

SUMMARY

The present disclosure encompasses a PD1 binder (*e.g.*, an immunoglobulin single variable domain (ISVD) or a Nanobody that binds to PD1 (*e.g.*, human PD1) comprising the amino acid sequence set forth in SEQ ID NO: 1 or 2; but which comprises a mutation at one or more of positions 1, 11, 14, 52a, 73, 74, 83, 89, 100a, 110 and 112 wherein said positions are numbered according to Kabat (*e.g.*, L11V, A14P, A74S, K83R, I89L and, optionally, E1D; or L11V, A14P, W52aV, N73P, A74S, K83R, I89L, W100a and, optionally, E1D), comprising CDR1 that comprises the amino acid sequence: IHAMG (SEQ ID NO: 3) or GSIASIHAMG (SEQ ID NO: 6); CDR2 that comprises the amino acid sequence: VITXSGGITYYADSVKG (SEQ ID NO: 4; wherein X is W or V) or VITXSGGITY (SEQ ID NO: 7; wherein X is W or V); and CDR3 that comprises the amino acid sequence: DKHQSSXYDY (SEQ ID NO: 5, wherein X is W or F) or DKHQSSXYDY (SEQ ID NO: 8, wherein X is W or F). In one aspect, there is provided a PD1 binder comprising an immunoglobulin single variable domain (ISVD) that binds to PD1 comprising the amino acid sequence set forth in SEQ ID NO: 1 or 2 but comprising one or more mutations at a residue selected from 11 and 89; wherein said residue numbers are Kabat residue numbers; and, optionally, a half-life extender and/or a C-terminal extender. In an embodiment, the PD1 binder (*e.g.*, an ISVD such as a Nanobody) comprises an amino acid residue at position 11 that is chosen from L or V; an amino acid residue at position 89 chosen from T, V or L; an amino acid residue at position 110 chosen from T, K or Q; and/or an amino acid residue at position 112 chosen from S, K or Q. In an embodiment, the PD1 binder (*e.g.*, an ISVD such as a Nanobody) comprises one or more mutations described is a member selected from the group consisting of: 89T; 89L in combination with 11V; 89L in combination with 110K or 110Q; 89L in combination with 112K or 112Q; 89L in combination with 11V and 110K or 110Q; 89L in combination with 11V and 112K or 112Q; 11V in combination with 110K or 110Q; 11V in combination with 112K or 112Q. In an embodiment, the amino acid at positions 11, 89, 110 and 112 are as any of those set forth in the Table B herein. In an embodiment, the PD1 binder (*e.g.*, an ISVD such as a Nanobody) comprises one or more mutations at a position selected from the group consisting of 1, 14, 41, 74, 83, 87 and 108 and/or one or more humanizing substitutions known per se (for which reference is made to the prior art cited herein, such as WO 08/020079 or WO 09/138519. In an embodiment, the PD1 binder (*e.g.*, an ISVD such as a Nanobody)

comprises a C-terminal extension of 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids. For example, in an embodiment, the PD1 binder (*e.g.*, an ISVD such as a Nanobody) comprises a C-terminal extension according to the formula -X(n), wherein X and n are as follows: (a) n = 1 and X = Ala; (b) n = 2 and each X =

