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(54) Title: ANTIBODIES FOR TREATMENT AND DIAGNOSIS

(57) Abstract: The invention relates to the diagnosis and treatment of diseases, including cancer and inflammatory disorders. The invention provides, and involves the use of, antibodies that bind: i) the IIICS isoform of fibronectin, ii) matrix-metalloproteinase 3 (MMP3), iii) periostin, or iv) tenascin-W.

Antibodies for Treatment and Diagnosis

Field of the Invention

5 The present invention relates to the diagnosis and treatment of diseases, including cancer and inflammatory disorders. The invention provides, and involves the use of, antibodies that bind: i) the IIICS isoform of fibronectin, ii) matrix-metalloproteinase 3 (MMP3), iii) periostin, or iv) tenascin-W.

10 **Background to the invention**

Most conventional pharmaceuticals currently in use for the treatment of serious disorders such as cancer and inflammatory diseases do not selectively accumulate at the site of disease [Bosslet *et al.*, 58, 1195-1201 *Cancer Res.* (1998)]. For example, intravenously 15 administered drugs distribute evenly within the different organs and tissues of the body, rather than selectively accumulating at the site of disease.

One approach to circumvent the disadvantages of conventional pharmacological therapies involves the preferential delivery of a bioactive agent to the site of disease by means of a 20 binding molecule specific for a pathology-associated marker [Neri & Bicknell (2005) *Nature Rev. Cancer*, 4, 436-446]. The selective targeting of the drug to the diseased tissue will ultimately result in an increased local concentration at its site of action, sparing normal organs from the unwanted effects of the bioactive agent used to confer a pharmacological benefit (e.g., a growth factor, an enzyme, a hormone, an anti-inflammatory drug, a cytotoxic 25 drug, a cytokine, a radionuclide, a photosensitizer). In most cases, this will lead to an improved therapeutic index of the delivered pharmaceutical, i.e. a higher efficacy with minimized side effects. Indeed, the favourable toxicity profile of site-specific therapeutics may open new avenues in the therapy of angiogenesis-related diseases, allowing the 30 systemic administration of highly potent and promising agents, which are currently either given at suboptimal doses or whose clinical application has to date been impeded by unacceptable side-effects when applied in an unmodified form.

Ligand-based pharmacodelivery strategies fundamentally rely on the identification of good-quality markers of pathology, allowing a clear-cut discrimination between diseased tissues 35 and healthy organs. Monoclonal antibodies and their fragments represent the preferred agents for pharmacodelivery applications [Rybäk *et al.* 2, 22-40 *Chem. Med. Chem* (2007);

Shrama *et al.*, 5, 147-159 Nat. Rev. Drug Discovery (2006)], but globular protein mutants [Binz and Plückthun, 23, 1257-1268 Nature Biotechnology (2005)], peptides [Sergeeva *et al.*, 58, 1622-1654, Adv. Drug. Deliv. Rev. (2006)] and even small organic ligands [Low *et al.*, 41, 120-129, Acc. Chem. Res. (2008)] are also increasingly being used.

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Antibody-based targeted delivery of bioactive agents to sites of angiogenesis as a therapeutic strategy for cancer treatment has been described. In the case of inflammatory disorders, antibody-based targeted delivery is much less well studied. The applicant has previously demonstrated that the ED-A domain of fibronectin, and the ED-B domain of 10 fibronectin, two marker of angiogenesis, are expressed in the arthritic paws in the collagen-induced mouse model of rheumatoid arthritis. Using both radioactive and fluorescent techniques, the human monoclonal antibody F8, specific to ED-A, and the human monoclonal antibody L19, specific to ED-B, were found to selectively localize at sites of 15 inflammation *in vivo*, following intravenous administration. When such antibodies were fused to the anti-inflammatory cytokine interleukin-10 the conjugate strong therapeutic activity was also shown (PCT/EP2007/004044, PCT/EP2008/009070). Nevertheless there remains a need in the art for further antibodies which can be employed in ligand-based 20 pharmacodelivery applications for the treatment and diagnosis of diseases, such as cancer and inflammatory disorders.

20

IIICS isoform of fibronectin

Fibronectins (FN) are multifunctional, high molecular weight glycoprotein constituents of both the extracellular matrix and body fluids. They are involved in many different biological

25 processes such as the establishment and maintenance of normal cell morphology, cell migration, haemostasis and thrombosis, wound healing and oncogenic transformation [Alitalo *et al.*, (1982) Adv Cancer Res, 37 111-158; Yamada, (1983) Curr Opin Cell Biol, 1, 956-963; Hynes, (1985) Annu Rev Cell Biol, 1, 67-90; Ruoslahti *et al.*, (1988) Annu Rev Biochem, 57, 375-413; Owens *et al.*, (1986) Oxf Surv Eukaryot Gene, 3, 141-160]. Structural 30 diversity in FNs is brought about by alternative splicing of three regions (ED-A, ED-B and IIICS) of the primary FN transcript (Hynes, R., (1985) Annu Rev Cell Biol, 1, 67-90; Zardi *et al.*, (1987) EMBO J, 6, 2337-2342) to generate at least 20 different isoforms, some of which are differentially expressed in tumour and normal tissue. For example, five different splice 35 isoforms of the human IIICS isoform of fibronectin have been described. As well as being regulated in a tissue- and developmentally specific manner, it is known that the splicing pattern of FN-pre-mRNA is deregulated in transformed cells and in malignancies (Castellani

et al., (1986) J Cell Biol, 103, 1671-1677; Borsi et al., (1987) J Cell Biol, 104, 595-600; Vartio et al., (1987) J Cell Sci 88, 419-430, Zardi et al., (1987) EMBO J, 6, 2337-2342; Barone et al., (1989) EMBO J, 8, 1079-1085; Carnemolla et al., (1989) FEBS Letter 215, 269-273; Oyama et al., (1989) Biochemistry, 28, 1428-1433; Borsi et al., (1992) Exp Cell Res 199, 98-105). The FN isoforms containing the ED-A, ED-B and IIICS sequences are expressed to a greater extent in transformed and malignant tumour cells than in normal cells.

Much of the information relating to the expression of the IIICS isoform of fibronectin in healthy and diseased tissues derives either from mRNA studies or from studies with monoclonal antibodies (antibodies FDC-6 and X18A4). These antibodies were generated by hybridoma technology following immunization with fibronectin and immunosuppression with cyclophosphamide. Antibody FDC-6 binds to a specific O-linked N-acetylgalactosaminylated hexapeptide epitope within the fibronectin type III connecting segment (IIICS) [Matsuura et al., (1985) PNAS, 82, 6517-6521; Matsuura et al., (1988) J Biol Chem, 263, 3314-3322].

However, since the antibody requires both the peptide backbone and the carbohydrate moiety to recognize the epitope, it is not suitable for targeting application especially when cross-reactivity between species is needed. Antibody X18A4 recognizes a different IIICS region than FDC-6, but the binding epitope has never been fully characterized [Feinberg R. et al., (1995) Am J Obstet Gynecol, 172, 1526-1536]: the main application for antibody X18A4 is related to the detection of oncofetal fibronectin in the cervix of pregnant women to predict preterm labour. There is evidence that IIICS expression is modulated in rheumatoid arthritis and osteoarthritis: in particular, it seems that the isoform 89V (CS1) is up-regulated in inflammation [Kriegsmann J et al., (2004) Rheumatol Int, 24, 25-33; Elices MJ et al., (1994) J Clin Invest, 93, 405-416].

25

Matrix-metalloproteinase 3 (MMP3)

Matrix metalloproteinase 3 (also known as stromelysin 1) is a member of a family of more than 20 zinc-dependent extracellular enzymes with a key role in tissue remodeling [Nagase and Woessner, (1999) J Biol Chem, 274, 21491-21494; Martin and Matrisian, (2007) Cancer Metastasis Rev, 26, 717-724; Vartak and Gemeinhart, (2007) J Drug Target 15(1) 1-20]. Abnormal expression of various MMP proteins has been shown to play a role in a variety of disease types including cancer progression and in inflammatory conditions such as rheumatoid arthritis [Martin and Matrisian, (2007) Cancer Metastasis Rev, 26, 717-724; Brinckerhoff and Matrisian, (2002) Nat Rev Mol Cell Biol, 3, 207-214; Overall and Kleifeld,

(2006) *Nat Rev Cancer*, 6, 227-239]. The catalytic domain of MMP3 is known to be relatively well conserved between mouse, rat and man.

Periostin

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Periostin or Osteoblast Specific Factor 2 (OSF-2) was described for the first time in 1999 by the group of A. Kudo as a dimeric protein of 90 kDa secreted by osteoblasts and osteoblast-like cell lines. Periostin is mainly localized in the extracellular matrix of the periosteum and its main function is to act as a cell adhesion molecule for preosteoblasts and to induce 10 osteoblast attachment and spreading [Horiuchi K *et al.*, (1999) *J Bone Miner Res*, 14, 1239-1249].

The periostin N-terminal region contains four fasciclin-like domains (FAS1-4) as well as several glycosylation sites. Six different splice isoforms of periostin have been reported, but 15 only four of them have been sequenced and annotated: these splice isoforms are characterized by the presence or absence of cassette exons 17 to 21 at the C-terminus of the protein [Castronovo *et al.*, (2006) *Mol Cell Proteomics*, 5, 2083-2091; Litvin *et al.*, (2004) *J Cell Biochem*, 95, 1044-1061; Kim *et al.*, (2008) *Int J Oncol*, 32, 161-169].

20 Tai and colleagues produced a monoclonal anti-periostin antibody by hybridoma technology and detected, by Western blotting, expression of the human periostin protein in the adrenal glands, lung, thyroid, uterus, vagina, ovary, testis, prostate, and in the gastrointestinal tract, with a preferential expression in the stomach and colorectum, while lower levels were noted in the small intestine and esophagus (Tai *et al.*, *Carcinogenesis*, 26, 908-15, 2005). There 25 have been observations of periostin being associated with a number of disorders.

For instance, Morra and Moch [Virchows Archives., (2011) 459, 465-475] described the role of periostin in tumor microenvironment and tumor development. The N-terminal domain, with the FAS domains, bind to integrins and activates the Akt/PKB and the FAK-mediated 30 signaling pathways, thus leading to tumor invasion and metastasis. The C-terminus of the protein binds to ECM molecules and influences the organization of the ECM. It is not yet clear if the different splice isoforms play different roles in ECM modification in tumor invasion.

35 In an *in vivo* chemical proteomic analysis, based on the terminal perfusion of three mouse models of liver metastases, periostin was one of the most abundant accessible antigens identified [Borgia *et al.*, (2010) *Cancer Res*, 70, 309-318]. Immunofluorescence analysis

confirmed the proteomic findings, indicating that periostin can be expressed in the neovasculature of tissues undergoing extensive remodeling.

Tenascin-W

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Tenascin-W is the most recently discovered member of the tenascin gene family. Human tenascin-W is composed of a modular structure shared with all other tenascins (i.e. tenascin-C, -R, and -X respectively), which includes: N-terminal heptad repeats, 3.5 EGF-like repeats, 9 FN III domains and a C-terminal fibrinogen-related domain. In contrast to other tenascin 10 family members, the existence of tenascin-W splice isoforms has not been reported to date [Chiquet-Ehrismann *et al.*, (2011) *Cold Spring Harb Perspect Biol.* 3 (5), doi: 10.1101/cshperspect.a004960].

During embryonic development, tenascin-W is predominantly expressed in the extracellular 15 matrix of periosteal bone, and to a lesser extent in smooth muscle, tendons and ligaments [Weber *et al.*, (1998) *J Neurobiol.* 35, 1-16; Scherberich *et al.*, (2004) *J Cell Sci.* 117, 571-581; Meloty-Kapella *et al.*, (2006) *Dev Dyn.* 235, 1532-1542]. In healthy adults, the expression of tenascin-W is strongly reduced and restricted to the kidney, cardiac valves, corneal limbus and periosteum [Scherberich *et al.*, (2004) *J Cell Sci.* 117, 571-581].

20 Tenascin-W expression has been detected in the perichondrium/periosteum during endochondral ossification and bone fracture repair [Kimura *et al.*, (2007) *Biochem Biophys Res Commun.* 356, 935-941], suggesting its association with osteogenesis [Martina *et al.*, (2010) *Int J Biochem Cell Biol.* 42, 1412-1415].

25 Tenascin-W is a tumour-associated antigen; its expression partly overlaps with tenascin-C in various cancers. To date tenascin-W expression has been detected in the stroma of breast [Degen *et al.*, (2007) *Cancer Res.* 67, 9169-9179], and colorectal cancer [Degen *et al.*, (2008) *Int J Cancer.* 122, 2454-2461], gliomas [Martina *et al.*, (2010) *FASEB J.* 24, 778-787], melanomas, as well as pancreatic, kidney, and lung carcinomas [Brellier *et al.*, (2012) *BMC Clin Pathol.* 4, 12-14].

30 Tenascin-W was not detectable in the corresponding healthy tissues. Interestingly, in most tumor types, tenascin-W was detected in the perivascular region of newly formed blood vessels [Brellier *et al.*, (2012) *BMC Clin Pathol.* 4, 12-14, Martina *et al.*, (2010) *FASEB J.* 24, 778-787].

35 The amino acid sequence of tenascin-W is highly conserved between human, mouse and rat. However two major differences are present. Firstly, the three tenascin-W orthologues

differ in the number of FNIII domains, with the mouse and rat variants containing 3 additional FNIII domains. Secondly, the mouse and rat tenascin-W genes contain a putative integrin binding RGD motif located in the second FNIII domain, which is absent in the human orthologue.

5

Summary of the Invention

The present invention relates to the provision of novel antibody molecules for use in therapeutic and/or diagnostic applications. In particular, the antibody molecules of the 10 present invention find use in pharmacodelivery applications.

