towards c-Met. DN-30 Fab efficiently inhibited c-Met signalling by causing c-Met ectodomain shedding and receptor down regulation.

[0012] The one-arm 5D5 antibody (MetMab or clinically known as Onartuzumab) is a monovalent chimeric antibody targeted against c-Met. Like DN-30, bivalent 5D5 antibody became an antagonist when converted to a monovalent Fab. In contrast to Fab DN-30, MetMab acts as an antagonist by competing with HGF for c-Met binding and causes c-Met internalisation and down-regulation.

[0013] Thus, there is a need to provide new antagonist antibodies binding to c-Met that overcome, or at least ameliorate, one or more of the disadvantages described above.

## SUMMARY ~~OF THE INVENTION~~

[0014] Described below are antibodies against the α-chain of human c-Met. The development of a panel of bivalent anti-Met murine monoclonal antibodies, raised against the α-chain of human c-Met. These antibodies were characterised by Western blotting, immunoprecipitation, flow cytometry, epitope mapping and agonist/antagonist activity towards c-Met. Surprisingly, none of these antibodies were c-Met agonist. Two antibodies, mAb 2 and 13, showed the strongest binding to native c-Met by flow cytometry but work poorly to detect denatured c-Met on Western blots. mAb 2 was the most effective in reducing cell proliferation. Further analysis of mAb 2 on flow cytometry showed that its binding to c-Met on live cells is temperature sensitive. Detailed mapping of mAb 2 epitope revealed that part of mAb 2 epitope is buried within c-Met.

[0015] In one aspect, the present invention refers to an antibody specifically binding an epitope comprised in the α-chain of c-Met, wherein the heavy chain of the antibody comprises at least one, or at least two, or all of the following: CDR 1 comprising the sequence of SEQ ID NO: 2; CDR 2 comprising the sequence of SEQ ID NO: 3; or CDR 3 comprising the sequence of SEQ ID NO: 4; and/or wherein the light chain of the antibody comprises at least one, or at least two, or all of the following: CDR 1 comprising the sequence of SEQ ID NO: 5; CDR 2 comprising the sequence of SEQ ID NO: 6; or CDR 3 comprising the sequence of SEQ ID NO: 7. Thus, in ~~a first aspect~~ one example, there is disclosed ~~provided~~ an antibody specifically binding an epitope comprised in the α-chain of c-Met.

[0016] In another aspect, the present invention refers to a nucleic acid encoding an antibody as disclosed herein, wherein the heavy chain of the antibody comprises the sequence as

shown in SEQ ID NO: 10. In yet another aspect, the present invention refers to a nucleic acid encoding an antibody as disclosed herein, wherein the light chain of the antibody comprises the sequence as shown in SEQ ID NO: 11. In ~~a second aspect~~another example, there is disclosed ~~provided~~ nucleic acid encoding an antibody as described herein, wherein the heavy chain of the antibody comprises or consists of the sequence as shown in SEQ ID NO: 1.

[0017] In ~~a third aspect~~ yet another example, there is disclosed ~~provided~~ a pharmaceutical composition comprising or consisting of an antibody as described herein. In one aspect, the present invention refers to a pharmaceutical composition comprising an antibody as disclosed herein.

[0018] Also described herein is a method of treating and/or preventing cancer comprising administration of a therapeutically effective amount of an antibody as described herein.

[0019] Also described herein is a method of diagnosing cancer comprising detection of aberrant expression of c-Met by administering an antibody as described herein for detecting c-Met.

[0020] In ~~a fourth aspect~~one aspect, ~~there is provided~~ the present invention refers to ~~the~~ use of an antibody disclosed herein in the manufacture of a medicament for treating and/or preventing cancer.

[0021] In ~~a fifth aspect~~yet another aspect, ~~there is provided~~ the present invention refers to~~the~~ use of an antibody disclosed herein for detecting cells with aberrant c-Met expression.

[0022] In a ~~an sixth aspect~~further aspect, ~~there is provided~~ the present invention refers to the use of an antibody disclosed herein as cancer prognosis marker.

## BRIEF DESCRIPTION OF THE DRAWINGS

[0023] The accompanying drawings illustrate a disclosed embodiment and serves to explain the principles of the disclosed embodiment. It is to be understood, however, that the drawings are designed for purposes of illustration only, and not as a definition of the limits of the invention.

