CLAIMS:

[Claim 1]. ~~A method for producing a neoglycoconjugate, the method comprising:~~

~~(a) providing a neocarbohydrate antigen or neocarbohydrate antigen intermediate comprising a linker having a first end and a second end, wherein the first end is conjugated to a carbohydrate antigen via a thio-ether bond and the second end comprises a functional group reactable with a free amine group, the functional group being -COX, $-SO_2X$, -O-C(O)-X, -N=C=O , or -N=C=S, wherein X is a leaving group;~~

~~(b) providing a carrier protein or peptide having one or more free amine groups; and~~

~~(c) performing a coupling reaction to conjugate one or more of the purified neocarbohydrate antigens or neocarbohydrate antigen intermediates to the carrier protein or peptide at the one or more free amine groups via an amide, a carbamate, a sulfonamide, a urea, or a thiourea bond, thereby producing the neoglycoconjugate.~~

~~2. The method of claim 1, wherein prior to step (a), the neocarbohydrate antigen or neocarbohydrate antigen intermediate in (a) is prepared by a method comprising:~~

~~(i) providing a carbohydrate antigen covalently linked to a terminal alkene (alkenyl carbohydrate antigen), the terminal alkene being directly conjugatable to a thiol group via a thiol-ene reaction;~~

~~(ii) providing a thio-linker comprising a first functional group at a first end and a second functional group at a second end, the first functional group being a free thiol group and the second functional group being a carboxyl group, sulfinic acid group, carbonic acid group, isocyanate group, or thiocyanate group;~~

~~(iii) performing a photocatalytic thiol-ene reaction to directly conjugate the alkenyl carbohydrate antigen to the thio-linker at the first end, thereby producing a neocarbohydrate antigen comprising the carbohydrate antigen at the first end and the second functional group at a second end;~~

~~(iv) when the second functional group is a carboxyl group, sulfinic acid group, or carbonic acid group, converting the neocarbohydrate antigen to a neocarbohydrate antigen intermediate by replacing the carboxyl group's, sulfinic acid group's, or carbonic acid group's terminal hydroxyl group with a better leaving group for conjugation to a free amine group of a polypeptide; and~~

~~(v) purifying the neocarbohydrate antigen or the neocarbohydrate antigen intermediate.~~

3. The method of claim 2, wherein the photocatalytic thiol-ene reaction in (iii) is performed under reaction conditions that retain the carbohydrate antigen's antigenicity, and/or structure.

4. The method of claim 2 or 3, wherein said photocatalytic thiol-ene reaction is performed in the presence of a catalyst, wherein the catalyst is:

- a water-soluble catalyst, such as a water-soluble free radical-generating azo compound; 2,2'-azobis[2-(2-imidazolin-2-yl)propane]dihydrochloride (Vazo-44 or VA-044); 2,2'-azobis(2-amidinopropane) dihydrochloride (AAPH); lithium phenyl-2,4,6-trimethylbenzoylphosphinate (LAP); metals or metal ions having photoinitiator activity; a peroxide; *tert*-butyl hydroperoxide; benzoylperoxide; ammonium persulfate; or any derivative thereof having photoinitiator activity; or
- a water-insoluble catalyst, such as a water-insoluble free radical-generating azo compound, 2,2-dimethoxy-2-phenylacetophenone (DMPA), azobisisobutyronitrile (AIBN), 2,2′-azobis(2-methylpropionitrile), 4,4′-Azobis(4-cyanopentanoic acid) (ACVA), 1,1′-azobis(cyanocyclohexane) (ACHN), diazenedicarboxylic acid bis(*N*,*N*-dimethylamide) (TMAD); azodicarboxylic acid dipiperidide (ADD), or any derivative thereof having photoinitiator activity.

5. The method of any one of claims 2 to 4, wherein said photocatalytic thiol-ene reaction comprises irradiation under ultraviolet light (e.g., short-wave ultraviolet light such as at about 254 nm, or long-wave ultraviolet light such as at about 355 nm or 365 nm).