Specifically, the present inventors have isolated novel antibody molecules which bind i) the IIICS isoform of fibronectin, ii) matrix-metalloproteinase 3 (MMP3), iii) periostin, or iv) tenascin-W, and have shown that these antibody molecules are capable of targeting 15 vascular structures, including the neovasculature of tumour tissues and neovasculature associated with inflammatory disorders, such as rheumatoid arthritis (RA). These antibody molecules can thus be used for the targeted delivery of therapeutic and/or diagnostic agents to the neovasculature for which there is a continued need.

20 In a first aspect, the present invention relates to an antibody molecule that binds the IIICS isoform of fibronectin. Preferably, the antibody molecule binds the IIICS domain of fibronectin. More preferably, the antibody molecule binds the 89V splice-isoform and/or the 120V splice-isoform of the IIICS domain of fibronectin (see Figure 1). The fibronectin is preferably human fibronectin. The antibody molecule may comprise the VH domain 25 complementary determining region 3 (HCDR3) of the SW01 antibody molecule set forth in SEQ ID NO: 5, or an HCDR3 with the amino acid sequence set forth in SEQ ID NO: 5 with three or fewer amino acid substitutions, deletions, or insertions. In addition, the antibody molecule may comprise the HCDR1, HCDR2, LCDR1, LCDR2, and/or LCDR3 sequences of the SW01 antibody molecule set forth in SEQ ID NOs 3-4 and 6-8. For example, the 30 antibody molecule may comprise the VH domain and/or VL domain of the SW01 antibody molecule set forth in SEQ ID NOs 1 and 2, respectively. Alternatively, the antibody molecule may comprise the HCDR3 of antibody molecule SW02 set forth in SEQ ID NO: 13, or an HCDR3 with the amino acid sequence set forth in SEQ ID NO: 13 with three or fewer amino acid substitutions, deletions, or insertions. In addition, the antibody molecule may comprise 35 the HCDR1, HCDR2, LCDR1, LCDR2, and/or LCDR3 sequences of the SW02 antibody molecule set forth in SEQ ID NOs 11-12 and 14-16. For example, the antibody molecule

may comprise the VH domain and/or VL domain of the SW02 antibody molecule set forth in SEQ ID NOs 9 and 10, respectively.

In a second aspect, the present invention relates to an antibody molecule that binds matrix-

5 metalloproteinase 3 (MMP3). Preferably, the antibody molecule binds to the catalytic domain of MMP3. The MMP3 is preferably human MMP3. The antibody molecule preferably comprises the HCDR3 of the CH01 antibody molecule set forth in SEQ ID NO: 21, or an HCDR3 with the amino acid sequence set forth in SEQ ID NO: 21 with three or fewer amino acid substitutions, deletions, or insertions. In addition, the antibody molecule may comprise 10 the HCDR1, HCDR2, LCDR1, LCDR2, and/or LCDR3 sequences of the CH01 antibody molecule set forth in SEQ ID NOs 19-20 and 22-24. For example, the antibody molecule may comprise the VH domain and/or VL domain of the CH01 antibody molecule set forth in SEQ ID NOs 17 and 18, respectively.

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In a third aspect, the present invention relates to an antibody molecule that binds periostin. Preferably, the antibody molecule binds to FAS domains 1-4 of periostin. The periostin is preferably human periostin. Periostin is also known as Osteoblast Specific Factor 2 (OSF-2).

The antibody molecule may comprise the HCDR3 of the LG1 antibody molecule set forth in

20 SEQ ID NO: 29, or an HCDR3 with the amino acid sequence set forth in SEQ ID NO: 29 with three or fewer amino acid substitutions, deletions, or insertions. In addition, the antibody molecule may comprise the HCDR1, HCDR2, LCDR1, LCDR2, and/or LCDR3 sequences of the LG1 antibody molecule set forth in SEQ ID NOs 27-28 and 30-32. For example, the antibody molecule may comprise the VH domain and/or VL domain of the LG1 antibody

25 molecule set forth in SEQ ID NOs 25 and 26, respectively. Alternatively, the antibody molecule may comprise the HCDR3 of antibody molecule LG2 set forth in SEQ ID NO: 37, or an HCDR3 with the amino acid sequence set forth in SEQ ID NO: 37 with three or fewer amino acid substitutions, deletions, or insertions. In addition, the antibody molecule may comprise the HCDR1, HCDR2, LCDR1, LCDR2, and/or LCDR3 sequences of the LG2

30 antibody molecule set forth in SEQ ID NOs 35-36 and 38-40. For example, the antibody molecule may comprise the VH domain and/or VL domain of the LG2 antibody molecule set forth in SEQ ID NOs 33 and 34, respectively. As a further alternative, the antibody molecule may comprise the HCDR3 of antibody molecule LG3 set forth in SEQ ID NO: 45, or an HCDR3 with the amino acid sequence set forth in SEQ ID NO: 45 with three or fewer amino

35 acid substitutions, deletions, or insertions. In addition, the antibody molecule may comprise the HCDR1, HCDR2, LCDR1, LCDR2, and/or LCDR3 sequences of the LG3 antibody

molecule set forth in SEQ ID NOs 43-44 and 46-48. For example, the antibody molecule may comprise the VH domain and/or VL domain of the LG3 antibody molecule set forth in SEQ ID NOs 41 and 42, respectively. As a yet further alternative, the antibody molecule may comprise the HCDR3 of antibody molecule 1E1 set forth in SEQ ID NO: 53, or an HCDR3 with the amino acid sequence set forth in SEQ ID NO: 53 with three or fewer amino acid substitutions, deletions, or insertions. In addition, the antibody molecule may comprise the HCDR1, HCDR2, LCDR1, LCDR2, and/or LCDR3 sequences of the 1E1 antibody molecule set forth in SEQ ID NOs 51-52 and 54-56. For example, the antibody molecule may comprise the VH domain and/or VL domain of the 1E1 antibody molecule set forth in SEQ ID NOs 49 and 50, respectively.

In a fourth aspect, the present invention relates to an antibody molecule that binds tenascin-W. The tenascin-W is preferably human tenascin-W. The antibody molecule preferably comprises the HCDR3 of the G10 antibody molecule set forth in SEQ ID NO: 61, or an HCDR3 with the amino acid sequence set forth in SEQ ID NO: 61 with three or fewer amino acid substitutions, deletions, or insertions. In addition, the antibody molecule may comprise the HCDR1, HCDR2, LCDR1, LCDR2, and/or LCDR3 sequences of the G10 antibody molecule set forth in SEQ ID NOs 59-60 and 62-64. For example, the antibody molecule may comprise the VH domain and/or VL domain of the SW01 antibody molecule set forth in SEQ ID NOs 57 and 58, respectively. Optionally the residue at position 67 of SEQ ID NO 57 may be an arginine (R) instead of a Glutamine (Q).

As mentioned above, an antibody molecule of the invention may comprise a HCDR3 sequence as disclosed herein with three or fewer amino acid substitutions, deletions, or insertions. For example, an antibody molecule of the invention may comprise a HCDR3 sequence as disclosed herein with two or fewer, or one, amino acid substitution(s), deletion(s), or insertion(s). As with regard to the HCDR3 sequences, an antibody molecule of the invention may comprise a HCDR1, HCDR2, LCDR1, LCDR2, and/or LCDR3 sequence, as disclosed herein, with three or fewer, two or fewer, or one, amino acid substitution(s), deletion(s), or insertion(s). Similarly, an antibody molecule of the invention may comprise a VH and/or VL domain sequence as disclosed with ten or fewer, e.g. nine or fewer, eight or fewer, seven or fewer, six or fewer, five or fewer, four or fewer, three or fewer, two or fewer, or one, amino acid substitution(s), deletion(s), or insertion(s).

An antibody molecule, as referred to herein, may be in any suitable format. Many antibody molecule formats are known in the art and include both complete antibody molecule

molecules, such as IgG, as well as antibody molecule fragments, such as a single chain Fv (scFv). The term “antibody molecule” as used herein encompasses both complete antibody molecule molecules and antibody molecule fragments, in particular antigen-binding fragments. Preferably, an antibody molecule comprises a VH domain and a VL domain. In a 5 preferred embodiment, the antibody molecule is or comprises a scFv, is a small immunoprotein (SIP), is a diabody, or is a (complete) IgG molecule.

An antibody molecule of the present invention may be conjugated to a molecule to provide a conjugate. The choice of molecule conjugated to the antibody molecule will depend on the 10 intended application of the conjugate. For example, where the conjugate is intended for the treatment of a disease or disorder, the conjugate may comprise an antibody molecule of the invention and a biocidal molecule, a cytotoxic molecule, a radioisotope, a photosensitizer, an enzyme, a hormone, an anti-inflammatory agent, or a cytokine. Where the conjugate is intended for use in imaging, detecting, or diagnosing a disease or disorder, the conjugate 15 may comprise an antibody molecule of the invention and a detectable label, such as a radioisotope, e.g. a non-therapeutic radioisotope. Depending on the molecule conjugated to the antibody molecule, the conjugate may be or may comprise a single chain protein. When the conjugate is a single chain protein, the entire protein can be expressed as a single polypeptide or fusion protein. In this case, the molecule may be conjugated to the antibody 20 molecule by means of a peptide linker. Fusion proteins have the advantage of being easier to produce and purify since they consist of one single species. This facilitates production of clinical-grade material. Alternatively, the molecule may be conjugated to the antibody molecule by means of a cleavable linker.

25 The invention also provides isolated nucleic acids encoding the antibodies and conjugates of the invention. The skilled person would have no difficulty in preparing such nucleic acids using methods well-known in the art. An isolated nucleic acid may be used to express the antibody molecule or conjugate of the invention, for example by expression in a bacterial, yeast, insect or mammalian host cell. A preferred host cell is *E. coli*. The nucleic acid will 30 generally be provided in the form of a recombinant vector for expression. Host cells *in vitro* comprising such vectors are part of the invention, as is their use for expressing the antibodies and conjugates of the invention, which may subsequently be purified from cell culture and optionally formulated into a pharmaceutical composition.

35 An antibody molecule or conjugate of the invention may be provided for example in a pharmaceutical composition, and may be employed for medical use as described herein,

either alone or in combination with one or more further therapeutic agents. Alternatively, the antibody molecule or conjugate of the invention may be provided in a diagnostic composition and may be employed for diagnostic use as described herein.

5 In a fifth aspect, the invention relates to an antibody molecule or conjugate of the invention for use in a method for treatment of the human or animal body by therapy. For example, an antibody molecule or conjugate of the invention may for use in a method of treating an inflammatory disorder, inhibiting angiogenesis, treating cancer, and/or treating an autoimmune disease in a patient. The invention also relates to a method of treating an
10 inflammatory disorder, inhibiting angiogenesis, treating cancer, and/or treating an autoimmune disease in a patient, the method comprising administering a therapeutically effective amount of an antibody molecule or conjugate of the invention to the patient.

In a sixth aspect, the invention relates to an antibody molecule of the invention for use in a
15 method of delivering a molecule to sites of an inflammatory disorder, sites of neovasculature which are the result of angiogenesis, sites of cancer and/or sites of autoimmune disease in a patient. The invention also relates to a method of delivering a molecule to sites of an inflammatory disorder, sites of neovasculature which are the result of angiogenesis, sites of cancer and/or sites of autoimmune disease in a patient comprising administering to the
20 patient an antibody molecule of the invention, wherein the antibody molecule is conjugated to the molecule.

In a seventh aspect, the invention relates to an antibody molecule or conjugate of the invention for use in a method of imaging, detecting, or diagnosing an inflammatory disorder,
25 angiogenesis, cancer, and/or an autoimmune disease in a patient. The invention further relates to a method of imaging, detecting, or diagnosing an inflammatory disorder, angiogenesis, cancer, and/or an autoimmune disease in a patient comprising administering an antibody molecule or conjugate of the invention to the patient.

30 A patient, as referred to herein, is preferably a human patient.

Brief Description of the Figures

Figure 1 is schematic diagram showing the 5 possible splice isoforms of the IIICS isoform of
35 fibronectin.

Figure 2A shows staining of human placenta (hPlacenta), human tumours (A375 and H460) and murine tumours (K1735 and F9) with antibodies SW01 and SW02, which bind to the IIICS isoform of fibronectin, and negative control antibodies (neg. ctr). The negative control antibodies used were anti-human Von Willebrand Factor (Anti huVWF) in the human 5 placenta experiments and anti-murine CD31 (muCD31) in the tumour experiments. Figure 2B shows Biacore data demonstrating binding of antibody SW01 to IIICS.

Figure 3 shows staining of human placenta using the anti-human MMP3 antibody CH01 in scFv format. The anti-hen egg lysozyme antibody KSF in scFv format was used as a 10 negative control. Staining by the two scFv antibodies is shown in red, staining with the vascular marker human Von Willebrand factor is shown in green and nuclei were stained in blue using DAPI.

Figure 4A shows the ability of anti-human MMP3 antibody CH01 to bind to the biotinylated 15 catalytic domains of human (HsMMP3), mouse (MmMMP3) and rat (RnMMP3) MMP3 in an ELISA. CH01 recognizes both human and mouse MMP3 and to a lesser extent rat MMP3.

Figure 4B shows Biacore data demonstrating binding of antibody CH01 to human and mouse MMP3.

20 Figure 5 is a schematic diagram showing four known isoforms of periostin.

Figure 6A shows Biacore data demonstrating binding of antibodies LG1, LG2 and LG3 (in scFv format) to periostin. Figure 6B shows Biacore data demonstrating binding of antibody 1E1 (in SIP format) to periostin.

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Figure 7 shows Biacore data demonstrating binding of antibody G10 (in scFv format) to tenascin-W.

Detailed Description

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The invention includes the combination of the aspects and preferred features described except where such a combination is clearly impermissible or expressly avoided.

35 In one aspect, the present invention relates to an antibody which binds i) the IIICS isoform of fibronectin, ii) matrix-metalloproteinase 3 (MMP3), iii) periostin, or iv) tenascin-W).

Antibody molecule

The term "antibody molecule" describes an immunoglobulin whether natural or partly or wholly synthetically produced. The term also covers any polypeptide or protein having a

5 binding domain which is, or is substantially homologous to, an antibody binding domain.

