

WHAT IS CLAIMED IS:

1. A method for producing an antibody that specifically binds to a protein comprising:

(a) producing a plurality of extracellular vesicles (EVs) comprising a heterologous protein by (i) expressing the heterologous protein in a cell exposed to a vesicle factor, (ii) culturing the cell in a medium and (iii) isolating the plurality of EVs comprising the heterologous protein from the medium, wherein the vesicle factor is selected from the group consisting of Acyl.Hrs, ARRDC1, ARF6 and a combination thereof;

(b) immunizing an animal by administering the plurality of EVs to the animal; and

(c) isolating an antibody that binds to the heterologous protein from the animal.

2. The method of claim 1, wherein the cell is a non-adherent cell.

~~3. A method for producing an antibody that specifically binds to a protein comprising:~~

~~(a) producing a plurality of extracellular vesicles (EVs) comprising a heterologous protein by (i) expressing the heterologous protein in a cell, (ii) culturing the cell in a medium and (iii) isolating the plurality of EVs comprising the heterologous protein from the medium, wherein the cell is a non-adherent cell;~~

~~(b) immunizing an animal by administering the plurality of EVs to the animal; and~~

~~(c) isolating an antibody that binds to the heterologous protein from the animal.~~

~~4. The method of claim 3, wherein producing the plurality of EVs further comprises expressing a vesicle factor in the cell.~~

~~5.3.~~ The method of claim ~~41~~, wherein the vesicle factor is selected from the group consisting of ~~MLGag~~, Acyl.Hrs, ARRDC1, ARF6 and a combination thereof.

~~6.4.~~ The method of any one of claims 1-~~53~~, wherein the heterologous protein is a membrane protein.

~~7.5.~~ The method of claim ~~64~~, wherein the membrane protein is a single-pass membrane protein.

~~8.6.~~ The method of claim ~~64~~, wherein the membrane protein is a multi-pass membrane protein.

9.7. The method of any one of claims ~~64-86~~, wherein the membrane protein is a member of a protein complex.

10.8. The method of claim ~~64~~, wherein the membrane protein is not a transmembrane protein but is a protein that is part of a complex with a transmembrane protein.

11.9. The method of any one of claims 2-~~108~~, wherein the non-adherent cell is a 293S cell or an Expi293F™ cell.

12.10. The method of any one of claims 1-~~119~~, wherein the EVs are isolated from the medium by ultracentrifugation.

13.11. The method of any one of claims 1-~~1210~~, wherein the plurality of EVs is administered to the animal on week 0, week 2 and week 4.

14.12. The method of any one of claims 1-~~1311~~, further comprising administering an adjuvant to the animal concurrently with the EVs.

15.13. The method of claim ~~1412~~, wherein the adjuvant is a Ribi adjuvant.

16.14. The method of any one of claims 1-~~1513~~, further comprising administering a boost to the animal to enhance an immune response in the animal to the protein.

17.15. The method of claim ~~1614~~, wherein the boost comprises the protein, a polynucleotide encoding the protein or a combination thereof.

18.16. The method of claim ~~1715~~, wherein the boost comprises the protein.

19.17. The method of claim ~~1715~~, wherein the boost comprises a polynucleotide encoding the protein.

20.18. The method of any one of claims 1-~~1917~~, wherein the antibody is a monoclonal antibody.

21.19. The method of any one of claims 1-~~2018~~, wherein the antibody is a human, humanized or chimeric antibody.

22.20. An isolated antibody or an antigen-binding portion thereof produced by the method of any one of claims 1-~~2119~~.

23.21. An isolated nucleic acid encoding the antibody or antigen-binding portion thereof of claim ~~2220~~.

~~24.22.~~ A host cell comprising the nucleic acid of claim ~~23~~21.

~~25.23.~~ A method of producing an antibody or antigen-binding portion thereof comprising culturing the host cell of claim ~~24~~22 under conditions suitable for expression of the antibody.

~~26.24.~~ The method of claim ~~25~~23, further comprising recovering the antibody from the host cell.

~~27.25.~~ A pharmaceutical composition comprising the isolated antibody or antigen-binding portion thereof of claim ~~22~~20 and a pharmaceutically acceptable carrier.

~~28.26.~~ The pharmaceutical composition of claim ~~27~~25, further comprising an additional therapeutic agent.

~~29.27.~~ The isolated antibody or antigen-binding portion thereof of claim ~~22~~20 for use as a medicament.

~~30.28.~~ The isolated antibody or antigen-binding portion thereof of claim ~~22~~20 for use in treating a disease.

~~31.29.~~ Use of the isolated antibody or antigen-binding portion thereof of claim ~~22~~20 in the manufacture of a medicament.

~~32.30. Use of the isolated antibody or antigen-binding portion thereof of claim 20 in the manufacture of a medicament for A method of treating an individual having a disease comprising administering to the individual an effective amount of the isolated antibody or antigen-binding portion thereof of claim 22.~~

~~33.31. The method use of claim 32-30, wherein the medicament is to be further comprising administering administered with an additional therapeutic agent to the individual.~~

~~34.32. The pharmaceutical composition of claim 25 or 26 for use in A method of treating an individual having a disease comprising administering to the individual the pharmaceutical composition of claim 27 or 28.~~

~~35. A method for detecting an antibody in a sample comprising:~~

~~(a) incubating a sample with a capture reagent, wherein the capture reagent comprises a plurality of EVs comprising membrane-bound antigen, and the antibody binds specifically to the membrane-bound antigen; and~~

~~(b) contacting the antibody binding to the capture reagent with a detectable antibody to detect the bound antibody, wherein the detectable antibody binds specifically to the antibody;~~