6. The method of any one of claims 2 to 5, wherein:

- said photocatalytic thiol-ene reaction comprises reacting between 1 to 200 or 1 to 100 molar equivalents of the alkenyl carbohydrate antigen per free thiol group of the thio-linker;
- said photocatalytic thiol-ene reaction is performed for 10 to 300, 10 to 270, 10 to 240, 10 to 210, 10 to 180, 10 to 150, 10 to 120, 10 to 90, 10 to 60, or 10 to 30 minutes;
- is performed at a pH between about 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, or 4.0, and about 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, or 10; or
- any combination thereof.

7. The method of any one of claims 2 to 6, wherein said carbohydrate antigen is linked to the terminal alkene preferably using a linker, by a via glycosidic bond, such as is an O-glycosidic bond, an S-

glycosidic bond, an N-glycosidic bond, or a C-glycosidic bond, or a bond obtained by reductive amination, such as between an allyl amine and a reducing sugar.

8. The method of any one of claims 2 to 7, wherein the thio-linker in (ii) comprises the structure:



wherein:

- Y is $-(CH_2)_n-$ or $-(OCH_2CH_2O)_n-$;
- Z is $-CO_2H$, $-SO_2H$, $-O-C(O)-H$, $-N=C=O$, or $-N=C=S$;
- O is 1, 2, 3, 4, or 5; O is 0 and Z is $-CO-$ and Y is $-(OCH_2CH_2O)_n-$; or O is 0 and Z is $-SO_2-$ and Y is $-(OCH_2CH_2O)_n-$.

9. The method of any one of claims 1 to 8, wherein the carbohydrate portion of the carbohydrate antigen, the alkenyl carbohydrate antigen, the neocarbohydrate antigen, the neocarbohydrate antigen intermediate, and/or the neoglycoconjugate remain unprotected throughout the method.

10. The method of any one of claims 1 to 9, wherein the leaving group is an active ester group (e.g., a fluorophenyl group (e.g., OPhF5, OPhF4 (para SO_3Na)), or a succinimidyl group).

11. The method of any one of claims 1 to 10, wherein the method avoids carrier protein or peptide self-crosslinks between aspartic/glutamic acid residues and ε-lysine amines present in the same carrier protein or peptide.

12. The method of any one of claims 1 to 11, wherein the number of neocarbohydrate antigens conjugated to the carrier protein or peptide is controlled by the efficacy and/or stoichiometry of the reactants (e.g., the molar ratio of the carrier protein or peptide to the neocarbohydrate antigen or the neocarbohydrate antigen intermediate).

13. The method of any one of claims 1 to 12, wherein the carbohydrate antigen is or comprises:

- a tumor associated carbohydrate antigen (TACA) (e.g., Tn, S-Tn, *Thomsen-Friedenreich* (TF), (2,3)-S-TF, (2,6)-S-TF, Globo H, PSA, GD2, GD3, GM2, GM3, N-glycolyl-GM3, Fucosyl GM1, Le^a, sLe^a, Le^x, sLe^x, Le^y, or any combination thereof);
- a viral polysaccharide antigen; or

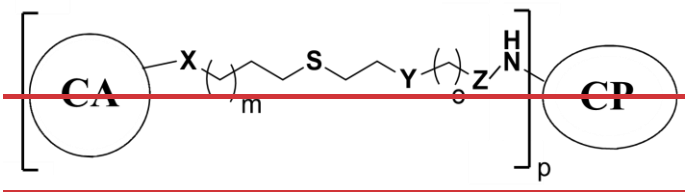
- a bacterial capsular polysaccharide (CPS) (e.g., a CPS which is, is from, or comprises a Pneumococcal and/or Streptococcal polysaccharide serotype, meningococcal CPS, or influenza CPS (such as influenza type a or b CPS).

