CLAIMS

1. A method of producing a library, the method comprising the steps of:
   (1) contacting a library comprising a plurality of antigen-binding molecules having binding activity to a small molecule compound with the small molecule compound; and
   (2) concentrating nucleic acids from the library, wherein the nucleic acids encode a plurality of variants of antigen-binding molecules having binding activity to the small molecule compound;
   wherein the produced library comprises mainly:
   (i) a plurality of antigen-binding domains or antigen-binding molecules comprising an antigen-binding domain, which have different sequences from one another; or
   (ii) nucleic acids that encode the plurality of antigen-binding domains or antigen-binding molecules comprising an antigen-binding domain, which have different sequences from one another;
   wherein the aforementioned antigen-binding domains or antigen-binding molecules are antigen-binding domains or antigen-binding molecules comprising an antigen-binding domain whose antigen-binding activity varies depending on the concentration of a small molecule compound.

2. The method of claim 1, wherein the library used in step (1) is produced by a method comprising the steps of:
   (a) identifying amino acid sites that fulfill any one or more of (i) to (iii) below in antigen-binding domains whose antigen-binding activity varies depending on the concentration of a small molecule compound or in antigen-binding domains that have binding activity to a small molecule compound:
      (i) one or more amino acid sites that are not involved in the binding to the small molecule compound;
      (ii) one or more amino acid sites that show diversity of amino acid occurrence frequency in the antibody repertoire of the animal species to which the parent antigen-binding domain belongs; and
      (iii) one or more amino acid sites that are not important for canonical structure formation; and
   (b) designing a library that comprises nucleic acids encoding unmodified antigen-binding domains/molecules, and nucleic acids that encode individually a plurality of variants of the aforementioned antigen-binding domains or antigen-binding molecules comprising an antigen-binding domain which have different sequences from one another and have modifications at one or more of the amino acid sites identified in step (a).

3. The method of claim 1, wherein the library used in step (1) of claim 1 is produced by a method comprising the steps of:

(a) identifying amino acid sites that fulfill any one or more of (i) to (iii) below in antigen-binding domains whose antigen-binding activity varies depending on the concentration of a small molecule compound or in antigen-binding domains that have binding activity to a small molecule compound:

(i) one or more amino acid sites that are not involved in the binding to the small molecule compound;

(ii) one or more amino acid sites that show diversity of amino acid occurrence frequency in the antibody repertoire of the animal species to which the parent antigen-binding domain belongs; and

(iii) one or more amino acid sites that are not important for canonical structure formation;

(b) producing a plurality of variants of the aforementioned antigen-binding domains or antigen-binding molecules comprising an antigen-binding domain, which have different sequences from one another and have modifications at one or more of the amino acid sites identified in step (a);

(c) identifying one or more amino acid modifications that do not substantially change the binding activity of each of the aforementioned variants to the small molecule compound; and

(d) producing a library comprising nucleic acids that encode unmodified antigen-binding domains/molecules, and nucleic acids that encode a plurality of variants of the aforementioned antigen-binding domains or antigen-binding molecules comprising an antigen-binding domain, which have different sequences from one another and have one or more of the amino acid modifications identified in step (c).

4. The method of any one of claims 1 to 3, wherein the aforementioned antigen-binding molecules are antigen-binding molecules that comprise heavy-chain variable regions and light-chain variable regions of an antibody, and the library used in step (1) of claim 1 is produced by a method comprising any one of the steps of:

1) designing a library by concentrating nucleic acids that encode a plurality of variants of antigen-binding molecules having binding activity to a small molecule compound from a library which comprises nucleic acids encoding one or more variants produced by modifying amino acids positioned in the heavy chain variable regions;

2) designing a library by concentrating nucleic acids that encode a plurality of variants of antigen-binding molecules having binding activity to a small molecule compound from a library which comprises nucleic acids encoding one or more variants produced by modifying amino acids positioned in the light chain variable regions; and

3) designing a library by combining the antigen-binding molecule-encoding nucleic acids concentrated from each of the variable region libraries of steps 1) and 2).

5. The method of any one of claims 1 to 4, wherein the aforementioned antigen-binding molecules are fusion polypeptides formed by fusing an antigen-binding domain with at least a portion of a virus coat protein.

6. The method of any one of claims 1 to 4, wherein the aforementioned antigen-binding molecules are antigen-binding molecules comprising antibody heavy chains and light chains, and the method further comprises a step of designing a synthetic library of the heavy chains and/or light chains.

7. The method of claim 6, wherein the antibody heavy chains variable regions and/or light chain variable regions comprise a germline-derived framework sequence.

8. The method of any one of claims 1 to 7, wherein the aforementioned small molecule compound is a target tissue-specific compound or an unnatural compound.

9. The method of claim 8, wherein the aforementioned target tissue is a cancer tissue or an inflammatory tissue, and the aforementioned small molecule compound is a cancer tissue-specific compound or an inflammatory tissue-specific compound.