[0024] **Fig. 1** is a cartoon illustrating the mapping of the anti-α-chain c-Met monoclonal antibody epitope mapping. **A**) Schema of antibody binding regions. Pepscan, an ELISA-based assay, was used to determine the binding region of 21 monoclonal supernatants. Consecutive overlapping peptides that span the entire c-Met α-chain were synthesised and coated in 96-wells. To determine the region of antibody binding on the α-chain, monoclonal cell supernatants were added to each peptide. Antibody binding results in a colourmetric reaction which is analysed by absorbance reading at 450 nM. The epitope of the antibodies were categorised into regions. Antibodies that share the same binding region are indicated. Figure not drawn to scale. **B & C**) Mapping of antibody binding regions to the crystal structure of c-Met. Crystal structure of c-Met extracellular domain (amino acid residues 25 – 567), binding to HGF β-chain. Crystal structure was obtained from Protein Data Bank (PDB), accession number 1SHY. c-Met is highlighted in green and HGF in blue. The protein complex is shown from two different viewpoints (**B**) and (**C**) to allow visualisation of the different antibody binding regions in relation to ligand-receptor interaction site. **(D)** is a schematic diagram illustrating the outline of monoclonal antibody screening. 768 cell lines were screened for the production of anti-α-chain antibodies after hybridoma fusion. 57 lines were found to express anti-α-chain c-Met antibodies in the primary screen. These lines were

**Claims**

1. An antibody specifically binding an epitope comprised in the α-chain of c-Met, wherein the heavy chain of the antibody comprises at least one, or at least two, or all of the following:

    CDR 1 comprising the sequence of SEQ ID NO: 2;
    CDR 2 comprising the sequence of SEQ ID NO: 3; or
    CDR 3 comprising the sequence of SEQ ID NO: 4; and/or

    wherein the light chain of the antibody comprises at least one, or at least two, or all of the following:

    CDR 1 comprising the sequence of SEQ ID NO: 5;
    CDR 2 comprising the sequence of SEQ ID NO: 6; or
    CDR 3 comprising the sequence of SEQ ID NO: 7.

2. The antibody of any one of the preceding claims, wherein the antibody has a heavy chain comprising the sequence of SEQ ID NO: 8 or a sequence which is at least 95%, or 96%, or 97%, or 98% identical to the sequence of SEQ ID NO: 8.

3. The antibody of any one of the preceding claims, wherein the antibody has a light chain comprising the sequence of SEQ ID NO: 9 or a sequence which is at least 95%, or 96%, or 97%, or 98% identical to the sequence of SEQ ID NO: 9.

4. The antibody of any one of the preceding claims, wherein the antibody is coupled to an agent.

5. The antibody of claim 4, wherein the agent is a cytotoxic agent.

6. The antibody of claim 5, wherein the agent is selected from the group consisting of mertansine, emtansine, monomethyl auristatin E, ricin, diphtheria toxin, doxorubicin, *Pseudomonas aeruginosa* exotoxin, and pyrrolobenzodiazepine.

7. The antibody of claim 1 or 2, wherein the antibody is a monoclonal or polyclonal antibody.

8. The antibody according to any one of the preceding claims wherein the antibody is a murine antibody.

9. The antibody of any one of the preceding claims, wherein the antibody is a murine monoclonal antibody.

10. The antibody of claim 8 or 9, wherein the murine antibody is humanized.

11. The antibody of any one of the preceding claims, wherein the antibody is a chimeric antibody.

12. A nucleic acid encoding an antibody of any one of claims 1 to 11, wherein the heavy chain of the antibody comprises the sequence as shown in SEQ ID NO: 10.

13. A nucleic acid encoding an antibody of any one of claims 1 to 11, wherein the light chain of the antibody comprises the sequence as shown in SEQ ID NO: 11.

14. A pharmaceutical composition comprising an antibody of any one of claims 1 to 11.

15. The pharmaceutical composition of claim 14 further comprising one or more pharmaceutically acceptable excipients, or vehicles, or carriers.

16. Use of an antibody of any one of claims 1 to 11 in the manufacture of a medicament for treating and/or preventing cancer.

17. Use of an antibody of any one of claims 1 to 11 for detecting cells with aberrant c-Met expression.

18. Use of an antibody of any one of claims 1 to 11 as cancer prognosis marker.

19. The use of claim 16, wherein cancer is selected from the group consisting of breast cancer, lung cancer, liver cancer, gastric cancer, brain cancer, blood cancer, colon cancer, pancreatic cancer and prostate cancer.