Examples of antibodies are the immunoglobulin isotypes and their isotypic subclasses; fragments which comprise an antigen binding domain such single chain diabodies. The antibody molecule or fragment thereof may be human or humanised. It is possible to take monoclonal and other antibodies and use techniques of recombinant DNA technology to 10 produce other antibodies or chimeric molecules which retain the specificity of the original antibody. Such techniques may involve introducing DNA encoding the immunoglobulin variable region, or the CDRs of an antibody to the constant regions, or constant regions plus framework regions, of a different immunoglobulin. See, for instance, EP-A-184187, GB 2188638A or EP-A-239400. A hybridoma or other cell producing an antibody may be subject 15 to genetic mutation or other changes, which may or may not alter the binding specificity of antibodies produced.

As antibodies can be modified in a number of ways, the term "antibody molecule" should be construed as covering antibody fragments, derivatives, functional equivalents and

20 homologues of antibodies, including any polypeptide comprising an immunoglobulin binding domain, whether natural or wholly or partially synthetic. Chimeric molecules comprising an immunoglobulin binding domain, or equivalent, fused to another polypeptide are therefore included. Cloning and expression of chimeric antibodies are described in EP-A- 0120694 and EP-A-0125023.

25

The term "specific" may be used to refer to the situation in which the antibody molecule will not show any significant binding to molecules other than its specific binding partner(s). The term is also applicable where e.g. an antigen-binding site of an antibody molecule is specific for a particular epitope that is carried by a number of antigens, in which case the antibody

30 molecule carrying the antigen-binding site will be able to bind to the various antigens carrying the epitope.

The antibody molecule may be monovalent or bivalent i.e. may have two antigen binding

sites. Where the antibody molecule is bivalent, the two antigen binding sites may be identical

35 or different. An "antigen binding site" describes the part of an antibody which comprises the area which specifically binds to and is complementary to part or all of an antigen. Where an

antigen is large, an antibody molecule may only bind to a particular part of the antigen, which part is termed an epitope. An antigen binding site may be provided by one or more antibody variable domains (e.g. a so-called Fd antibody fragment consisting of a VH domain).

Preferably, an antigen binding site comprises an antibody light chain variable region (VL)

5 and an antibody heavy chain variable region (VH).

An antibody molecule of the invention preferably comprises the HCDR3 of antibody SW01, antibody SW02, antibody CH01, antibody LG1, antibody LG2, antibody LG3, antibody 1E1, or antibody G10. The HCDR3 is known to play a role in determining the specificity of an antibody molecule (Segal *et al.*, (1974), PNAS, 71:4298-4302; Amit *et al.*, (1986), Science, 233:747-753; Chothia *et al.*, (1987), J. Mol. Biol., 196:901-917; Chothia *et al.*, (1989), Nature, 342:877-883; Caton *et al.*, (1990), J. Immunol., 144:1965-1968; Sharon *et al.*, (1990a), PNAS, 87:4814-4817; Sharon *et al.*, (1990b), J. Immunol., 144:4863-4869; Kabat *et al.*, (1991b), J. Immunol., 147:1709-1719).

15

The antibody molecule may further comprise the HCDR1, HCDR2, LCDR1, LCDR2 and/or LCDR3 of antibody SW01, antibody SW02, antibody CH01, antibody LG1, antibody LG2, antibody LG3, antibody 1E1, or antibody G10.

20 The antibody may also comprise the VH and/or VL domain of antibody SW01, antibody SW02, antibody CH01, antibody LG1, antibody LG2, antibody LG3, antibody 1E1, or antibody G10.

25 An antibody molecule of the invention may have a VH domain having at least 70%, more preferably one of at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, sequence identity to the VH domain of antibody SW01, antibody SW02, antibody CH01, antibody LG1, antibody LG2, antibody LG3, antibody 1E1, or antibody G10.

30 An antibody molecule of the invention may have a VL domain having at least 70%, more preferably one of at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, sequence identity to the VL domain of antibody SW01, antibody SW02, antibody CH01, antibody LG1, antibody LG2, antibody LG3, antibody 1E1, or antibody G10.

35 Sequence identity is commonly defined with reference to the algorithm GAP (Wisconsin GCG package, Accelerys Inc, San Diego USA). GAP uses the Needleman and Wunsch algorithm to align two complete sequences that maximizes the number of matches and

minimizes the number of gaps. Generally, default parameters are used, with a gap creation penalty = 12 and gap extension penalty = 4. Use of GAP may be preferred but other algorithms may be used, e.g. BLAST (which uses the method of Altschul *et al.* (1990) *J. Mol. Biol.* 215: 405-410), FASTA (which uses the method of Pearson and Lipman (1988) *PNAS USA* 85: 2444-2448), or the Smith-Waterman algorithm (Smith and Waterman (1981) *J. Mol. Biol.* 147: 195-197), or the TBLASTN program, of Altschul *et al.* (1990) *supra*, generally employing default parameters. In particular, the psi-Blast algorithm (*Nucl. Acids Res.* (1997) 25 3389-3402) may be used.

5 Variants of these VH and VL domains and CDRs may also be employed in antibody molecules for use in as described herein. Suitable variants can be obtained by means of methods of sequence alteration, or mutation, and screening.

10 Particular variants for use as described herein may include one or more amino acid sequence alterations (addition, deletion, substitution and/or insertion of an amino acid residue), maybe less than about 20 alterations, less than about 15 alterations, less than about 10 alterations or less than about 5 alterations, 4, 3, 2 or 1.

15 Alterations may be made in one or more framework regions and/or one or more CDRs. In particular, alterations may be made in HCDR1, HCDR2 and/or HCDR3.

20 The antibody molecule may be a whole antibody or a fragment thereof, in particular an antigen-binding fragment thereof.

25 Whole antibodies include IgA, IgD, IgE, IgG or IgM. Preferably, the whole antibody is IgG.

Antigen-binding fragments of whole antibodies include (i) the Fab fragment consisting of VL, VH, CL and CH1 domains; (ii) the Fd fragment consisting of the VH and CH1 domains; (iii) the Fv fragment consisting of the VL and VH domains of a single antibody; (iv) the dAb fragment (Ward *et al.* (1989) *Nature* 341, 544-546; McCafferty *et al.*, (1990) *Nature*, 348, 552-554; Holt *et al.* (2003) *Trends in Biotechnology* 21, 484-490), which consists of a VH or a VL domain; (v) isolated CDR regions; (vi) F(ab')2 fragments, a bivalent fragment comprising two linked Fab fragments (vii) single chain Fv molecules (scFv), wherein a VH domain and a VL domain are linked by a peptide linker which allows the two domains to associate to form an antigen binding site (Bird *et al.* (1988) *Science*, 242, 423-426; Huston *et al.* (1988) *PNAS USA*, 85, 5879-5883); (viii) bispecific single chain Fv dimers

(PCT/US92/09965) and (ix) "diabodies", multivalent or multispecific fragments constructed by gene fusion (WO2013/014149; WO94/13804; Holliger *et al.* (1993a), Proc. Natl. Acad. Sci. USA 90 6444-6448). Fv, scFv or diabody molecules may be stabilized by the incorporation of disulphide bridges linking the VH and VL domains (Reiter *et al.* (1996),

5 Nature Biotech, 14, 1239-1245). Minibodies comprising a scFv joined to a CH3 domain may also be made (Hu *et al.* (1996), Cancer Res., 56(13):3055-61). Other examples of binding fragments are Fab', which differs from Fab fragments by the addition of a few residues at the carboxyl terminus of the heavy chain CH1 domain, including one or more cysteines from the antibody hinge region, and Fab'-SH, which is a Fab' fragment in which the cysteine
10 residue(s) of the constant domains bear a free thiol group.

A single chain Fv (scFv) may be comprised within a mini-immunoglobulin or small immunoprotein (SIP), e.g. as described in (Li *et al.*, (1997), Protein Engineering, 10: 731-736). An SIP may comprise an scFv molecule fused to the CH4 domain of the human IgE
15 secretory isoform IgE-S2 (ϵ_{S2} -CH4; Batista *et al.*, (1996), J. Exp. Med., 184: 2197-205) forming an homo-dimeric mini-immunoglobulin antibody molecule

Preferably the antibody molecule comprises or consists of a single chain Fv, a small immunoprotein, a diabody, or a (whole) IgG molecule.

20

Conjugates

Conjugates of the invention comprise an antibody molecule of the invention and a therapeutic or diagnostic agent. The therapeutic agent may be a biocidal molecule, a
25 cytotoxic molecule, a radioisotope, a photosensitizer, an enzyme, a hormone, or an anti-inflammatory agent. Preferably, the therapeutic agent is a biocidal molecule, a cytotoxic molecule, a radioisotope, or an anti-inflammatory agent. The biocidal molecule, cytotoxic molecule, or anti-inflammatory agent may be a cytokine.

30 The diagnostic agent may be radioisotope, e.g. a non-therapeutic radioisotope.

Radioisotopes which may be conjugated to a binding member of the invention include isotopes such as ^{94m}Tc , ^{99m}Tc , ^{186}Re , ^{188}Re , ^{203}Pb , ^{67}Ga , ^{68}Ga , ^{47}Sc , ^{111}In , ^{97}Ru , ^{62}Cu , ^{64}Cu , ^{86}Y ,
35 ^{88}Y , ^{90}Y , ^{121}Sn , ^{161}Tb , ^{153}Sm , ^{166}Ho , ^{105}Rh , ^{177}Lu , ^{123}I , ^{124}I , ^{125}I , ^{131}I , ^{18}F , ^{211}At and ^{225}Ac . Preferably, positron emitters, such as ^{18}F and ^{124}I , or gamma emitters, such as ^{99m}Tc , ^{111}In and ^{123}I , are

used for diagnostic applications (e.g. for PET), while beta-emitters, such as ^{131}I , ^{90}Y and ^{177}Lu , are preferably used for therapeutic applications. Alpha-emitters, such as ^{211}At and ^{225}Ac may also be used for therapy. In one example, the specific binding member may be conjugated to ^{177}Lu or ^{90}Y .

5

The specific binding member may be conjugated with the therapeutic agent by means of a peptide bond or linker, i.e. within a fusion polypeptide comprising said molecule and the specific binding member or a polypeptide chain component thereof. Other means for conjugation include chemical conjugation, especially cross-linking using a bifunctional reagent (e.g. employing DOUBLE-REAGENTSTM Cross-linking Reagents Selection Guide, Pierce).

10

Linkers

15 The antibody molecule and the therapeutic or diagnostic agent may be connected to each other directly, for example through any suitable chemical bond or through a linker, for example a peptide linker.

The peptide linker may be a short (2-20, preferably 2-15, residue stretch of amino acids).

20 Suitable examples of peptide linker sequences are known in the art. One or more different linkers may be used. The linker may be about 5 amino acids in length.

The chemical bond may be, for example, a covalent or ionic bond. Examples of covalent bonds include peptide bonds (amide bonds) and disulphide bonds. For example the

25 antibody molecule and therapeutic or diagnostic agent may be covalently linked. For example by peptide bonds (amide bonds). Thus, the antibody molecule and therapeutic or diagnostic agent may be produced (secreted) as a single chain polypeptide. The individual components that form the antibody molecule or the therapeutic or diagnostic agent may also be connected directly, for example through any suitable chemical bond, or through a linker, for example a peptide linker. Examples of individual components which may be linked within 30 the antibody molecule are CDRs or VH or VL sequences.

Methods of treatment and diagnosis

35 An antibody molecule or conjugate of the invention may be used in a method of treatment of the human or animal body, such as a method of treatment (which may include prophylactic

treatment) of a disease or disorder in a patient (typically a human patient) comprising administering the antibody molecule or conjugate to the patient.

Accordingly, such aspects of the invention provide methods of treatment comprising

5 administering an antibody molecule or conjugate of the invention, pharmaceutical compositions comprising such an antibody molecule or conjugate for the treatment of a condition or disease, and a method of making a medicament or pharmaceutical composition comprising formulating the antibody molecule or conjugate of the present invention with a physiologically acceptable carrier or excipient.

10

An antibody molecule or conjugate as herein described may be used in a method of treating an inflammatory disorder, inhibiting angiogenesis, treating cancer, and/or treating an autoimmune disease in a patient. The method may comprise targeting a therapeutic agent to the neovasculature *in vivo*. The agent may be any therapeutic agent discussed herein, 15 which is suitable for treatment of the disease or disorder in question.

Also contemplated is a method of treating an inflammatory disorder, inhibiting angiogenesis, treating cancer, and/or treating an autoimmune disease in a patient by targeting a therapeutic agent to the neovasculature in a patient, the method comprising administering a 20 therapeutically effective amount of an antibody molecule or conjugate as herein described to the patient.

An antibody molecule or conjugate as herein described may also be used in a method of imaging, detecting, or diagnosing a disease or disorder in a patient. A method of imaging, 25 detecting, or diagnosing a disease or disorder comprising administering an antibody or conjugate as described herein to a patient is similarly contemplated. The disease or disorder may be an inflammatory disorder, angiogenesis, cancer, and/or an autoimmune disease. The method may comprise targeting a diagnostic agent, such as a detectable label, to the neovasculature *in vivo*.

30

Inflammatory disorders include any disease or disorder which is characterised by an inflammatory abnormality. Such disease include, for example, immune system disorders, such as autoimmune diseases, and cancer.

35 Angiogenesis is a feature of many known diseases and disorders and inhibition of angiogenesis using an antibody or conjugate of the invention may be used to treat such

diseases and disorders. Similarly, diseases and disorders characterised by angiogenesis may be imaged, detected, or diagnosed using an antibody or conjugate described herein. Disease characterised by angiogenesis include, for example, rheumatoid arthritis, diabetic retinopathy, age-related muscular degeneration, angiomas, tumours and cancer.

5

As mentioned above, conditions which may be treated, imaged, detected, or diagnosed using an antibody or conjugate as described herein include cancer, as well as other tumours and neoplastic conditions.