Ala; (c) $n = 3$ and each $X = \text{Ala}$; (d) $n = 2$ and at least one $X = \text{Ala}$ and wherein the remaining amino acid residue(s) X are independently chosen from any naturally occurring amino acid; (e) $n = 3$ and at least one $X = \text{Ala}$ and wherein the remaining amino acid residue(s) X are independently chosen from any naturally occurring amino acid; (f) $n = 3$ and at least two $X = \text{Ala}$ and wherein the remaining amino acid residue(s) X are independently chosen from any naturally occurring amino acid; (g) $n = 1$ and $X = \text{Gly}$; (h) $n = 2$ and each $X = \text{Gly}$; (i) $n = 3$ and each $X = \text{Gly}$; (j) $n = 2$ and at least one $X = \text{Gly}$ wherein the remaining amino acid residue(s) X are independently chosen from any naturally occurring amino acid; (k) $n = 3$ and at least one $X = \text{Gly}$ wherein the remaining amino acid residue(s) X are independently chosen from any naturally occurring amino acid; (l) $n = 3$ and at least two $X = \text{Gly}$ wherein the remaining amino acid residue(s) X are independently chosen from any naturally occurring amino acid; (m) $n = 2$ and each $X = \text{Ala}$ or Gly ; (n) $n = 3$ and each $X = \text{Ala}$ or Gly ; (o) $n = 3$ and at least one $X = \text{Ala}$ or Gly wherein remaining amino acid residue(s) X are independently chosen from any naturally occurring amino acid; or (p) $n = 3$ and at least two $X = \text{Ala}$ or Gly wherein the remaining amino acid residue(s) X are independently chosen from any naturally occurring amino acid, *e.g.*, A, AA, AAA, G, GG, GGG, AG, GA, AAG, AGG, AGA, GGA, GAA or GAG. The present disclosure also provides a PD1 binder (*e.g.*, an ISVD such as a Nanobody) comprising one or mutations at position 11, 89, 110 and 112 and an amino acid sequence having at least 85% (*e.g.*, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5, 99.9 or 100%) sequence identity with the amino acid sequence set forth in a member selected from the group consisting of SEQ ID NOs: 9-40 (in which any C-terminal extension that may be present as well as any CDRs are not taken into account for determining the degree of sequence identity). The present disclosure also provides a multispecific immunoglobulin comprising a PD1 binder (*e.g.*, an ISVD such as a Nanobody) that binds to PD1 linked to one or more molecules that bind to an epitope that is not the epitope to which the PD1 binder binds (*e.g.*, PD1, CTLA4, LAG3, BTLA and/or CD27), *e.g.*, comprising a PD1 binding moiety and a CTLA4 binding moiety; a PD1 binding moiety and a BTLA binding moiety; a PD1 binding moiety and a LAG3 binding moiety; or a PD1 binding moiety, a LAG3 binding moiety and a BTLA binding moiety, optionally linked via one or more linkers, *e.g.*, peptide linkers. In one embodiment, the multispecific immunoglobulin comprises a first PD1 Nanobody linked to one or more molecules selected from the group consisting of an CTLA4 Nanobody, an LAG3 Nanobody, an BTLA Nanobody, an

CD27 Nanobody and an PD1 Nanobody that binds to the same or a different epitope as that of the first PD1 Nanobody; *e.g.*, comprising a PD1 binding moiety and a CTLA4 binding moiety; a PD1 binding moiety and a BTLA binding moiety; a PD1 binding moiety and a LAG3 binding moiety; or a PD1 binding moiety, a LAG3 binding moiety and a BTLA binding moiety.

5 The present disclosure includes a polypeptide, ISVD or Nanobody comprising an amino acid sequence that is described herein, *e.g.*, which is selected from SEQ ID NOs: 9-40.

 The present disclosure also provides a PD1 binder of the present disclosure (*e.g.*, an immunoglobulin single variable domain (ISVD) or multispecific ISVD such as a Nanobody) in association with a further therapeutic agent.

10 Injection devices and vessels comprising PD1 binder (*e.g.*, immunoglobulin single variable domain (ISVD) or multispecific ISVD such as a Nanobody) optionally in association with a further therapeutic agent are provided by the present disclosure .

 The present disclosure provides a polynucleotide encoding a PD1 binder (*e.g.*, immunoglobulin single variable domain (ISVD) or multispecific ISVD such as a Nanobody); or a
15 vector comprising the polynucleotide or a host cell comprising the polynucleotide or vector.

 The present disclosure provides a method for making an PD1 binder (*e.g.*, immunoglobulin single variable domain (ISVD) or multispecific ISVD such as a Nanobody) comprising introducing a polynucleotide encoding the immunoglobulins into a host cell and culturing the host cell in a medium under conditions favorable to expression of said
20 immunoglobulin from said polynucleotide and, optionally, purifying the immunoglobulin from said host cell and/or said medium. PD1 binders (*e.g.*, an ISVDs such as a Nanobodies) produced by such methods are part of the present disclosure .

 The present disclosure also provides a method for preventing PD1 from binding to PD-L1 and/or PD-L2 comprising contacting said PD1 with a PD1 binder (*e.g.*, immunoglobulin single
25 variable domain (ISVD) or multispecific ISVD such as a Nanobody) optionally in association with a further therapeutic agent.