10. The method of claim 9, wherein the cancer tissue-specific compound is at least one compound selected from the group consisting of nucleosides that have a purine ring structure, amino acids and their metabolites, lipids and their metabolites, primary metabolites from sugar metabolism, and nicotinamide and its metabolites.

11. The method of any one of claims 1 to 10, wherein the small molecule compound is adenosine, adenosine monophosphate, adenosine diphosphate, adenosine triphosphate or kynurenine.

12. The method of any one of claims 2 to 11, wherein the amino acid sites not involved in binding with the small molecule compound are sites other than any one or more of the amino acids selected from below:
H chain: 33, 50, 52, 56, 57, 58, 99, 100, 100a, 54, 55, 97, 100c, 101, 94, 95, 100d, 100e (Kabat Numbering); and
L chain: 95c, 96, 95a, 95b, 49, 55 (Kabat Numbering).

13. A method for producing an antigen-binding molecule comprising an antigen-binding domain whose antigen-binding activity varies depending on the concentration of a small molecule compound, which comprises the steps of:

(a) contacting a library produced by the method of any one of claims 1 to 12 with an antigen in the

absence of a small molecule compound;

(b) selecting an antigen-binding domain that does not bind to the antigen in step (a) above;

(c) contacting the antigen-binding domain selected in step (b) above with the antigen in the presence of the small molecule compound;

(d) selecting the antigen-binding domain that binds to the antigen in step (c) above;

(e) linking the polynucleotide that encodes the antigen-binding domain selected in step (d) above with a polynucleotide that encodes a polypeptide comprising an Fc region;

(f) culturing a cell introduced with a vector in which the polynucleotide obtained in step (e) above is operably linked; and

(g) collecting the antigen-binding molecule from the culture solution of the cell cultured in step (f) above.

14. A method for producing an antigen-binding molecule comprising an antigen-binding domain whose antigen-binding activity varies depending on the concentration of a small molecule compound, which comprises the steps of:
    (a) contacting a library produced by the method of any one of claims 1 to 12 with an antigen in the presence of a small molecule compound;
    (b) collecting an antigen-binding domain by dissociating it using the small molecule compound at a lower concentration than in step (a) above;
    (c) linking the polynucleotide that encodes the antigen-binding domain collected in step (b) above with a polynucleotide that encodes a polypeptide comprising an Fc region;
    (d) culturing a cell introduced with a vector in which the polynucleotide obtained in step (c) above is operably linked; and
    (e) collecting the antigen-binding molecule from the culture solution of the cell cultured in step (d) above.

15. A method for producing an antigen-binding molecule that comprises an antigen-binding domain whose antigen-binding activity varies depending on the concentration of a small molecule compound, which further comprises the steps of:
    (a) contacting a library that comprises mainly:
        (i) a plurality of antigen-binding domains or antigen-binding molecules comprising an antigen-binding domain, which have different sequences from one another; or
        (ii) nucleic acids that encode the plurality of antigen-binding domains or antigen-binding molecules comprising an antigen-binding domain, which have different sequences from one another;

and wherein the aforementioned antigen-binding domains comprising an antigen-binding domain whose antigen-binding activity varies depending on the concentration of a small molecule compound;
with a small molecule compound; and
(b) selecting antigen-binding domains that bind to the small molecule compound.

16. The method of claim 15 that further comprises the steps of:
(c) contacting the antigen-binding domains selected in step (b) with an antigen in the absence of a small molecule compound;
(d) selecting an antigen-binding domain that does not bind to the antigen in step (c) above;
(e) contacting the antigen-binding domain selected in step (c) above with the antigen in the presence of the small molecule compound;
(f) selecting the antigen-binding domain that binds to the antigen in step (e) above;
(g) linking the polynucleotide that encodes the antigen-binding domain selected in step (f) above with a polynucleotide that encodes a polypeptide comprising an Fc region;
(h) culturing a cell introduced with a vector in which the polynucleotide obtained in step (g) above is operably linked; and
(i) collecting the antigen-binding molecule from the culture solution of the cell cultured in step (h) above.

17. The method of claim 15 that further comprises the steps of:
(c) contacting the antigen-binding domains selected in step (b) with an antigen in the presence of a small molecule compound;
(d) collecting an antigen-binding domain by dissociating it using the small molecule compound at a lower concentration than in step (c) above;
(e) linking the polynucleotide that encodes the antigen-binding domain collected in step (d) above with a polynucleotide that encodes a polypeptide comprising an Fc region;
(f) culturing a cell introduced with a vector in which the polynucleotide obtained in step (e) above is operably linked; and
(g) collecting the antigen-binding molecule from the culture solution of the cell cultured in step (f) above.

18. The method of any one of claims 14 to 17 for producing an antigen-binding molecule, wherein the small molecule compound is adenosine, adenosine monophosphate, adenosine diphosphate, adenosine triphosphate or kynurenine.

19. An antigen-binding molecule comprising an antigen-binding domain whose antigen-binding activity varies depending on the concentration of an unnatural compound.

20. A pharmaceutical composition that comprises the antigen-binding molecule of claim 19.