Exemplary cancers include any type of solid or non-solid cancer or malignant lymphoma and 10 especially liver cancer, lymphoma, leukaemia (e.g. acute myeloid leukaemia), sarcomas, skin cancer, bladder cancer, breast cancer, uterine cancer, ovarian cancer, prostate cancer, lung cancer, colorectal cancer, cervical cancer, head and neck cancer, oesophageal cancer, pancreatic cancer, renal cancer, stomach cancer and cerebral cancer. Cancers may be familial or sporadic. Cancers may be metastatic or non-metastatic. The cancer, tumour, or 15 neoplastic condition may express i) the IIICS isoform of fibronectin, ii) matrix-metalloproteinase 3 (MMP3), iii) periostin, and/or iv) tenascin-W.

Autoimmune disease which may be treated, imaged, detected, or diagnosed using an 20 antibody or conjugate as described herein include lupus erythematosus, rheumatoid arthritis, and psoriatic arthritis.

A further disease or disorder which may treated, imaged, detected, or diagnosed using an antibody or conjugate described herein is osteoarthritis.

25 Pharmaceutical compositions

A further aspect of the present invention relates to a pharmaceutical composition comprising at least one antibody molecule or conjugate of the invention and optionally a pharmaceutically acceptable excipient.

30

Pharmaceutical compositions of the present invention typically comprise a therapeutically effective amount of an antibody molecule or conjugate according to the invention and optionally auxiliary substances such as pharmaceutically acceptable excipient(s). Said pharmaceutical compositions are prepared in a manner well known in the pharmaceutical art. A carrier or excipient may be a liquid material which can serve as a vehicle or medium 35 for the active ingredient. Suitable carriers or excipients are well known in the art and include,

for example, stabilisers, antioxidants, pH-regulating substances, controlled-release excipients. The pharmaceutical composition of the invention may be adapted, for example, for parenteral use and may be administered to the patient in the form of solutions or the like.

- 5 Pharmaceutical compositions comprising the antibody molecule or conjugate of the present invention may be administered to a patient. Administration is preferably in a "therapeutically effective amount", this being sufficient to show benefit to the patient. Such benefit may be amelioration of at least one symptom. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of what is being treated.
- 10 Prescription of treatment, e.g. decisions on dosage etc., is within the responsibility of general practitioners and other medical doctors. Treatments may be repeated at daily, twice-weekly, weekly, or monthly intervals at the discretion of the physician.

A pharmaceutical composition of the invention may be administered to a patient in need of treatment via any suitable route, usually by injection into the bloodstream and/or directly into the site to be treated. The precise dose and its frequency of administration will depend upon a number of factors, the route of treatment, the size and location of the area to be treated.

20 Pharmaceutical compositions for oral administration may be in tablet, capsule, powder or liquid form. A tablet may comprise a solid carrier such as gelatin or an adjuvant. Liquid pharmaceutical compositions generally comprise a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, dextrose or other saccharide solution or glycols such as ethylene glycol, propylene glycol or polyethylene glycol may be included

25 For intravenous injection, or injection at the site of affliction, the pharmaceutical composition will be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles such as Sodium Chloride.

30 Injection, Ringer's Injection, Lactated Ringer's Injection. Preservatives, stabilisers, buffers, antioxidants and/or other additives may be included, as required.

A pharmaceutical composition may be administered alone or in combination with other treatments, either simultaneously or sequentially dependent upon the condition to be treated.

Kits

Another aspect of the invention provides a therapeutic kit for use in the treatment of a disease or disorder comprising an antibody molecule or conjugate as described herein. The 5 components of a kit are preferably sterile and in sealed vials or other containers.

A kit may further comprise instructions for use of the components in a method described herein. The components of the kit may be comprised or packaged in a container, for example a bag, box, jar, tin or blister pack.

10

Further aspects and embodiments of the invention will be apparent to those skilled in the art given the present disclosure including the following experimental exemplification.

15 All documents mentioned in this specification are incorporated herein by reference in their entirety.

20 “and/or” where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. For example “A and/or B” is to be taken as specific disclosure of each of (i) A, (ii) B and (iii) A and B, just as if each is set out individually herein.

25 Unless context dictates otherwise, the descriptions and definitions of the features set out above are not limited to any particular aspect or embodiment of the invention and apply equally to all aspects and embodiments which are described.

25

Certain aspects and embodiments of the invention will now be illustrated by way of example and with reference to the figures described above.

Examples

30

Example 1 – Preparation and characterisation of two new antibodies against the IIICS isoform of fibronectin

35 Antibodies SW01 and SW02 were isolated in single-chain Fv (scFv) configuration from phage display libraries which include the libraries described in PCT/EP2009/006487, in Weber *et al.* (PLoS One, 2014, 9 (6) doi: 10/1361) and in Silacci *et al.* (Protein Engineering

Design & Selection, 2006, 19, 471-478) according to the screening technique described by Silacci *et al.* (Protein Engineering Design & Selection, 2006, 19, 471-478) using fibronectin IIICS as the screening antigen.

5 The SW01 and SW02 antibodies when used in monomeric scFv format, bind to the IIICS (89V) and IIICS (120V) isoforms (**Figure 1**). Furthermore, using ELISA antibodies SW01 and SW02 were shown to recognize both the human and the rat recombinant IIICS (120V) isoform.

10 Antibodies SW01 and SW02 display good performance in immunofluorescence analyses. **Figure 2A** shows staining of human placenta, human tumours (A375, H460) and murine tumours (K1735, F9) by SW01 and SW02 in SIP format. Specifically, SW01 and SW02 show distinct staining of vascular and perivascular structures in these tissues/tumours. As negative controls (neg ctr) an anti-human von Willebrand factor antibody (anti huVWF) was

15 used for the human placenta experiments and an anti-murine CD31 antibody (muCD31) was used for the tumor experiments.

Binding of antibody SW01 and SW02 to IIICS was further confirmed by Biacore analysis. The results are shown in **Figure 2B**.

20 Immunofluorescence on tumour sections:

Cryostat sections (10 μ m) of tumors were fixed in ice-cold acetone, rehydrated with PBS and blocked with 20% foetal bovine serum in PBS.

25 The SW01 and SW02 anti-IIICS antibodies and the KSF anti-hen egg lysozyme antibodies (all in SIP format) were diluted in 3% BSA to a final concentration of 5 μ g/mL and then added to the tissue sections. Rabbit-a-Human IgE antibody (Dako) and rat-a-mouse-CD31 antibody (BD Biosciences) were used for co-staining of SIP antibody fusion proteins and

30 endothelial cells from blood vessels, respectively. Anti-Rabbit-Alexa488 and anti-Rat-Alexa594 (Invitrogen) secondary antibodies were used for detection.

Immunofluorescence on human placenta:

35 Cryostat sections (10 μ m) of human placenta were fixed in ice-cold acetone, rehydrated with

PBS and blocked with 20% foetal bovine serum in PBS.

The SW01 and SW02 anti-IIICS antibodies and the KSF anti-hen egg lysozyme antibody (all in SIP format) were biotinylated and diluted in 3% BSA to a final concentration of 5 µg/mL 5 and then added to the tissue. Rabbit-anti-Human Von Willebrand antibody (Dako) was used for staining of endothelial cells from blood vessels. Anti-Rabbit-Alexa594 and Streptavidin-Alexa488 (Invitrogen) secondary antibodies were used for detection.

Biacore analysis:

10

Binding of antibodies SW01 and SW02 to IIICS was further determined by Biacore analysis. A CM5 chip was coated with 14(89V)15 (a recombinant polypeptide which includes domain 14, extra domain-89V of IIICS and domain 15 of fibronectin) to achieve a final coating density of 1400 resonance units (RU). The SW01 and SW02 antibodies produced in SIP 15 format were diluted in 30mM Na₂HPO₄, 20mM NaH₂PO₄, 100mM NaCl pH 7.4 to provide solutions with the following concentrations:

- 1) SIP(SW01): 500 nM, 250 nM, and 125 nM
- 2) SIP(SW02): 250 nM, 125 nM, and 62.5 nM

The flow rate for the Biacore analysis was set at 10µL/min. 10µL of each antibody sample 20 were injected into the system. Analysis was performed in HBS-EP buffer. After each injection, the chip was regenerated by the injection of 5µL of 10mM HCl.

Example 2 – Preparation and characterisation of a new antibody against MMP3

25 The CH01 antibody was isolated in scFv configuration from phage display libraries which include the libraries described in PCT/EP2009/006487, in Weber *et al.* (PLoS One, 2014, 9 (6) doi: 10/1361) and in Silacci *et al.* (Protein Engineering Design & Selection, 2006, 19, 471-478) according to the screening technique described by Silacci *et al.* (Protein 30 Engineering Design & Selection, 2006, 19, 471-478) using a recombinant version of the catalytic domain of human MMP3 (amino acids 100-273). The antigen was produced in a bacterial expression system and biotinylated according to the standard protocol.

Antibody CH01 displays good staining of neovascular structures as shown by 35 Immunofluorescence analyses. **Figure 3** shows staining of human placenta samples, in which 10 µm thick tissue samples were stained with the anti-human MMP3 antibody CH01 in

scFv format. The anti-hen egg lysozyme antibody KSF in scFv format was used as an isotype-negative control for the staining. ScFv staining is shown in red, the vascular marker human Von Willebrand factor is shown in green and nuclei were stained in blue using DAPI. Unlike the negative control, the CH01 antibody stains neovascular structures in the placenta

5 specimens.

The cross-reactivity of the CH01 antibody for the MMP3 of different species was analysed by determining binding of the CH01 antibody to the biotinylated catalytic domains of human, mouse and rat MMP3 in an ELISA. The results shown in **Figure 4A**, indicate that CH01

10 recognize both mouse and human MMP3 and to a lesser extent rat MMP3.

Binding of antibody CH01 to the catalytic domain of human and mouse MMP3 was also confirmed by Biacore analysis. The results are shown in **Figure 4B**.

15 Immunofluorescence on human placenta samples:

Dual staining for MMP3 and von Willebrand factor (vWF, an endothelial marker) was performed on human placenta samples. 10µm thick frozen specimens were defrosted at room temperate and treated with ice-cold acetone, rehydrated in PBS and blocked with 3%

20 BSA. Affinity-purified myc-tagged scFv antibodies (final concentration 5 mg/ml) were first incubated with the tissue sample, followed by the biotinylated monoclonal anti-myc 9E10 antibody (5 mg/ml) and the endothelial marker antibody. Bound scFvs were detected with Streptavidin Alexa 594 (Molecular Probes). The anti-vWF antibody (DAKO) was detected using goat anti-rabbit IgG Alexa 488. DAPI was used for nuclei staining. The anti-hen egg

25 lysozyme antibody scFv(KSF) was used as an isotype-negative control for the staining.

Cross-reactivity ELISA:

30 Streptawell High Bind strips (Roche) were coated with biotinylated Human, Mouse or Rat MMP3 catalytic domain at 100 nM. ScFv fragments were incubated for 1 hour, bound antibody was detected with the anti-Myc antibody 9E10 and an HRP-conjugated anti-Murine F_c antibody (Sigma). The plate coating density was assessed by detecting the MMP3 catalytic domains using an HRP-conjugated anti-6xHis antibody (Sigma). Colorimetric detection of antibody-antigen binding was performed using BM-Blue POD soluble substrate

35 (Roche).

Biacore Analysis:

Purified CH01 in scFv format was injected over a CM5 chip coated with both human and mouse MMP3 catalytic domains. Response units were normalised to give a baseline value of 5 zero. Samples were injected at a flow rate of 10 μ L/min in 50 mM Tris-HCl pH 7.4, 200 mM NaCl, 1 mM CaCl₂.

Example 3 – Preparation and characterisation of four new antibodies against periostin

10 The LG1, LG2, LG3 and 1E1 antibodies were isolated in scFv configuration from phage display libraries which include the libraries described in PCT/EP2009/006487, in Weber *et al.* (PLoS One, 2014, 9 (6) doi: 10/1361) and in Silacci *et al.* (Protein Engineering Design & Selection, 2006, 19, 471-478) according to the screening technique described by Silacci *et al.* (Protein Engineering Design & Selection, 2006, 19, 471-478). To generate antibodies 15 against periostin, a recombinant version of the FAS domains (from 1 to 4; **Figure 5**) was produced in a mammalian cell expression system. The antigen was biotinylated according to the standard protocol.

20 Binding of antibodies LG1, LG2 and LG3 (in scFv format) and 1E1 (in SIP format) to periostin was confirmed by Biacore analysis. The results are shown in **Figures 6A and 6B**.

Biacore analysis:

25 Monomeric fractions of purified antibodies were analyzed by surface plasmon resonance (BIAcore, 3000 system). Recombinant Human Periostin was covalently coupled to the surface of the CM-3 sensor Chip. Thirty microliters of each sample were injected at the flow rate of 10 μ L/min. The regeneration of the chip was performed with 5 μ L of 10 mM HCl.

Example 4 – Preparation and characterisation of a new antibody against tenascin-W

The G10 antibody was isolated in scFv configuration from phage display libraries which include the libraries described in PCT/EP2009/006487, in Weber *et al.* (PLoS One, 2014, 9 (6) doi: 10/1361) and in Silacci *et al.* (Protein Engineering Design & Selection, 2006, 19, 471-478) according to the screening technique described by Silacci *et al.* (Protein Engineering Design & Selection, 2006, 19, 471-478). The G10 antibody was isolated by screening the libraries against a recombinant fragment corresponding to residues 262-534 (numbering including the leader sequence) of human tenascin-W. The recombinant fragment 10 also contained an N-terminal Methionine and a C-terminal His6 tag. The sequence of this peptide is shown in SEQ ID NO: 65.

The binding of G10 to Tenascin-W was confirmed by Biacore analysis. The results are shown in **Figure 7**.

15

Biacore analysis:

A monomeric fraction of the purified G10 antibody was analyzed by surface plasmon resonance (BIAcore, 3000 system). A recombinant peptide consisting of amino acids 262-20 534 of tenascin-W was covalently coupled to the surface of the CM-5 sensor Chip. Twenty-five microliters of each sample were injected at the flow rate of 10 μ L/min. The regeneration of the chip was performed with 5 μ L of 10 mM glycine-HCl, pH 2.5 (GE Healthcare).