 The present disclosure also provides a method for enhancing an immune response in the body of a subject comprising administering an effective amount of a PD1 binder of the present disclosure (*e.g.*, immunoglobulin single variable domain (ISVD) or multispecific ISVD such as a
30 Nanobody) to the subject optionally in association with a further therapeutic agent. In addition, the present disclosure also provides a method for treating or preventing cancer (*e.g.*, metastatic

cancer, a solid tumor, a hematologic cancer, leukemia, lymphoma, osteosarcoma, rhabdomyosarcoma, neuroblastoma, kidney cancer, leukemia, renal transitional cell cancer, bladder cancer, Wilm's cancer, ovarian cancer, pancreatic cancer, breast cancer, prostate cancer, bone cancer, lung cancer, non-small cell lung cancer, gastric cancer, colorectal cancer, cervical cancer, synovial sarcoma, head and neck cancer, squamous cell carcinoma, multiple myeloma, renal cell cancer, retinoblastoma, hepatoblastoma, hepatocellular carcinoma, melanoma, rhabdoid tumor of the kidney, Ewing's sarcoma, chondrosarcoma, brain cancer, glioblastoma, meningioma, pituitary adenoma, vestibular schwannoma, a primitive neuroectodermal tumor, medulloblastoma, astrocytoma, anaplastic astrocytoma, oligodendroglioma, ependymoma, choroid plexus papilloma, polycythemia vera, thrombocythemia, idiopathic myelofibrosis, soft tissue sarcoma, thyroid cancer, endometrial cancer, carcinoid cancer or liver cancer, breast cancer or gastric cancer) or an infectious disease (bacterial infection, a viral infection or a fungal infection) in the body of a subject comprising administering an effective amount of PD1 binder (*e.g.*, immunoglobulin single variable domain (ISVD) or multispecific ISVD such as a Nanobody) optionally in association with a further therapeutic agent to the subject. In an embodiment, the subject is also administered a further therapeutic agent or a therapeutic procedure in association with the PD1 binder.

In another aspect, there is provided a PD1 binder comprising one or more immunoglobulin single variable domains (ISVDs) that binds to PD1 comprising: a CDR1 comprising the amino acid sequence IHAMG (SEQ ID NO: 3) or GSIASIHAMG (SEQ ID NO: 6); a CDR2 comprising the amino acid sequence VITXSGGITYYADSVKG (SEQ ID NO: 4; wherein X is W or V) or VITXSGGITY (SEQ ID NO: 7; wherein X is W or V); and a CDR3 comprising the amino acid sequence DKHQSSXYDY (SEQ ID NO: 5, wherein X is W or F); comprising one or more mutations at a residue selected from 11 and 89, wherein said residue numbers are Kabat residue numbers. The present invention provides PD1 binders (*e.g.*, ISVDs such as Nanobodies) that bind to PD1 comprising: CDR1 comprising the amino acid sequence IHAMG (SEQ ID NO: 3) or GSIASIHAMG (SEQ ID NO: 6); CDR2 comprising the amino acid sequence VITXSGGITYYADSVKG (SEQ ID NO: 4; wherein X is W or V) or VITXSGGITY (SEQ ID NO: 7; wherein X is W or V); and CDR3 comprising the amino acid sequence DKHQSSXYDY (SEQ ID NO: 5, wherein X is W or F), which comprise one or more mutations at position 11 (*e.g.*, L11V) and 89 (*e.g.*, I89L) or one or more mutations selected from

E1D, L11V, A14P, W52aV, N73(Q, P or S), A74S, K83R, I89L, W100aF with respect to SEQ ID NO: 1 or 2. In an embodiment of the disclosure, the mutations are E1D, L11V, A14P, K83R and I89L; or L11V, A14P, K83R and I89L. In an embodiment, the mutations are E1D, L11V, A14P, W52aV, N73(Q, P or S), A74S, K83R, I89L, W100aF or L11V, A14P, W52aV, N73(Q, P or S), A74S, K83R, I89L, W100aF. In an embodiment, the PD1 binder comprises the amino acid sequence: DVQLVESGGG VVQPGGSLRL SCAASGSIAS IHAMGWFRQA PGKEREVAV ITWSGGITYY ADSVKGRFTI SRDNSKNTVY LQMNSLRPED TALYYCAGDK HQSSWYDYWG QGTLVTVSS (SEQ ID NO: 57).