14. The method of any one of claims 1 to 19, wherein the coupling reaction in (c) conjugates at least two of the same neocarbohydrate antigen or more than one type of neocarbohydrate antigen to the carrier protein or peptide, thereby producing a multi-valent neoglycoconjugate (e.g., a multi-valent neoglycoconjugate comprising 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or more of the same or different types of neocarbohydrate antigens conjugated to the carrier protein or peptide).

15. The method of any one of claims 1 to 14, wherein the carrier protein or peptide is a protein or peptide that was engineered to add one or more further lysine residues, for example at the amino terminus, the carboxy terminus, or at a solvent-accessible position of the carrier protein or peptide.

16. The method of any one of claims 1 to 15, wherein the carrier protein or peptide is, is from, or comprises: Tetanus Toxoid (TT), Diphtheria Toxoid (DT), cross-reacting material 197 (CRM197), Meningococcal Outer Membrane Protein Complex (OMPC), H. Influenzae Protein D (HiD), a cytokine, an immunogenic peptide such as Tetanus Toxin 831-844 (**SEQ ID NO: 1 or 2**), albumin (such as bovine serum albumin or human serum albumin), keyhole limpet hemocyanin (KLH), or an immunogenic fragment thereof.

17. The method of any one of claims 1 to 16, wherein the neoglycoconjugate has the structure:



wherein:

- CA is or comprises the carbohydrate antigen;
- CP-NH is the carrier protein or peptide having one or more amine groups;
- X is O, S, NR_1, or CH_2 ;
- R_1 is H, COH (formamide), COMe, or COEt ;
- m is 1, 2, 3, 4, or 5 ;
- Y is $-(CH_2)_n-$ or $-(OCH_2CH_2O)_n-$;
- n is 0, 1, 2, 3, 4, or 5 ;

- o is 0, 1, 2, 3, 4, or 5 ; or o is 0 and Z is -CO- and Y is $-(OCH_2CH_2O)_n-$; or o is 0 and Z is $-SO_2-$ and Y is $-(OCH_2CH_2O)_n-$;
- Z is -CO- , $-NR_2SO_2-$, -OCO- , $-NR_2CO-$, or $-NR_2CS-$,
- R_2 is H, Me, or Et ; and
- p is 1 to 50.

18. The method of any one of claims 1 to 18, wherein the neoglycoconjugate is a neoglycoconjugate immunogen, the carrier protein or peptide is immunogenic when administered to a subject, and conjugation of the carbohydrate antigen to the carrier protein or peptide via the thio-linker increases the immunogenicity of the carbohydrate antigen upon administration to the subject as compared to a corresponding administration of the unconjugated carbohydrate antigen.

19. The method of claim 18, wherein the thio-linker is non-immunogenic to the subject such that administration of the neoglycoconjugate immunogen to the subject does not trigger antibodies against the thio-linker comprised in the neoglycoconjugate immunogen.

20. The method of claim 18 or 19, wherein said neocarbohydrate antigen, following conjugation to the carrier protein or peptide, is not cleavable from the carrier protein or peptide by an endogenous enzyme of the subject.

21. The method of any one of claims 18 to 20, wherein the neocarbohydrate antigen comprises a B cell epitope, and/or induces a humoral immune response in the subject; and/or comprises a T cell epitope, and/or induces a cell-mediated immune response in the subject.

22. The method of any one of claims 18 to 21, wherein the carrier protein or peptide comprises a human T cell epitope, and/or induces a cell-mediated immune response in the subject.

23. The method of any one of claims 18 to 22, wherein the neoglycoconjugate immunogen induces a cell-mediated immune response to the carbohydrate antigen upon administration to the subject.

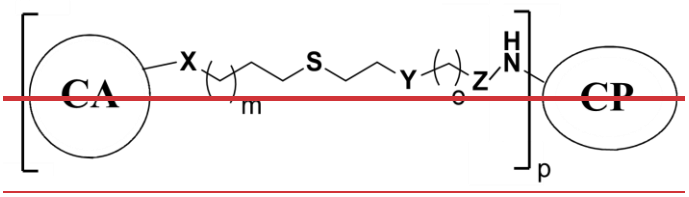
24. A neocarbohydrate antigen or neocarbohydrate antigen intermediate comprising a linker having a first end and a second end, wherein the first end is conjugated to a carbohydrate antigen via a thio ether bond and the second end comprises a functional group reactable with a free amine group, the functional group being -COX, $-SO_2X$, -O-C(O)-X, -N=C=O , or -N=C=S, wherein X is a leaving group.