25

Sequence listing**Amino acid sequences of antibody SW01 specific for the IIICS isoform of fibronectin**

5 SEQ ID NO: 1 (SW01 – VH)
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKNRYIFDYWGQGTLTVSS

SEQ ID NO: 2 (SW01 – VL)
10 SELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPSGIPDRFSGSSSG
NTASLTITGAQAEDEADYYCNSSPKAPRPVVFGGGTKLTVLG

SEQ ID NO: 3 (SW01 – VH CDR1)
GFTFSSYAMS
15

SEQ ID NO: 4 (SW01 – VH CDR2)
AISGSGGSTYYADSVKG

SEQ ID NO: 5 (SW01 – VH CDR3)
20 NRYIFDY

SEQ ID NO: 6 (SW01 – VL CDR1)
QGDSLRSYYAS

25 SEQ ID NO: 7 (SW01 – VL CDR2)
GKNNRPS

SEQ ID NO: 8 (SW01 – VL CDR3)
NSSPKAPRPVV
30

Amino acid sequences of antibody SW02 specific for the IIICS isoform of fibronectin

SEQ ID NO: 9 (SW02 – VH)
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVK
35 GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGRFLFDYWGQGTLTVSS

SEQ ID NO: 10 (SW02 – VL)
SELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPSGIPDRFSGSSSG
NTASLTITGAQAEDEADYYCNSSPLYNPYVVFGGGTKLTVLG

SEQ ID NO: 11 (SW02 – VH CDR1)

GFTFSSYAMS

5 SEQ ID NO: 12 (SW02 – VH CDR2)

AISGGGGSTYYADSVKG

SEQ ID NO: 13 (SW02 – VH CDR3)

GRFLFDY

10

SEQ ID NO: 14 (SW02 – VL CDR1)

QGDSLRSYYAS

SEQ ID NO: 15 (SW02 – VL CDR2)

15 GKNNRPS

SEQ ID NO: 16 (SW02 – VL CDR3)

NSSPLYNPYVV

20 Amino acid sequences of antibody CH01 specific for MMP3

SEQ ID NO: 17 (CH01 - VH)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSPYAMSWVRQAPGKGLEWVSAITGQGGVTYYADSVK

GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKISSFHFDYWGQQGTLVTVSS

25

SEQ ID NO: 18 (CH01- VL)

EIVLTQSPGTLSSLSPGERATLSCRASQSVSSHHLAWYQQKPGQAPRLLIYDASSRATGIPDRFSGSG

SGTDFTLTISRLEPEDFAVYYCQQPRGAPTTFGQQGKVEIK

30 SEQ ID NO: 19 (CH01 – VH CDR1)

GFTFSPYAMS

SEQ ID NO: 20 (CH01 – VH CDR2)

AITGQGGVTYYADSVKG

35

SEQ ID NO: 21 (CH01 – VH CDR3)

ISSFHFDY

SEQ ID NO: 22 (CH01 – VL CDR1)

RASQSVSSHHLA

SEQ ID NO: 23 (CH01 – VL CDR2)

DASSRAT

5

SEQ ID NO: 24 (CH01 – VL CDR3)

QQPRGAPTT

Amino acid sequences of antibody LG1 specific for periostin

10

SEQ ID NO: 25 (LG1 - VH)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKHTPSFDYWGQGTLTVSS

15 SEQ ID NO: 26 (LG1 - VL)

SELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPSGIPDRFSGSSSG
NTASLTITGAQAEDEADYYCNSPYRPKKLVVFGGGTKLTVLG

SEQ ID NO: 27 (LG1 – VH CDR1)

20 GFTFSSYAMS

SEQ ID NO: 28 (LG1 – VH CDR2)

AISGSGGSTYYADSVKG

25 SEQ ID NO: 29 (LG1 – VH CDR3)

HTPSFDY

SEQ ID NO: 30 (LG1 – VL CDR1)

30 QGDSLRSYYAS

30

SEQ ID NO: 31 (LG1 – VL CDR2)

GKNNRPS

SEQ ID NO: 32 (LG1 – VL CDR3)

35 NSPYRPKKLVV

Amino acid sequences of antibody LG2 specific for periostin

SEQ ID NO: 33 (LG2 - VH)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKARYPFDYWGQGTLTVSS

SEQ ID NO: 34 (LG2 - VL)

5 SELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPSGIPDRFSGSSSG
NTASLTITGAQAEDeadYYCNSFGRALPSVVFGGGTKLTVLG

SEQ ID NO: 35 (LG2 – VH CDR1)

GFTFSSYAMS

10

SEQ ID NO: 36 (LG2 – VH CDR2)

AISGSGGSTYYADSVKG

SEQ ID NO: 37 (LG2 – VH CDR3)

15 ARYPFDY

SEQ ID NO: 38 (LG2 – VL CDR1)

QGDDSLRSYYAS

20 SEQ ID NO: 39 (LG2 – VL CDR2)

GKNNRPS

SEQ ID NO: 40 (LG2 – VL CDR3)

NSFGRALPSVV

25

Amino acid sequences of antibody LG3 specific for periostin

SEQ ID NO: 41 (LG3 - VH)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVK

30 GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKRARLFDYWGQGTLTVSS

SEQ ID NO: 42 (LG3 - VL)

EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGS
GTDFTLTISRLEPEDFAVYYCQQGGSLPLTFGQQGKVEIK

35

SEQ ID NO: 43 (LG3 – VH CDR1)

GFTFSSYAMS

SEQ ID NO: 44 (LG3 – VH CDR2)

AISGGGGSTYYADSVKG

SEQ ID NO: 45 (LG3 – VH CDR3)

RARLFDY

5

SEQ ID NO: 46 (LG3 – VL CDR1)

RASQSVSSSYLA

SEQ ID NO: 47 (LG3 – VL CDR2)

10 GASSRAT

SEQ ID NO: 48 (LG3 – VL CDR3)

QQGGSLPLT

15 Amino acid sequences of antibody 1E1 specific for periostin

SEQ ID NO: 49 (1E1 - VH)

EVQLLESGGGLVQPGGLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGGGGSTYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKHEPYIGFDYWGQGTLVTVSS

20

SEQ ID NO: 50 (1E1 - VL)

SELTQDPAVSVALGQTVRITCQGDSLRTFYASWYQQKPGQAPVLVIYGKNNRPSGIPDRFSGSSGN
TASLTITGAQAEDEADYYCNSSLYPRTPVVFGGGTKLTVLG

25 SEQ ID NO: 51 (1E1 – VH CDR1)

GFTFSSYAMS

SEQ ID NO: 52 (1E1 – VH CDR2)

AISGGGGSTYYADSVKG

30

SEQ ID NO: 53 (1E1 – VH CDR3)

HEPYIGFDY

SEQ ID NO: 54 (1E1 – VL CDR1)

35 QGDSLRTFYAS

SEQ ID NO: 55 (1E1 – VL CDR2)

GKNNRPS

SEQ ID NO: 56 (1E1 – VL CDR3)

NSSLYPRTPVV

Amino acid sequences of antibody G10 specific for tenascin W

5

SEQ ID NO: 57 (G10 - VH)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVK
GQFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKANPWFYWGQGTLTVSS

10 SEQ ID NO: 58 (G10 - VL)

SELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPSGIPDRFSGSSSG
NTASLTITGAQAEDEADYYCNSSGSQRSPVVFGGGTKLTVLG

SEQ ID NO: 59 (G10– VH CDR1)

15 GFTFSSYAMS

SEQ ID NO: 60 (G10 – VH CDR2)

AISGSGGSTYYADSVKG

20 SEQ ID NO: 61 (G10– VH CDR3)

ANPWFYD

SEQ ID NO: 62 (G10– VL CDR1)

QGDSLRSYYAS

25

SEQ ID NO: 63 (G10 – VL CDR2)

GKNNRPS

SEQ ID NO: 64 (G10 – VL CDR3)

30 NSSGSQRSPVV

Amino acid sequence of the recombinant tenascin-W peptide used to isolate the G10 antibody

SEQ ID NO: 65

35 MVVTPQGLQLLKNTEDSLLSWEPSQVNHYLLSYYPLGKELSGKQIQVPKEQHSYEILGLLPGTKYI
VTLRNVKNEVSSSPQHLLATTDLAVLGTAWVTDETENSLDVEWENPSTEVDYYKLRYGPMTGQEVA
EVTVPKSSDPKSRYDITGLHPGTEYKITVPMRGELEGKPIIILNGRTEIDSPTNVVTDRVTEDTATVSW
DPVQAVIDKYVVRYTSADGDTKEMAVHKDESSTVLTGLKPGEAYKVVWAERGNQGSKKADTNALT
EIDSPHHHHHH

40

Claims

1. An antibody molecule that binds the IIICS isoform of fibronectin, wherein the antibody molecule comprises a VH domain comprising a framework and a set of complementarity

5 determining regions HCDR1, HCDR2 and HCDR3, and a VL domain comprising a framework and a set of complementarity determining regions LCDR1, LCDR2 and LCDR3, wherein:

HCDR3 has the amino acid sequence of SEQ ID NO: 5, or the amino acid sequence of SEQ ID NO: 5 with three or fewer amino acid substitutions.

10

2. The antibody molecule according to claim 1, wherein LCDR3 has the amino acid sequence of SEQ ID NO: 8, or the amino acid sequence of SEQ ID NO: 8 with three or fewer amino acid substitutions.

15

3. The antibody molecule according to claim 1 or 2, wherein

HCDR1 has the amino acid sequence of SEQ ID NO: 3, or the amino acid sequence of SEQ ID NO: 3 with three or fewer amino acid substitutions;

HCDR2 has the amino acid sequence of SEQ ID NO: 4, or the amino acid sequence of SEQ ID NO: 4 with three or fewer amino acid substitutions;

20

LCDR1 has the amino acid sequence of SEQ ID NO: 6, or the amino acid sequence of SEQ ID NO: 6 with three or fewer amino acid substitutions; and/or

LCDR2 has the amino acid sequence of SEQ ID NO: 7, or the amino acid sequence of SEQ ID NO: 7 with three or fewer amino acid substitutions.

25

4. The antibody molecule according to claim 3, wherein the VH domain has the amino acid sequence of SEQ ID NO: 1, and/or the VL domain has the amino acid sequence of SEQ ID NO: 2.

30

5. An antibody molecule that binds the IIICS isoform of fibronectin, wherein the antibody molecule comprises a VH domain comprising a framework and a set of complementarity determining regions HCDR1, HCDR2 and HCDR3, and a VL domain comprising a framework and a set of complementarity determining regions LCDR1, LCDR2 and LCDR3, wherein:

HCDR3 has the amino acid sequence of SEQ ID NO: 13, or the amino acid

35

sequence of SEQ ID NO: 13 with three or fewer amino acid substitutions.

6. The antibody molecule according to claim 5, wherein LCDR3 has the amino acid sequence of SEQ ID NO: 16, or the amino acid sequence of SEQ ID NO: 16 with three or fewer amino acid substitutions.

5 7. The antibody molecule according to claim 5 or 6, wherein HCDR1 has the amino acid sequence of SEQ ID NO: 11, or the amino acid sequence of SEQ ID NO: 11 with three or fewer amino acid substitutions; HCDR2 has the amino acid sequence of SEQ ID NO: 12, or the amino acid sequence of SEQ ID NO: 12 with three or fewer amino acid substitutions; LCDR1 has the amino acid sequence of SEQ ID NO: 14, or the amino acid sequence of SEQ ID NO: 14 with three or fewer amino acid substitutions; and/or LCDR2 has the amino acid sequence of SEQ ID NO: 15, or the amino acid sequence of SEQ ID NO: 15 with three or fewer amino acid substitutions.

10 15 8. The antibody molecule according to claim 7, wherein the VH domain has the amino acid sequence of SEQ ID NO: 9, and/or the VL domain has the amino acid sequence of SEQ ID NO: 10.

15 9. An antibody molecule that binds matrix-metalloproteinase 3 (MMP3, wherein the antibody molecule comprises a VH domain comprising a framework and a set of complementarity determining regions HCDR1, HCDR2 and HCDR3, and a VL domain comprising a framework and a set of complementarity determining regions LCDR1, LCDR2 and LCDR3, wherein:

20 25 HCDR3 has the amino acid sequence of SEQ ID NO: 21, or the amino acid sequence of SEQ ID NO: 21 with three or fewer amino acid substitutions.

10. The antibody molecule according to claim 9, wherein LCDR3 has the amino acid sequence of SEQ ID NO: 24, or the amino acid sequence of SEQ ID NO: 24 with three or fewer amino acid substitutions.

30 35 11. The antibody molecule according to claim 9 or 10, wherein HCDR1 has the amino acid sequence of SEQ ID NO: 19, or the amino acid sequence of SEQ ID NO: 19 with three or fewer amino acid substitutions; HCDR2 has the amino acid sequence of SEQ ID NO: 20, or the amino acid sequence of SEQ ID NO: 20 with three or fewer amino acid substitutions;

LCDR1 has the amino acid sequence of SEQ ID NO: 22, or the amino acid sequence of SEQ ID NO: 22 with three or fewer amino acid substitutions; and/or

LCDR2 has the amino acid sequence of SEQ ID NO: 23, or the amino acid sequence of SEQ ID NO: 23 with three or fewer amino acid substitutions.

5

12. The antibody molecule according to claim 11, wherein the VH domain has the amino acid sequence of SEQ ID NO: 17, and/or the VL domain has the amino acid sequence of SEQ ID NO: 18.

10 13. An antibody molecule that binds periostin, wherein the antibody molecule comprises a VH domain comprising a framework and a set of complementarity determining regions HCDR1, HCDR2 and HCDR3, and a VL domain comprising a framework and a set of complementarity determining regions LCDR1, LCDR2 and LCDR3, wherein:

15 HCDR3 has the amino acid sequence of SEQ ID NO: 29, or the amino acid sequence of SEQ ID NO: 29 with three or fewer amino acid substitutions.

14. The antibody molecule according to claim 13, wherein LCDR3 has the amino acid sequence of SEQ ID NO: 32, or the amino acid sequence of SEQ ID NO: 32 with three or fewer amino acid substitutions.

