ID NO. 466;

(ao) — a VL region as depicted in SEQ ID NO. 478 and a VH region as depicted in SEQ ID NO. 477;

(ap) — a VL region as depicted in SEQ ID NO. 489 and a VH region as depicted in SEQ ID NO. 488;

- (aq) ~~a VL region as depicted in SEQ ID NO. 500 and a VH region as depicted in SEQ ID NO. 499;~~
- (ar) ~~a VL region as depicted in SEQ ID NO. 511 and a VH region as depicted in SEQ ID NO. 510;~~
and
- (as) ~~a VL region as depicted in SEQ ID NO. 522 and a VH region as depicted in SEQ ID NO. 521;~~
53. ~~The method of treatment according to any one of claims 26 to 52, wherein the drug is an antibody construct, wherein the antibody construct comprises a sequence selected from an amino acid sequence as depicted in any of SEQ ID NOs: 39, 50, 61, 72, 83, 94, 105, 116, 127, 138, 149, 160, 171, 182, 193, 204, 215, 226, 237, 248, 259, 270, 281, 292, 303, 314, 325, 336, 347, 358, 369, 380, 391, 402, 413, 424, 435, 446, 457, 468, 479, 490, 501, 512, and 523.~~
54. ~~The method of treatment according to any one of claims 26 to 53, wherein the drug is an antibody construct, wherein the antibody construct comprises in an amino to carboxyl order:~~
- (a) ~~the first domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 39, 50, 61, 72, 83, 94, 105, 116, 127, 138, 149, 160, 171, 182, 193, 204, 215, 226, 237, 248, 259, 270, 281, 292, 303, 314, 325, 336, 347, 358, 369, 380, 391, 402, 413, 424, 435, 446, 457, 468, 479, 490, 501, 512, and 523;—~~
- (b) ~~a peptide linker having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10-12;—~~
- (c) ~~the second domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 23, 25, 41, 43, 59, 61, 77, 79, 95, 97, 113, 115, 131, 133, 149, 151, 167, 169, 185 or 187 of WO 2008/119567 or as depicted in SEQ ID NO: 13.~~
55. ~~The method of treatment according to any one of claims 26 to 54, wherein the drug is an antibody construct claim 25, wherein the antibody construct further comprises in an amino to carboxyl order:—~~
- (d) ~~a peptide linker having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 11, 12, 17, 18, 19 and 20.~~
- (e) ~~the first polypeptide monomer of the third domain having a polypeptide sequence selected from the group consisting of SEQ ID NOs: 22-29;—~~
- (f) ~~a peptide linker having an amino acid sequence selected from the group consisting of SEQ ID NOs: 13, 14, 15 and 16; and—~~

~~(g) the second polypeptide monomer of the third domain having a polypeptide sequence selected from the group consisting of SEQ ID NOs: 22-29.~~

~~56. The method of treatment according to any one of claims 26 to 55, wherein the drug is an antibody construct having an amino acid sequence selected from the group consisting of:~~

~~— SEQ ID NOs: 40, 41, 51, 52, 62, 63, 73, 74, 84, 85, 95, 96, 106, 107, 117, 118, 128, 129, 139, 140, 150, 151, 161, 162, 172, 173, 183, 184, 194, 195, 205, 206, 216, 217, 227, 228, 238, 239, 249, 250, 260, 261, 271, 272, 282, 283, 293, 294, 304, 305, 315, 316, 326, 327, 337, 338, 348, 349, 359, 360, 370, 371, 381, 382, 392, 393, 403, 404, 414, 415, 424, 426, 436, 437, 447, 448, 458, 459, 469, 470, 480, 481, 491, 492, 502, 503, 513, 514, 524 and 525, or having an amino acid having at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99% identity to said sequences.~~

~~57~~17. A diagnostic kit comprising the antibody or the composition and/or detection system according to any one of claims ~~1-7, 13, 14, 17, 18, and 19,~~ 2, 5 and 6.