25. The neocarbohydrate antigen or neocarbohydrate antigen intermediate of claim 24, wherein:

- the carbohydrate antigen is unprotected;
- the leaving group is as defined in claim 10;
- the carbohydrate antigen is as defined in claim 13; or
- any combination thereof.

26. A synthetic neoglycoconjugate comprising a linker having a first end and a second end, wherein the first end is conjugated to a carbohydrate antigen via a thio ether bond and the second end is conjugated to a carrier protein or peptide at one or more free amine groups therein via an amide, a carbamate, a sulfonamide, a urea, or a thiourea bond.

27. A synthetic neoglycoconjugate comprising one or more carbohydrate antigens (CA) conjugated to one or more amine groups of a carrier protein or peptide (CP-NH) via a linker, the synthetic neoglycoconjugate having the structure:



wherein:

- X is O, S, NR_1, or CH_2 ;
- R_1 is H, COH (formamide), COMe, or COEt ;
- m is 1, 2, 3, 4, or 5 ;
- Y is $-(CH_2)_n-$ or $-(OCH_2CH_2O)_n-$;
- n is 0, 1, 2, 3, 4, or 5 ;
- o is 0, 1, 2, 3, 4, or 5 ; or o is 0 and Z is -CO- and Y is $-(OCH_2CH_2O)_n-$; or o is 0 and Z is $-SO_2-$ and Y is $-(OCH_2CH_2O)_n-$;
- Z is -CO- , $-NR_2SO_2-$, -OCO- , $-NR_2CO-$, or $-NR_2CS-$;
- R_2 is H, Me, or Et ; and
- p is 1 to 50.

28. The synthetic neoglycoconjugate of claim 26 or 27, wherein:

- the carbohydrate antigen is unprotected;
- the carbohydrate antigen is as defined in claim 13;

- the neoglycoconjugate is a multivalent neoglycoconjugate as defined in claim 14;
- the carrier protein or peptide is as defined in claim 15, 16, 18, or 22;
- the neoglycoconjugate has the structure as defined in claim 17;
- the linker is as defined in claim 19;
- the neocarbohydrate antigen is as defined in claim 20 or 21;
- the synthetic neocarbohydrate is produced by the method of any one of claims 1 to 25; or
- any combination thereof.

29. A method for producing a neoglycoconjugate vaccine or an adaptive immune response-triggering composition, the method comprising formulating the neoglycoconjugate prepared by the method of any one of claims 1 to 23 or as defined in any one of claims 24 to 28, with a pharmaceutically acceptable excipient, and/or an adjuvant.

30. The method of claim 29, wherein the adjuvant is or comprises: an inorganic compound, a mineral oil, a microbial derivative, a plant derivative, a cytokine, squalene, alum, aluminum hydroxide, aluminum phosphate, calcium phosphate hydroxide, a toll-like receptor agonist, an immunostimulatory polynucleotide (such as CPG), an immunostimulatory lipid, Freund's adjuvant, RIBI's adjuvant, QS-21, muramyl dipeptide, TiterMax, Steviune, Stimune, or any combination thereof.

31. A neoglycoconjugate vaccine or an adaptive immune response-triggering composition produced by the method of claim 29 or 30, and/or comprising the neoglycoconjugate as defined in any one of claims 1 to 28 and a pharmaceutically acceptable excipient and/or an adjuvant.

32. The neoglycoconjugate vaccine of claim 31, which is a prophylactic vaccine or a therapeutic vaccine (e.g., against cancers that expresses tumor associated carbohydrate antigens, such as breast cancer, prostate cancer, stomach cancer, B-cell lymphoma, colon cancer, lung cancer, melanoma, neuroblastoma, ovarian cancer, sarcoma, small cell lung cancer; or against viruses or bacteria that express carbohydrate antigens).