20

15. The antibody molecule according to claim 13 or 14, wherein

HCDR1 has the amino acid sequence of SEQ ID NO: 27, or the amino acid sequence of SEQ ID NO: 27 with three or fewer amino acid substitutions;

25 HCDR2 has the amino acid sequence of SEQ ID NO: 28, or the amino acid sequence of SEQ ID NO: 28 with three or fewer amino acid substitutions;

LCDR1 has the amino acid sequence of SEQ ID NO: 30, or the amino acid sequence of SEQ ID NO: 30 with three or fewer amino acid substitutions; and/or

LCDR2 has the amino acid sequence of SEQ ID NO: 31, or the amino acid sequence of SEQ ID NO: 31 with three or fewer amino acid substitutions.

30

16. The antibody molecule according to claim 15, wherein the VH domain has the amino acid sequence of SEQ ID NO: 25, and/or the VL domain has the amino acid sequence of SEQ ID NO: 26.

35 17. An antibody molecule that binds periostin, wherein the antibody molecule comprises a VH domain comprising a framework and a set of complementarity determining regions

HCDR1, HCDR2 and HCDR3, and a VL domain comprising a framework and a set of complementarity determining regions LCDR1, LCDR2 and LCDR3, wherein:

HCDR3 has the amino acid sequence of SEQ ID NO: 37, or the amino acid sequence of SEQ ID NO: 37 with three or fewer amino acid substitutions.

5

18. The antibody molecule according to claim 17, wherein LCDR3 has the amino acid sequence of SEQ ID NO: 40, or the amino acid sequence of SEQ ID NO: 40 with three or fewer amino acid substitutions.

10 19. The antibody molecule according to claim 17 or 18, wherein

HCDR1 has the amino acid sequence of SEQ ID NO: 35, or the amino acid sequence of SEQ ID NO: 35 with three or fewer amino acid substitutions;

HCDR2 has the amino acid sequence of SEQ ID NO: 36, or the amino acid sequence of SEQ ID NO: 36 with three or fewer amino acid substitutions;

15 LCDR1 has the amino acid sequence of SEQ ID NO: 38, or the amino acid sequence of SEQ ID NO: 38 with three or fewer amino acid substitutions; and/or

LCDR2 has the amino acid sequence of SEQ ID NO: 39, or the amino acid sequence of SEQ ID NO: 39 with three or fewer amino acid substitutions.

20 20. The antibody molecule according to claim 19, wherein the VH domain has the amino acid sequence of SEQ ID NO: 33, and/or the VL domain has the amino acid sequence of SEQ ID NO: 34.

25 21. An antibody molecule that binds periostin, wherein the antibody molecule comprises a VH domain comprising a framework and a set of complementarity determining regions HCDR1, HCDR2 and HCDR3, and a VL domain comprising a framework and a set of complementarity determining regions LCDR1, LCDR2 and LCDR3, wherein:

HCDR3 has the amino acid sequence of SEQ ID NO: 45, or the amino acid sequence of SEQ ID NO: 45 with three or fewer amino acid substitutions.

30

22. The antibody molecule according to claim 21, wherein LCDR3 has the amino acid sequence of SEQ ID NO: 48, or the amino acid sequence of SEQ ID NO: 48 with three or fewer amino acid substitutions.

35 23. The antibody molecule according to claim 21 or 22, wherein

HCDR1 has the amino acid sequence of SEQ ID NO: 43, or the amino acid sequence of SEQ ID NO: 43 with three or fewer amino acid substitutions;

HCDR2 has the amino acid sequence of SEQ ID NO: 44, or the amino acid sequence of SEQ ID NO: 44 with three or fewer amino acid substitutions;

5 LCDR1 has the amino acid sequence of SEQ ID NO: 46, or the amino acid sequence of SEQ ID NO: 46 with three or fewer amino acid substitutions; and/or

LCDR2 has the amino acid sequence of SEQ ID NO: 47, or the amino acid sequence of SEQ ID NO: 47 with three or fewer amino acid substitutions.

10 24. The antibody molecule according to claim 23, wherein the VH domain has the amino acid sequence of SEQ ID NO: 41, and/or the VL domain has the amino acid sequence of SEQ ID NO: 42.

15 25. An antibody molecule that binds periostin, wherein the antibody molecule comprises a VH domain comprising a framework and a set of complementarity determining regions HCDR1, HCDR2 and HCDR3, and a VL domain comprising a framework and a set of complementarity determining regions LCDR1, LCDR2 and LCDR3, wherein:

HCDR3 has the amino acid sequence of SEQ ID NO: 53, or the amino acid sequence of SEQ ID NO: 53 with three or fewer amino acid substitutions.

20 26. The antibody molecule according to claim 25, wherein LCDR3 has the amino acid sequence of SEQ ID NO: 56, or the amino acid sequence of SEQ ID NO: 56 with three or fewer amino acid substitutions.

25 27. The antibody molecule according to claim 25 or 26, wherein HCDR1 has the amino acid sequence of SEQ ID NO: 51, or the amino acid sequence of SEQ ID NO: 51 with three or fewer amino acid substitutions;

HCDR2 has the amino acid sequence of SEQ ID NO: 52, or the amino acid sequence of SEQ ID NO: 52 with three or fewer amino acid substitutions;

30 LCDR1 has the amino acid sequence of SEQ ID NO: 54, or the amino acid sequence of SEQ ID NO: 54 with three or fewer amino acid substitutions; and/or

LCDR2 has the amino acid sequence of SEQ ID NO: 55, or the amino acid sequence of SEQ ID NO: 55 with three or fewer amino acid substitutions.

28. The antibody molecule according to claim 27, wherein the VH domain has the amino acid sequence of SEQ ID NO: 49, and/or the VL domain has the amino acid sequence of SEQ ID NO: 50.

5 29. An antibody molecule that binds tenascin W, wherein the antibody molecule comprises a VH domain comprising a framework and a set of complementarity determining regions HCDR1, HCDR2 and HCDR3, and a VL domain comprising a framework and a set of complementarity determining regions LCDR1, LCDR2 and LCDR3, wherein:
HCDR3 has the amino acid sequence of SEQ ID NO: 61, or the amino acid
10 sequence of SEQ ID NO: 61 with three or fewer amino acid substitutions.

30. The antibody molecule according to claim 29, wherein LCDR3 has the amino acid sequence of SEQ ID NO: 64, or the amino acid sequence of SEQ ID NO: 64 with three or fewer amino acid substitutions.

15 31. The antibody molecule according to claim 29 or 30, wherein
HCDR1 has the amino acid sequence of SEQ ID NO: 59, or the amino acid
sequence of SEQ ID NO: 59 with three or fewer amino acid substitutions;
HCDR2 has the amino acid sequence of SEQ ID NO: 60, or the amino acid
20 sequence of SEQ ID NO: 60 with three or fewer amino acid substitutions;
LCDR1 has the amino acid sequence of SEQ ID NO: 62, or the amino acid sequence
of SEQ ID NO: 62 with three or fewer amino acid substitutions; and/or
LCDR2 has the amino acid sequence of SEQ ID NO: 63, or the amino acid sequence
of SEQ ID NO: 63 with three or fewer amino acid substitutions.

25 32. The antibody molecule according to claim 31, wherein the VH domain has the amino acid sequence of SEQ ID NO: 57, and/or the VL domain has the amino acid sequence of SEQ ID NO: 58.

30 33. The antibody molecule according to any one of claims 1 to 32, wherein the antibody molecule is or comprises a single chain Fv (scFv), is a small immunoprotein (SIP), is a diabody, or is an IgG molecule.

35 34. A conjugate comprising an antibody molecule according to any one of claims 1 to 33 and a biocidal molecule, a cytotoxic molecule, or a radioisotope.

35. A conjugate comprising an antibody molecule according to any one of claims 1 to 33 and an anti-inflammatory agent.

36. The conjugate according to claim 34 or 35, wherein the biocidal molecule, cytotoxic molecule, or anti-inflammatory agent is a cytokine.

37. The conjugate according to any one of claims 34 to 36, wherein the conjugate is a fusion protein comprising the antibody molecule and a biocidal molecule, cytotoxic molecule, anti-inflammatory agent, or cytokine.

10

38. A conjugate comprising an antibody molecule according to any one of claims 1 to 33 and a detectable label.

39. The antibody molecule or conjugate according to any one of claims 1 to 37 for use in 15 a method for treatment of the human or animal body by therapy.

40. The antibody molecule or conjugate according to any one of claims 1 to 37 for use in a method of treating an inflammatory disorder in a patient.

20 41. A method of treating an inflammatory disorder in a patient comprising administering a therapeutically effective amount of a medicament comprising an antibody molecule or conjugate according to any of claims 1 to 37 to the patient.

42. The antibody molecule or conjugate according to any one of claims 1 to 34, or 36 to 25 37 for use in a method of inhibiting angiogenesis in a patient.

43. A method of inhibiting angiogenesis in a patient comprising administering a therapeutically effective amount of a medicament comprising an antibody molecule or conjugate according to any of claims 1 to 34, or 36 to 37 to the patient.

30

44. The antibody molecule or conjugate according to any one of claims 1 to 34, or 36 to 37 for use in a method of treating cancer in a patient.

45. A method of treating cancer in a patient comprising administering a therapeutically 35 effective amount of a medicament comprising an antibody molecule or conjugate according to any of claims 1 to 34, or 36 to 37 to the patient.

46. The antibody molecule or conjugate according to any one of claims 1 to 33, or 35 to 37 for use in a method of treating an autoimmune disease in a patient.

5 47. A method of treating an autoimmune disease in a patient comprising administering a therapeutically effective amount of a medicament comprising an antibody molecule or conjugate according to any of claims 1 to 33, or 35 to 37 to the patient.

10 48. The antibody molecule according to any one of claims 1 to 33 for use in a method of delivering a molecule to sites of an inflammatory disorder in a patient.

49. A method of delivering a molecule to sites of an inflammatory disorder in a patient comprising administering to the patient an antibody molecule according to any one of claims 1 to 33, wherein the antibody molecule is conjugated to the molecule.

15 50. The antibody molecule for use according to claim 48, or method according to claim 49, wherein the molecule is a biocidal molecule, a cytotoxic molecule, a radioisotope, or an anti-inflammatory agent.

20 51. The antibody molecule according to any one of claims 1 to 33 for use in a method of delivering a molecule to sites of neovasculature, which are the result of angiogenesis, in a patient.

25 52. A method of delivering a molecule to sites to sites of neovasculature, which are the result of angiogenesis, in a patient comprising administering to the patient an antibody molecule according to any one of claims 1 to 33, wherein the antibody molecule is conjugated to the molecule.

30 53. The antibody molecule according to any one of claims 1 to 33 for use in a method of delivering a molecule to sites of cancer in a patient.

54. A method of delivering a molecule to sites of cancer in a patient comprising administering to the patient an antibody molecule according to any one of claims 1 to 33, wherein the antibody molecule is conjugated to the molecule.

55. The antibody molecule for use according to claim 51 or 53, or method according to claim 52 or 54, wherein the molecule is a biocidal molecule, a cytotoxic molecule, or a radioisotope.

5 56. The antibody molecule according to any one of claims 1 to 33 for use in a method of delivering a molecule to sites of autoimmune disease in a patient.

57. A method of delivering a molecule to sites of autoimmune disease in a patient comprising administering to the patient an antibody molecule according to any one of claims 10 1 to 33, wherein the antibody molecule is conjugated to the molecule.

58. The antibody molecule for use according to claim 56, or method according to claim 57, wherein the molecule is an anti-inflammatory agent.

15 59. The antibody molecule or conjugate according to any one of claims 1 to 33 or 38 for use in a method of imaging, detecting, or diagnosing an inflammatory disorder in a patient.

60. A method of imaging, detecting, or diagnosing an inflammatory disorder in a patient comprising administering an antibody molecule or conjugate according to any of claims 1 to 20 33 or 38 to the patient.

61. The antibody molecule or conjugate according to any one of claims 1 to 33 or 38 for use in a method of imaging, detecting, or diagnosing angiogenesis in a patient.

25 62. A method of imaging, detecting, or diagnosing angiogenesis in a patient comprising administering an antibody molecule or conjugate according to any of claims 1 to 33 or 38 to the patient.

30 63. The antibody molecule or conjugate according to any one of claims 1 to 33 or 38 for use in a method of imaging, detecting, or diagnosing cancer in a patient.

64. A method of imaging, detecting, or diagnosing cancer in a patient comprising administering an antibody molecule or conjugate according to any of claims 1 to 33 or 38 to the patient.

65. The antibody molecule or conjugate according to any one of claims 1 to 33 or 38 for use in a method of imaging, detecting, or diagnosing an autoimmune disease in a patient.

66. A method of imaging, detecting, or diagnosing an autoimmune disease in a patient
5 comprising administering an antibody molecule or conjugate according to any of claims 1 to 33 or 38 to the patient.