The present disclosure also provides LAG3 binders that bind to LAG3 comprising CDR1 comprising the amino acid sequence GRTFSDYVMG (SEQ ID NO: 65); CDR2 comprising the amino acid sequence AISESGGRTH (SEQ ID NO: 66); and CDR3 comprising the amino acid sequence TLLWWTSEYAPIKANDYDY (SEQ ID NO: 67), *e.g.*, comprising the amino acid sequence: EVQLVE
 5 SGGGVVQPGG SLRLSCAASG RTFSDYVMGW FRQAPGKERE FVA AISESGG RTHYADSVKG RFTISRDNK
 NTLYLQMNSL RPEDTALYYC ATTLLWWTSE YAPIKANDYD YWGQGTLLTV SS (SEQ ID NO: 64). In another aspect, there is provided a LAG3 binder comprising an immunoglobulin single variable domain (ISVD) that binds to LAG3 comprising a CDR1 comprising the amino acid sequence GRTFSDYVMG (SEQ ID NO: 65) or DYVMG (amino acids 6-10 of SEQ ID NO: 65); a CDR2
 10 comprising the amino acid sequence AISESGGRTHYADSVKG (SEQ ID NO: 66) or AISESGGRTH (amino acids 1-10 of SEQ ID NO: 66); and a CDR3 comprising the amino acid sequence TLLWWTSEYAPIKANDYDY (SEQ ID NO: 67); and, optionally, a half-life extender and/or a C-terminal extender.

In another aspect, there is provided a multispecific binder comprising an immunoglobulin
 15 single variable domain (ISVD) that binds to PD1 comprising: a CDR1 comprising the amino acid sequence IHAMG (SEQ ID NO: 3) or GSIASIHAMG (SEQ ID NO: 6); a CDR2 comprising the amino acid sequence VITXSGGITYYADSVKG (SEQ ID NO: 4; wherein X is W or V) or VITXSGGITY (SEQ ID NO: 7; wherein X is W or V); and a CDR3 comprising the amino acid sequence DKHQSSXYDY (SEQ ID NO: 5, wherein X is W or F); and an immunoglobulin single
 20 variable domain that binds to LAG3 comprising: a CDR1 comprising the amino acid sequence GRTFSDYVMG (SEQ ID NO: 65) or DYVMG (amino acids 6-10 of SEQ ID NO: 65); a CDR2 comprising the amino acid sequence AISESGGRTHYADSVKG (SEQ ID NO: 66) or AISESGGRTH (amino acids 1-10 of SEQ ID NO: 66); and a CDR3 comprising the amino acid sequence TLLWWTSEYAPIKANDYDY (SEQ ID NO: 67); and, optionally, a half-life extender
 25 and/or a C-terminal extender. The PD1 and LAG3 binders may be in a single molecule such as a PD1/LAG3 binder, which is part of the present disclosure, that binds to PD1 and LAG3 that comprises: a PD1 binder comprising: CDR1 comprising the amino acid sequence IHAMG (SEQ ID NO: 3) or GSIASIHAMG (SEQ ID NO: 6); CDR2 comprising the amino acid sequence VITXSGGITYYADSVKG (SEQ ID NO: 4; wherein X is W or V) or VITXSGGITY (SEQ ID NO: 7;
 30 wherein X is W or V); and CDR3 comprising the amino acid sequence DKHQSSXYDY (SEQ ID NO: 5, wherein X is W or F); and a LAG3 binder comprising: CDR1 comprising the amino acid

sequence GRTFSDYVMG (SEQ ID NO: 65); CDR2 comprising the amino acid sequence AISESGGRTH (SEQ ID NO: 66); and CDR3 comprising the amino acid sequence TLLWWTSEYAPIKANDYDY (SEQ ID NO: 67); and, optionally, a half-life extender, *e.g.*, wherein the PD1 binder comprises the amino acid sequence:

5 DVQLVESGGG VVQPGGSLRL SCAASGSIAS IHAMGWFRQA PGKEREVAV ITWSGGITYY
ADSVKGRFTI SRDNSKNTVY LQMNSLRPED TALYYCAGDK HQSSWYDYWG QGTLVTVSS; and
(SEQ ID NO: 57); and the LAG3 binder comprises the amino acid sequence:

EVQLVE SGGGVVQPGG SLRLSCAASG RTFSDYVMGW FRQAPGKERE FVAAISESGG RTHYADSVKG
RFTISRDNK NTLYLQMNSL RPEDTALYYC ATTLLWWTSE YAPIKANDYD YWGQGTLLTV SS

10 (SEQ ID NO: 64); and, optionally, a half-life extender. For example, in an embodiment, the PD1/LAG3 binder comprises the moieties, *e.g.*, in the order shown:

- the PD1 binder 102C12 (E1D,L11V,A14P,A74S,K83R,I89L) or 1PD102C12 (E1D, L11V, A14P, W52aV, N73X (*e.g.*, N73P or N73Q or N73S), A74S, K83R, I89L, W100aF);
- 15 • a peptide linker such as 9GS, 20GS or 35 GS (*e.g.*,
GGGGSGGGSGGGSGGGSGGGSGGGSGGGSGGGSGGGGS (SEQ ID NO: 70));
- the LAG3 binder 11B09 or 11B09 (L11V,A14P,R41P,N43K,A62S,A74S,K83R,V89L);
- a peptide linker such as 9GS, 20GS or 35 GS (*e.g.*,
GGGGSGGGSGGGSGGGSGGGSGGGSGGGSGGGSGGGGS (SEQ ID NO: 70));
- 20 • a half-life extender such as ALB11002; and, optionally,

In an embodiment, the PD1 binder, LAG3 binder, HSA binder and/or PD1/LAG3 binder is in an injection device or vessel optionally in association with a further therapeutic agent. Such a device or vessel is part of the present disclosure. In another aspect, there is provided an injection device or vessel that comprises the binder as disclosed herein, optionally in association
5 with a further therapeutic agent.

The present disclosure also provides a polynucleotide encoding any of the binders set forth herein as well as any vector (*e.g.*, plasmid) comprising the polynucleotide as well as any host cell (*e.g.*, CHO or fungal cell such as *Pichia*, *e.g.*, *P. pastoris*) comprising the polynucleotide or vector, *e.g.*, ectopic or integrated into one or more host cell chromosomes. In another aspect,
10 there is provided a polynucleotide encoding the binder as disclosed herein. In another aspect, there is provided a vector comprising the polynucleotide as disclosed herein. In another aspect, there is provided a host cell comprising the polynucleotide or vector as disclosed herein.

The present disclosure, in another aspect, provides a method for making any of the binders set forth herein comprising introducing a polynucleotide encoding the binder into a host cell (*e.g.*,
15 CHO or fungal cell such as *Pichia*, *e.g.*, *P. pastoris*) and culturing the host cell in a medium under conditions favorable to expression of said binder from said polynucleotide and, optionally, purifying the binder from said host cell and/or said medium. Optionally, the vector or polynucleotide is integrated into one or more host cell chromosomes. In another aspect, there is provided a binder produced by such a method.

The present disclosure also provides a method for preventing PD1 from binding to PD-L1 and/or PD-L2 or for inhibiting any PD1 activity, *e.g.*, as discussed herein, comprising contacting said PD1 with a PD1 binder of the present disclosure (*e.g.*, a PD1/LAG3 binder) optionally in association with a further therapeutic agent. In another aspect, there is provided a method for preventing PD1 from binding to PD-L1 and/or PD-L2 comprising contacting the PD1 with said
20 binder as disclosed herein optionally in association with a further therapeutic agent. The present disclosure also provides a method for preventing LAG3 from binding to MHC class II or for inhibiting any PD1 activity, *e.g.*, as discussed herein comprising contacting said LAG3 with a LAG3 binder of the present disclosure (*e.g.*, a PD1/LAG3 binder) optionally in association with a further therapeutic agent. In another aspect, there is provided a method for preventing LAG3
25 from binding to MHC class II comprising
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contacting said LAG3 with a binder as disclosed herein, optionally in association with a further therapeutic agent. The present disclosure also provides a method for enhancing an immune response in the body of a subject (*e.g.*, a human) comprising administering an effective amount of binder of the present disclosure (*e.g.*, PD1/LAG3 binder) to the subject optionally in association with a further therapeutic agent. In another aspect, there is provided a binder as disclosed herein for use in enhancing an immune response in a subject, optionally in association with a further therapeutic agent. The present disclosure also provides a method for treating or preventing cancer (*e.g.*, metastatic cancer, a solid tumor or a hematologic cancer) or an infectious disease (*e.g.*, bacterial infection, a viral infection or a fungal infection) in the body of a subject (*e.g.*, a human) comprising administering an effective amount of binder of the present disclosure (*e.g.*, a PD1/LAG3 binder) optionally in association with a further therapeutic agent to the subject. When administered to a subject, a PD1 and/or LAG3 binder of the present disclosure (*e.g.*, a PD1/LAG3 binder) is

optionally administered in association with a further therapeutic agent or a therapeutic procedure *e.g.*, surgical tumorectomy.

In another aspect, there is provided use of a binder as disclosed herein in the manufacture of a medicament for the treatment or prevention of cancer or an infectious disease, optionally in association with a further therapeutic agent.