**Claims**

1. An antibody specifically binding an epitope comprised in the α-chain of c-Met.

2. The antibody of claim 1 wherein the epitope comprises the sequence IEE or CPD; or IEE or CPDC; or IEE and CPD, or IEE and CPDC.

3. The antibody of claim 2, wherein the epitope comprises ******IEE***CPD (SEQ ID NO: 12) or *IEE***CPDC**** (SEQ ID NO: 13), wherein * can be any amino acid.

4. The antibody of claim 3, wherein ******IEE***CPD is C***P*IEEP**CPD (SEQ ID NO: 14).

5. The antibody of claim 3, wherein *IEE***CPDC**** is *IEEP**CPDC**** (SEQ ID NO: 15).

6. The antibody of claim 4, wherein C***P*IEEP**CPD is CIFSPQIEEPSQCPD (SEQ ID NO: 16).

7. The antibody of claim 5, wherein *IEEP**CPDC**** is QIEEPSQCPDCVVSA (SEQ ID NO: 17).

8. The antibody of claim 1, wherein c-Met is human c-Met.

9. The antibody of claim 1 or 2, wherein the antibody is a monoclonal or polyclonal antibody.

10. The antibody according to any one of the preceding claims wherein the antibody is a murine antibody.

11. The antibody of any one of the preceding claims, wherein the antibody is a murine monoclonal antibody.

12. The antibody of claim 10 or 11, wherein the murine antibody is humanized.

13. The antibody of any one of the preceding claims, wherein the antibody is a chimeric antibody.

14. The antibody of any one of the preceding claims, wherein the heavy chain of the antibody comprises at least one, or at least two, or all of the following:

CDR 1 comprising the sequence of SEQ ID NO: 2;
CDR 2 comprising the sequence of SEQ ID NO: 3; or
CDR 3 comprising the sequence of SEQ ID NO: 4.

15. The antibody of any one of the preceding claims, wherein the light chain of the antibody comprises at least one, or at least two, or all of the following:

CDR 1 comprising the sequence of SEQ ID NO: 5;
CDR 2 comprising the sequence of SEQ ID NO: 6; or
CDR 3 comprising the sequence of SEQ ID NO: 7.

16. The antibody of any one of the preceding claims, wherein the antibody has a heavy chain comprising the sequence of SEQ ID NO: 8 or a sequence which is at least 95%, or 96%, or 97%, or 98% identical to the sequence of SEQ ID NO: 8.

17. The antibody of any one of the preceding claims, wherein the antibody has a light chain comprising the sequence of SEQ ID NO: 9 or a sequence which is at least 95%, or 96%, or 97%, or 98% identical to the sequence of SEQ ID NO: 9.

18. The antibody of any one of the preceding claims, wherein the antibody is coupled to an agent.

19. The antibody of claim 18, wherein the agent is a cytotoxic agent.

20. The antibody of claim 19, wherein the agent is selected from the group consisting of mertansine, emtansine, monomethyl auristatin E, ricin, diphtheria toxin, doxorubicin, *Pseudomonas aeruginosa* exotoxin, and pyrrolobenzodiazepine.

21. A nucleic acid encoding an antibody of any one of claims 1 to 20, wherein the heavy chain of the antibody comprises the sequence as shown in SEQ ID NO: 10.

22. A nucleic acid encoding an antibody of any one of claims 1 to 20, wherein the light chain of the antibody comprises the sequence as shown in SEQ ID NO: 11.

23. A pharmaceutical composition comprising an antibody of any one of claims 1 to 20.

24. The pharmaceutical composition of claim 23 further comprising one or more pharmaceutically acceptable excipients, or vehicles, or carriers.

25. Use of an antibody of any one of claims 1 to 20 in the manufacture of a medicament for treating and/or preventing cancer.

26. Use of an antibody of any one of claims 1 to 20 for detecting cells with aberrant c-Met expression.

27. Use of an antibody of any one of claims 1 to 20 as cancer prognosis marker.

28. The use of claim 25, wherein cancer is selected from the group consisting of breast cancer, lung cancer, liver cancer, gastric cancer, brain cancer, blood cancer, colon cancer, pancreatic cancer and prostate cancer.