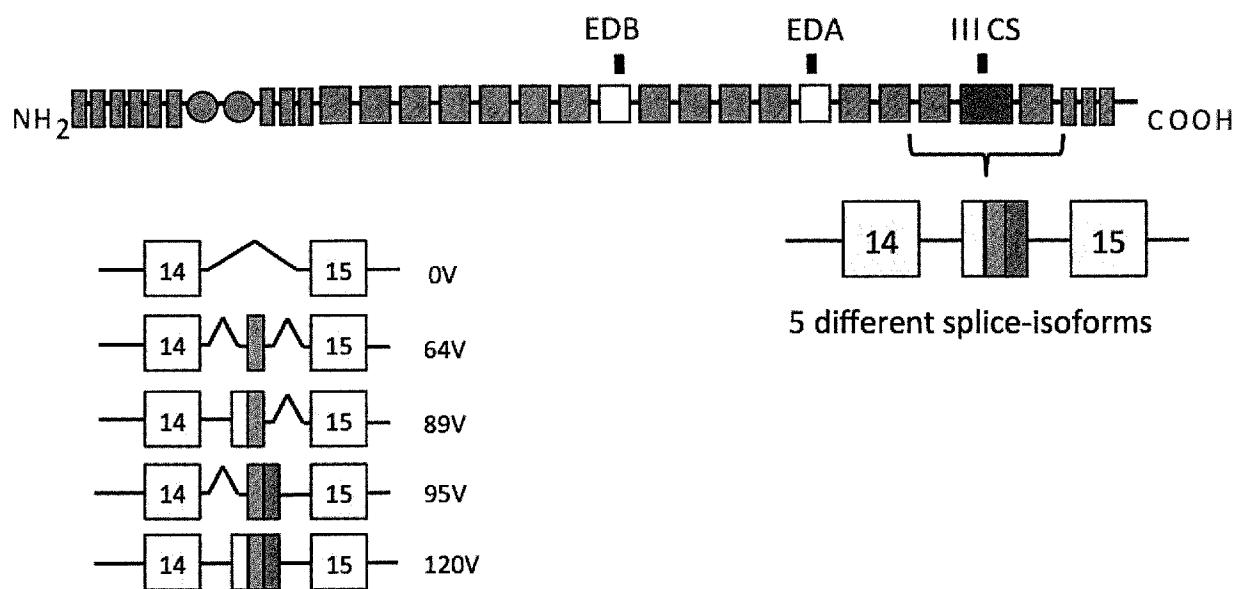
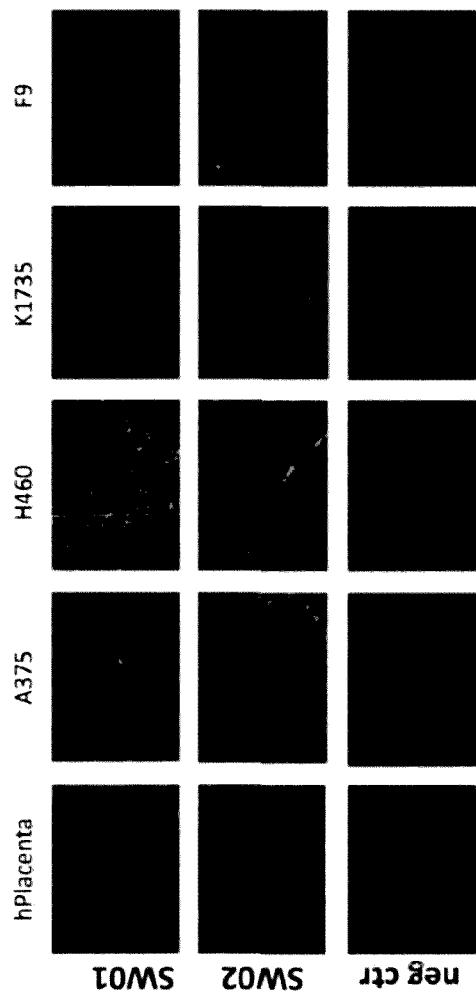
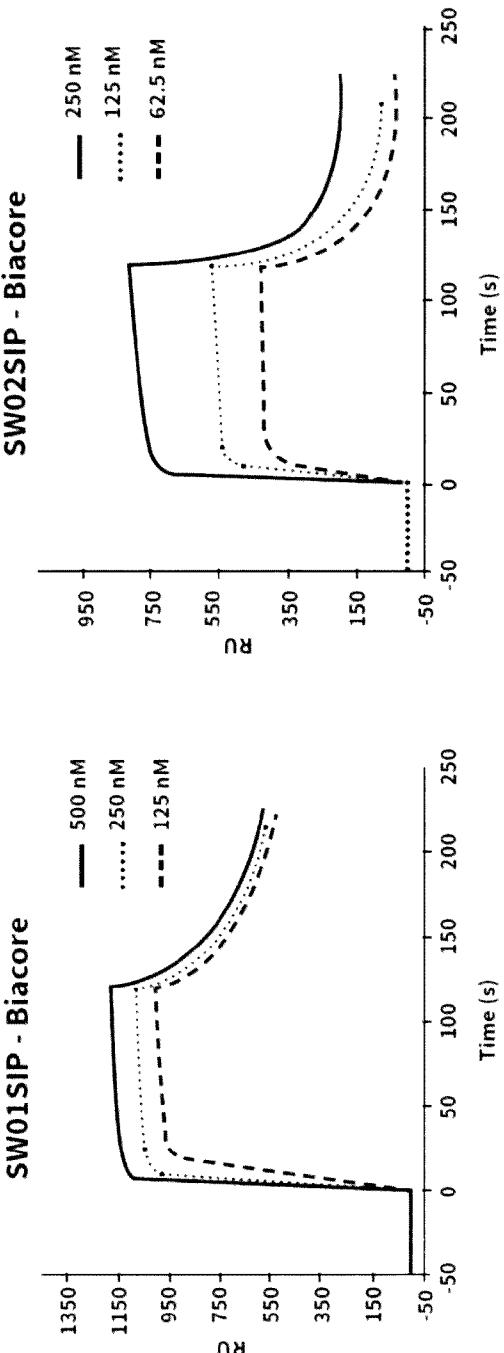


Figure 1

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Figure 2A**Figure 2B**

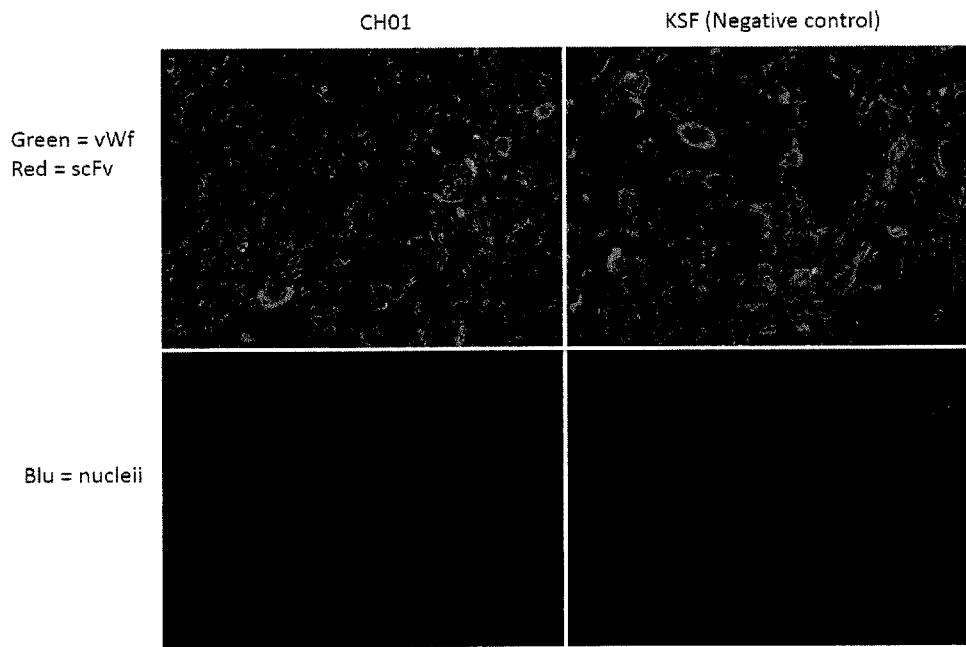
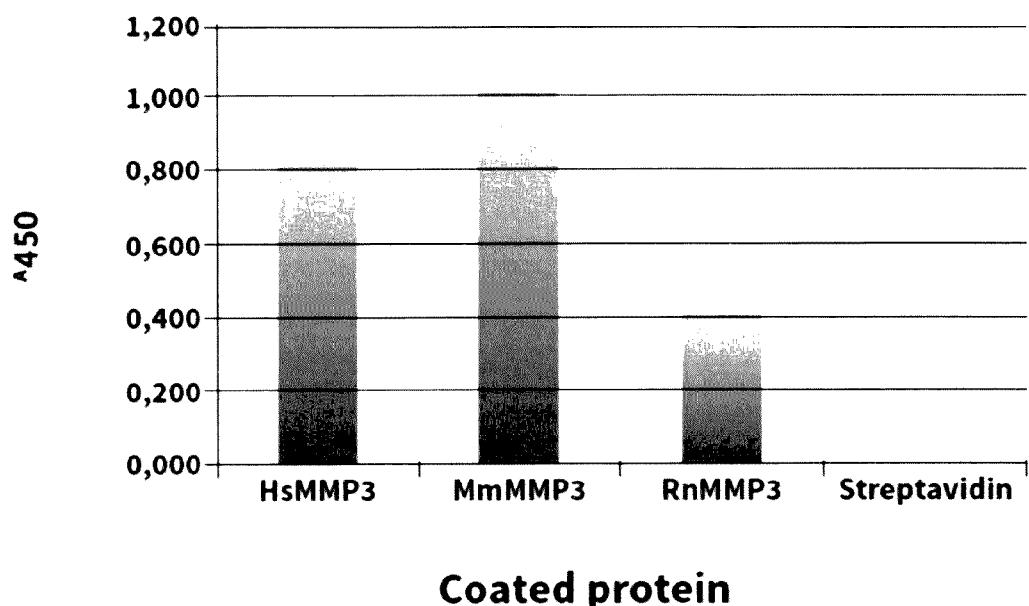
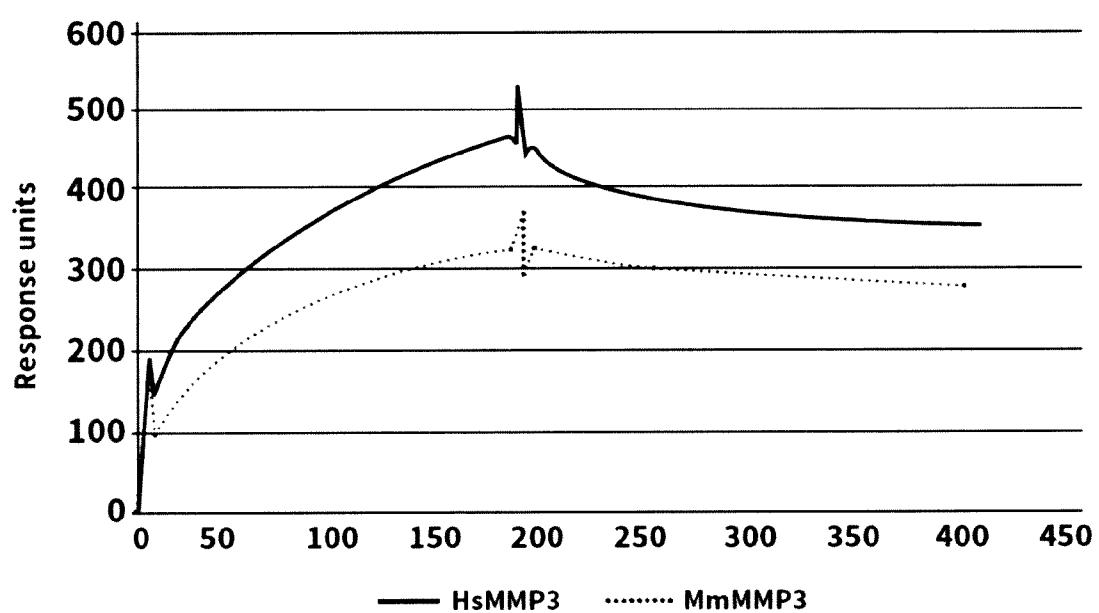
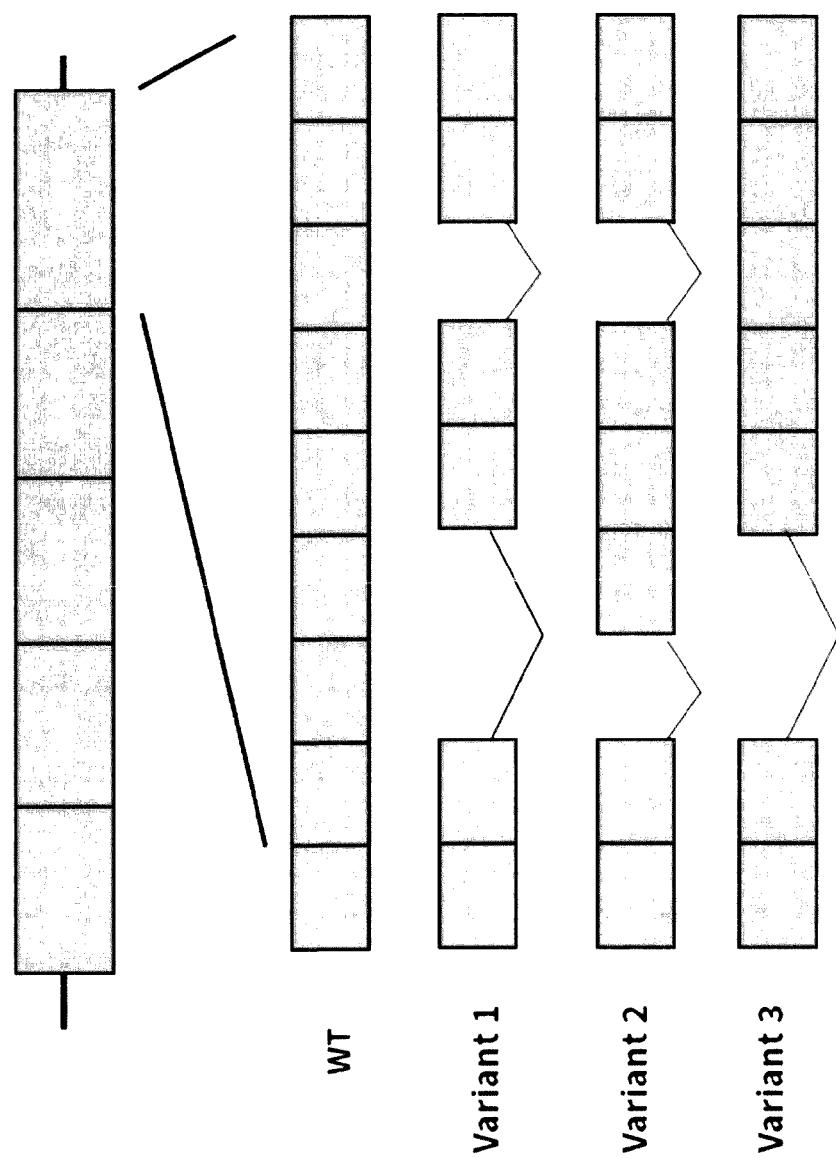