DESCRIPTION OF THE FIGURES

Figure 1. A table listing some of the amino acid positions that will be specifically referred to herein and their numbering according to some alternative numbering systems (such as Aho and IMGT)

Figure 2 (1-5). PD1 binder sequences.

Figure 3 (A-B). Alignment of 102C12 sequence with that of the SEQ ID NOs: 9-40 (see WO 2008/071447, SEQ ID NO: 348).

Figure 4. Predominant N-linked glycans for monoclonal antibodies produced in Chinese hamster ovary cells (CHO N-linked glycans) and in engineered yeast cells (engineered yeast N-linked glycans): squares: N-acetylglucosamine (GlcNAc); circles: mannose (Man); diamonds: galactose (Gal); triangles: fucose (Fuc).

Figure 5. Monovalent binding of CHO-K1 expressing human PD1 by F023700275 (1PD102C12(A14P,A74S,K83R)-FLAG3-HIS6) or F023700706 (1PD102C12(L11V,A14P,A74S,K83R,I89L)-FLAG3-HIS6). GAM=goat anti-mouse secondary antibody use to detect mouse antibody that binds to FLAG epitope; α -FLAG + GAM=goat anti-mouse secondary antibody used plus mouse antibody that binds to FLAG epitope that is at C-terminus of the construct.

Figure 6. Monovalent binding of 3A9 cells expressing human LAG3 by F0237611B09-FLAG-His6 or F023700842 (F0237611B09(L11V,A14P,R41P,N43K,A62S,A74S,K83R,V89L)-FLAG3-HIS6).

Figure 7 (A-B). Binding of (A) CHO expressing human PD-1 by F023700931, F023700924, F023700933 or F023700962 or (B) 3A9 expressing rhesus PD-1 by F023700931 (*Pichia* or CHO expressed), F023700924 (*Pichia* or CHO expressed), F023700933, F023700962, F023700678 (1PD102C12 (A14P,A74S,K83R)-35GS-ALB11002) or F023701127. ABH0074 + GAM=goat anti-mouse secondary antibody used plus mouse antibody ABH0074 that binds to nanobody frameworks.

conditions favorable to expression of said binder from said polynucleotide and, optionally, purifying the binder from said host cell and/or said medium.

20. A binder produced by the method of claim 19.

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21. A method for preventing PD1 from binding to PD-L1 and/or PD-L2 comprising contacting the PD1 with said binder of any one of claims 1, 2, 3 or 6-14 optionally in association with a further therapeutic agent.

10 22. A method for preventing LAG3 from binding to MHC class II comprising contacting said LAG3 with a binder of any one of claims 1-14, optionally in association with a further therapeutic agent.

15 23. A binder of any one of claims 1-14 for use in enhancing an immune response in a subject, optionally in association with a further therapeutic agent.

24. Use of a binder of any one of claims 1-14 in the manufacture of a medicament for the treatment or prevention of cancer or an infectious disease, optionally in association with a further therapeutic agent.

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25. The use of claim 24 wherein the cancer is metastatic cancer, a solid tumor, a hematologic cancer, leukemia, lymphoma, osteosarcoma, rhabdomyosarcoma, neuroblastoma, kidney cancer, leukemia, renal transitional cell cancer, bladder cancer, Wilm's cancer, ovarian cancer, pancreatic cancer, breast cancer, prostate cancer, bone cancer, lung cancer, non-small cell lung cancer, gastric cancer, colorectal cancer, cervical cancer, synovial sarcoma, head and neck cancer, squamous cell carcinoma, multiple myeloma, renal cell cancer, retinoblastoma, hepatoblastoma, hepatocellular carcinoma, melanoma, rhabdoid tumor of the kidney, Ewing's sarcoma, chondrosarcoma, brain cancer, glioblastoma, meningioma, pituitary adenoma, vestibular schwannoma, a primitive neuroectodermal tumor, medulloblastoma, astrocytoma, anaplastic astrocytoma, oligodendroglioma, ependymoma, choroid plexus papilloma, polycythemia vera,

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thrombocythemia, idiopathic myelofibrosis, soft tissue sarcoma, thyroid cancer, endometrial cancer, carcinoid cancer or liver cancer, breast cancer or gastric cancer.

26. The use of claim 24 wherein the infectious disease is a bacterial infection, a viral infection
5 or a fungal infection.

27. The use of any one of claims 24-26 further comprising a therapeutic agent or a therapeutic procedure in association with the binder.