~~wherein the plurality of EVs are generated by (i) expression of the membrane-bound antigen in a cell, (ii) culturing the cell *in vitro* in a medium to produce the plurality of EVs displaying the membrane-bound antigen and (iii) isolating the plurality of EVs displaying the membrane-bound antigen from the medium, and~~

~~wherein the cell is exposed to a vesicle factor selected from the group consisting of Acyl.Hrs, ARRDC1, ARF6 and a combination thereof and/or the cell is a non-adherent cell.~~

~~36. The method of claim 35 further comprising (c) measuring the amount of the antibody detected in (b), wherein the amount is quantitated using a standard curve.~~

~~37. The method of claim 35 or 36, wherein the sample is a plasma, a serum or a urine sample.~~

~~38. The method of any one of claims 35-37, wherein the capture reagent is immobilized on a solid support.~~

~~39. The method of claim 38, wherein the solid support is a microtiter plate.~~

~~40. The method of any one of claims 35-39, wherein the detectable antibody is fluorescently labeled.~~

~~41. The method of any one of claims 35-40, wherein the membrane-bound antigen is a membrane protein or a fragment thereof.~~

~~42. A method for sorting antibody-producing cells comprising:~~

~~(a) incubating the antibody-producing cells with a plurality of EVs wherein the plurality of EVs comprise:~~

~~i. a first population of EVs comprising a membrane-bound antigen and a first detectable marker, wherein a subset of the antibody-producing cells bind specifically to the membrane-bound antigen; and~~

~~ii. a second population of EVs lacking the membrane-bound antigen but comprising a second detectable marker distinguishable from the first marker; and~~

~~(b) sorting the antibody-producing cells based on their binding to either the first population of EVs or to a combination of the first population of EVs and the second population of EVs;~~

~~wherein the first population of EVs is generated by (i) expression of the membrane-bound antigen and the first detectable marker in a first cell, (ii) culturing the first cell *in vitro* in a medium to produce the plurality of EVs displaying the membrane-bound antigen and (iii) isolating the plurality of EVs displaying the membrane-bound antigen from the medium,~~

~~wherein the second population of EVs is generated by (i) expression of the second detectable marker in a second cell, (ii) culturing the second cell *in vitro* in a medium to produce the plurality of EVs comprising the second detectable marker and (iii) isolating the plurality of EVs displaying the second detectable marker from the medium, and~~

~~wherein (i) the first cell and/or the second cell is exposed to a vesicle factor selected from the group consisting of Acyl.Hrs, ARRDC1, ARF6 and a combination thereof and/or (ii) the first and/or second cell is a non-adherent cell.~~

~~43. The method of claim 42, where the first and second detectable markers are fluorescent markers.~~

~~44. The method of claim 43, wherein the first and second fluorescent markers are fluorescent proteins.~~

~~45. The method of any one of claims 42-44, wherein the sorting is performed by fluorescence-activated cell sorting.~~

~~46. The method of any one of claims 42-45, wherein the antibody-producing cells are B cells.~~

~~47. The method of any one of claims 42-45, wherein the antibody-producing cells are hybridoma cells.~~

~~48.~~33. A method for producing a plurality of extracellular vesicles (EVs) displaying a protein, comprising:

- (a) expressing a heterologous protein in a cell;
- (b) culturing the cell in a medium; and
- (c) isolating the plurality of EVs comprising the heterologous protein from the medium,

wherein the cell is exposed to a vesicle factor selected from the group consisting of Acyl.Hrs, ARRDC1, ARF6 and a combination thereof ~~and/or the cell is a non-adherent cell.~~

~~49.~~34. The method of claim ~~48~~33, wherein the heterologous protein is a membrane protein.

~~50.~~35. The method of claim ~~49~~34, wherein the membrane protein is a single-pass membrane protein.

~~51.36.~~ The method of claim ~~4934~~, wherein the membrane protein is a multi-pass membrane protein.

~~52.37.~~ The method of any one of claims ~~4934-5136~~, wherein the membrane protein is a member of a protein complex.

~~53.38.~~ The method of any one of claims ~~3533-5237~~, wherein the cell is a non-adherent cell which is a 293S cell or an Expi293F™ cell.

~~54.39.~~ The method of any one of claims ~~3533-5338~~, wherein the plurality of EVs are isolated from the medium by ultracentrifugation.

~~55.—— A kit for detecting an antibody in a sample comprising:~~

~~(a) a capture reagent that comprises a plurality of EVs comprising membrane bound antigen, wherein the antibody to be detected binds specifically to the antigen; and~~

~~(b) a detectable antibody that binds specifically to the antibody to be detected,~~

~~wherein the plurality of EVs are generated by (i) expression of the membrane bound antigen in a cell, (ii) culturing the cell *in vitro* in a medium to produce the plurality of EVs displaying the membrane bound antigen and (iii) isolating the plurality of EVs displaying the membrane bound antigen from the medium, and~~

~~wherein the cell is exposed to a vesicle factor selected from the group consisting of Aeyl.Hrs, ARRDC1, ARF6 and a combination thereof and/or the cell is a non-adherent cell.~~

~~56.—— The kit of claim 55, wherein the plurality of EVs are immobilized on a solid support.~~

~~57.—— The kit of claim 55 or 56, wherein the solid support is a microtiter plate.~~

~~58.—— The kit of any one of claims 55-57, wherein the detectable antibody is fluorescently labeled.~~

~~59.—— The kit of any one of claims 55-58, wherein the membrane bound antigen is a membrane protein or a fragment thereof.~~