Figure 3

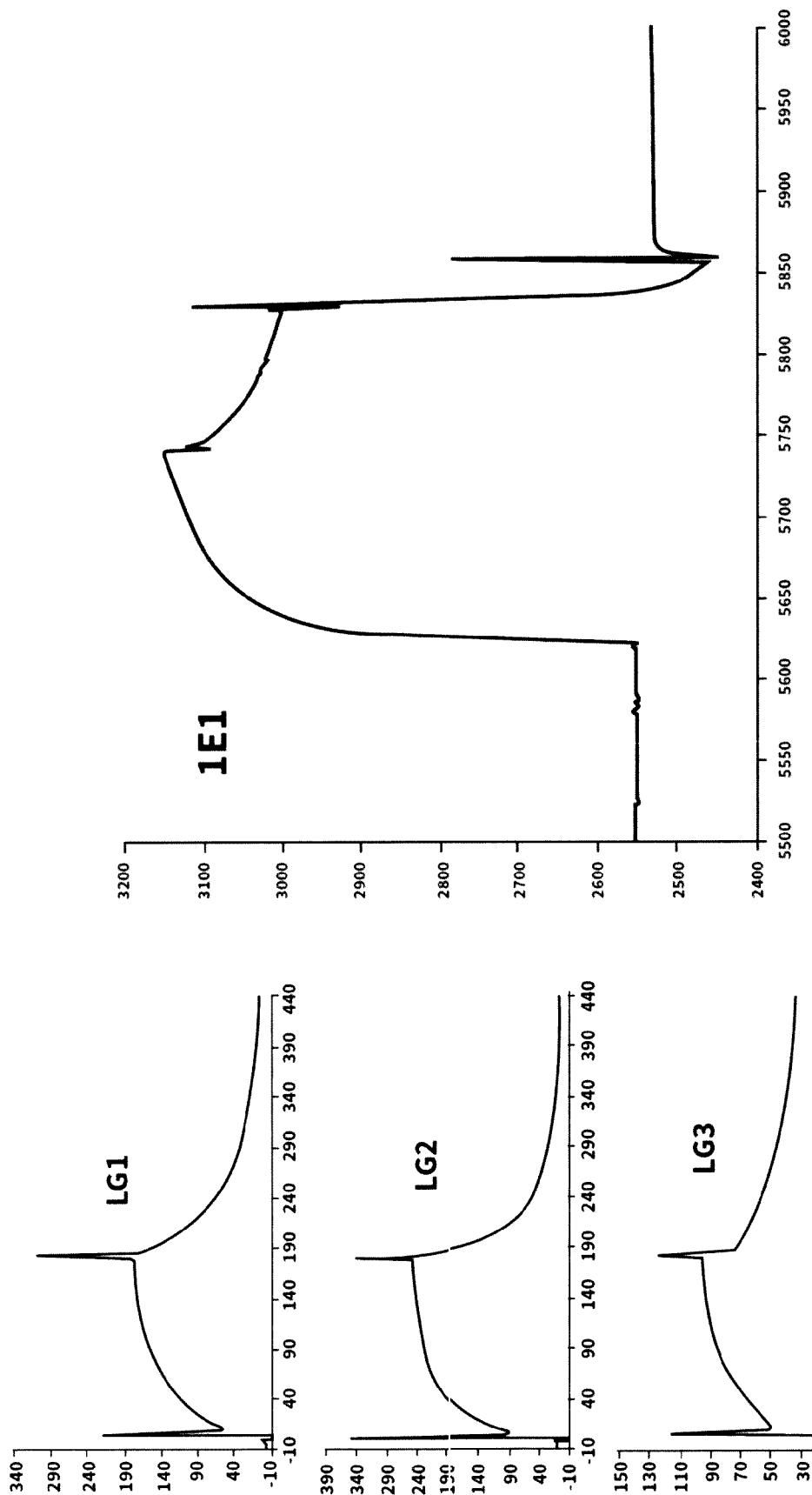
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**Figure 4A****Figure 4B**

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**Figure 5**

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**Figure 6A****Figure 6B**

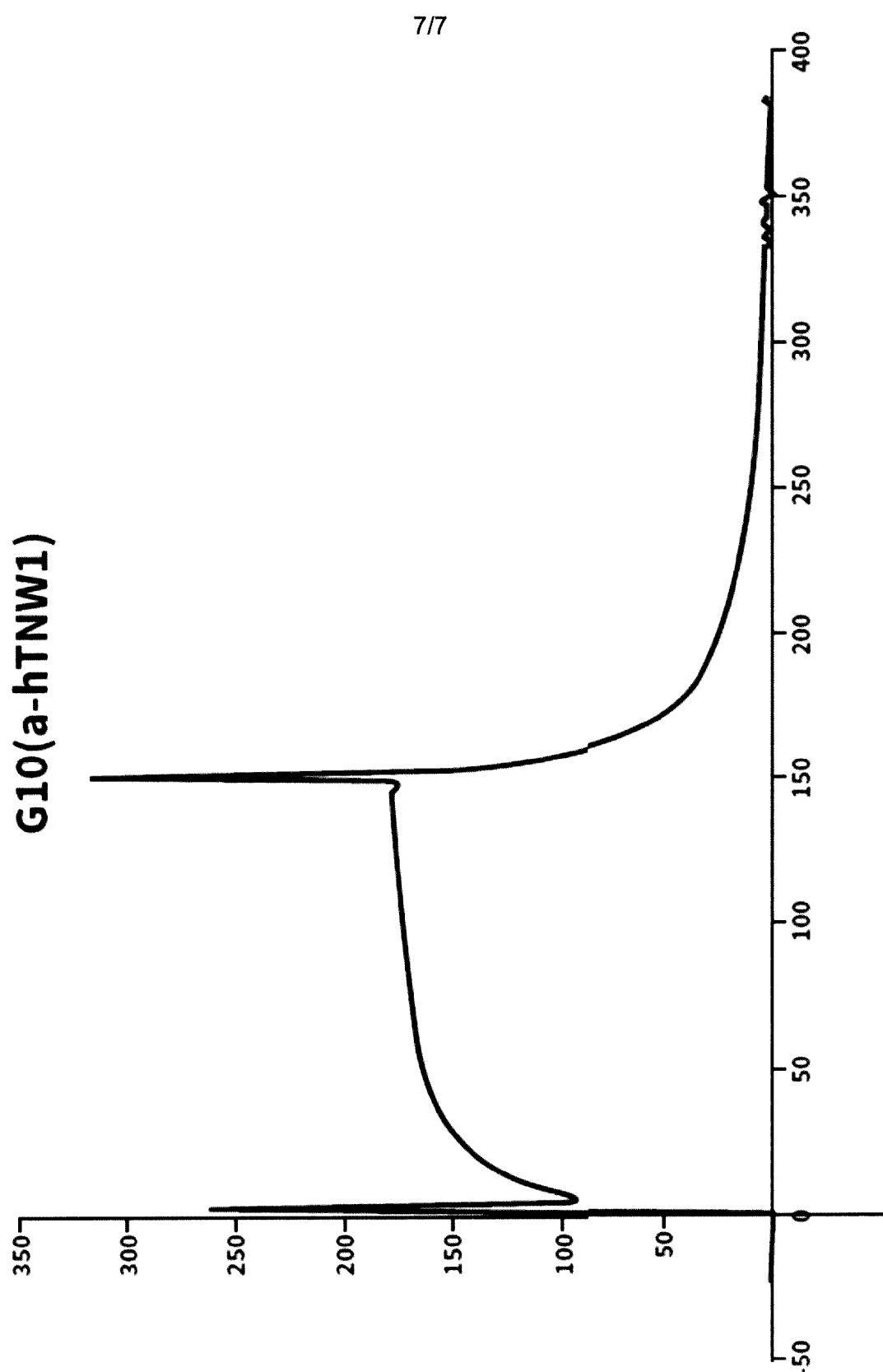


Figure 7

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/067309

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/18
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 03/019136 A2 (UNIV CALIFORNIA [US]; VARNER JUDITH A [US]) 6 March 2003 (2003-03-06) page 59, paragraph 2 figure 1B</p> <p>-----</p> <p style="text-align: center;">-/-</p>	1-4, 33-66

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 September 2015	04/01/2016
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Malamoussi, A

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/067309

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WARAWDEKAR U M ET AL: "Elevated levels and fragmented nature of cellular fibronectin in the plasma of gastrointestinal and head and neck cancer patients", CLINICA CHIMICA ACTA, ELSEVIER BV, AMSTERDAM, NL, vol. 372, no. 1-2, 1 October 2006 (2006-10-01), pages 83-93, XP027877703, ISSN: 0009-8981 [retrieved on 2006-10-01] abstract page 84, right-hand column, paragraph 3 - paragraph 4 -----	1-4, 33-66
X	ANGELES GARCIA-PARDO ET AL: "Two novel monoclonal antibodies to fibronectin that recognize the hep II and CS-1 regions respectively: Their differential effect on lymphocyte adhesion", BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 186, no. 1, 1 July 1992 (1992-07-01), pages 135-142, XP055216310, ISSN: 0006-291X, DOI: 10.1016/S0006-291X(05)80785-5 abstract -----	1-4, 33-66
X	AMY J. SANTAS ET AL: "Alternative Splicing of the IIICS Domain in Fibronectin Governs the Role of the Heparin II Domain in Fibrillogenesis and Cell Spreading", JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 277, no. 16, 19 April 2002 (2002-04-19), pages 13650-13658, XP055216313, ISSN: 0021-9258, DOI: 10.1074/jbc.M111361200 abstract page 13652, left-hand column, paragraph 2 -----	1-4, 33-66
X	PACHIYAPPAN KAMARAJAN ET AL: "The CS1 segment of fibronectin is involved in human OSCC pathogenesis by mediating OSCC cell spreading, migration, and invasion", BMC CANCER, vol. 10, no. 1, 1 January 2010 (2010-01-01), page 330, XP055216316, ISSN: 1471-2407, DOI: 10.1186/1471-2407-10-330 abstract page 3, right-hand column, paragraph 1 -----	1-4, 33-66
1	-/-	

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/067309

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ELICES M J ET AL: "EXPRESSION AND FUNCTIONAL SIGNIFICANCE OF ALTERNATIVELY SPLICED CS1 FIBRONECTIN IN RHEUMATOID ARTHRITIS MICROVASCULATURE", JOURNAL OF CLINICAL INVESTIGATION, AMERICAN SOCIETY FOR CLINICAL INVESTIGATION, US, vol. 93, no. 1, 1 January 1994 (1994-01-01), pages 405-416, XP009052418, ISSN: 0021-9738, DOI: 10.1172/JCI116975 abstract page 406, right-hand column, paragraph 1 -----	1-4, 33-66
A	SR BRAMHALL ET AL: "Expression of collagenase (MMP2), stromelysin (MMP3) and tissue inhibitor of the metalloproteinases (TIMP1) in pancreatic and ampullary disease", BRITISH JOURNAL OF CANCER, vol. 73, no. 8, 1 April 1996 (1996-04-01), pages 972-978, XP055216321, ISSN: 0007-0920, DOI: 10.1038/bjc.1996.190 page 973, right-hand column, paragraph 2 table II -----	1-4, 33-66
A	ISABELLA T TAI ET AL: "Periostin induction in tumor cell line explants and inhibition of in vitro cell growth by anti-periostin antibodies", CARCINOGENESIS, OXFORD UNIVERSITY PRESS, GB, vol. 26, no. 5, 1 January 2005 (2005-01-01), pages 908-915, XP008127943, ISSN: 0143-3334, DOI: 10.1093/CARCIN/BGI034 abstract -----	1-4, 33-66
A	ZHU MIN ET AL: "Neutralizing monoclonal antibody to periostin inhibits ovarian tumor growth and metastasis", MOLECULAR CANCER THERAPEUTICS, AMERICAN ASSOCIATION FOR CANCER RESEARCH, vol. 10, no. 8, 1 August 2011 (2011-08-01), pages 1500-1508, XP009164701, ISSN: 1538-8514 abstract ----- -/-	1-4, 33-66

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/067309

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FLORENCE BRELLIER ET AL: "Tenascin-W is a better cancer biomarker than tenascin-C for most human solid tumors", BMC CLINICAL PATHOLOGY, BIOMED CENTRAL, LONDON, GB, vol. 12, no. 1, 4 September 2012 (2012-09-04), page 14, XP021115769, ISSN: 1472-6890, DOI: 10.1186/1472-6890-12-14 abstract page 2, right-hand column, paragraph 3 -----	1-4, 33-66

INTERNATIONAL SEARCH REPORT

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-4(completely); 33-66(partially)

Remark on Protest

The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-4(completely); 33-66(partially)

antibody molecule that binds the IIICS isoform of fibronectin, sequences relating to clone SW01

2. claims: 5-8(completely); 33-66(partially)

antibody molecule that binds the IIICS isoform of fibronectin, sequences relating to clone SW02

3. claims: 9-12(completely); 33-66(partially)

antibody molecule that binds matrix-metalloproteinase 3 (MMP3), sequences relating to clone CH01

4. claims: 13-16(completely); 33-66(partially)

antibody molecule that binds periostin, sequences relating to clone LG1

5. claims: 17-20(completely); 33-66(partially)

antibody molecule that binds periostin, sequences relating to clone LG2

6. claims: 21-24(completely); 33-66(partially)

antibody molecule that binds periostin, sequences relating to clone LG3

7. claims: 25-28(completely); 33-66(partially)

antibody molecule that binds periostin, sequences relating to clone 1E1

8. claims: 29-32(completely); 33-66(partially)

antibody molecule that binds tenascin W, sequences relating to clone G10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2015/067309

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 03019136	A2 06-03-2003	AU 2002356180	A1 10-03-2003	CA 2494870 A1 06-03-2003