33. A method of immunizing, vaccinating, or treating a subject comprising administering to the subject the neoglycoconjugate produced by the method of any one of claims 1 to 23, the synthetic neoglycoconjugate of any one of claims 26 to 28, the neoglycoconjugate vaccine or an adaptive immune

~~response-triggering composition produced by the method of claim 29 or 30, or the neoglycoconjugate vaccine of claim 31 or 32.~~

~~34. The neoglycoconjugate produced by the method of any one of claims 1 to 23, the synthetic neoglycoconjugate of any one of claims 26 to 28, the neoglycoconjugate vaccine or an adaptive immune response-triggering composition produced by the method of claim 29 or 30, or the neoglycoconjugate vaccine of claim 31 or 32, for use in immunizing, vaccinating, or treating a subject having a disease (e.g., cancers that expresses tumor associated carbohydrate antigens, such as breast cancer, prostate cancer, stomach cancer, B-cell lymphoma, colon cancer, lung cancer, melanoma, neuroblastoma, ovarian cancer, sarcoma, small cell lung cancer; or viruses or bacteria that express carbohydrate antigens), or for detecting the presence of an antibody that specifically binds to the neoglycoconjugate or for detecting said immunization, vaccination, or treatment (e.g., in a biological sample from the subject).~~

~~35. Use of the neoglycoconjugate produced by the method of any one of claims 1 to 23, the synthetic neoglycoconjugate of any one of claims 26 to 28, the neoglycoconjugate vaccine or an adaptive immune response-triggering composition produced by the method of claim 29 or 30, or the neoglycoconjugate vaccine of claim 31 or 32, for immunizing, vaccinating, or treating a subject having a disease (e.g., cancers that expresses tumor associated carbohydrate antigens, such as breast cancer, prostate cancer, stomach cancer, B-cell lymphoma, colon cancer, lung cancer, melanoma, neuroblastoma, ovarian cancer, sarcoma, small cell lung cancer; or viruses or bacteria that express carbohydrate antigens), or for detecting the presence of an antibody that specifically binds to the neoglycoconjugate or for detecting said immunization, vaccination, or treatment (e.g., in a biological sample from the subject).~~

~~36. Use of the neoglycoconjugate produced by the method of any one of claims 1 to 23, the synthetic neoglycoconjugate of any one of claims 26 to 28, the adaptive immune response-triggering composition produced by the method of claim 29 or 30, for the manufacture of a vaccine for immunizing or treating a subject having a disease (e.g., cancers that expresses tumor associated carbohydrate antigens, such as breast cancer, prostate cancer, stomach cancer, B-cell lymphoma, colon cancer, lung cancer, melanoma, neuroblastoma, ovarian cancer, sarcoma, small cell lung cancer; or viruses or bacteria that express carbohydrate antigens), or for detecting the presence of an antibody that specifically binds to the neoglycoconjugate or for detecting said immunization or treatment (e.g., in a biological sample from the subject).~~

~~37. Use of the neoglycoconjugate produced by the method of any one of claims 1 to 23, the synthetic neoglycoconjugate of any one of claims 26 to 28, the neoglycoconjugate vaccine or an adaptive immune response-triggering composition produced by the method of claim 29 or 30, or the neoglycoconjugate~~

~~vaccine of claim 31 or 32, for the treatment of a subject having a disease associated with increased expression of said carbohydrate antigen (e.g., cancers such as breast cancer, prostate cancer, stomach cancer, B-cell lymphoma, colon cancer, lung cancer, melanoma, neuroblastoma, ovarian cancer, sarcoma, small cell lung cancer; or viruses or bacteria that express carbohydrate antigens).~~

~~38. Use of the neoglycoconjugate produced by the method of any one of claims 1 to 23, the synthetic neoglycoconjugate of any one of claims 26 to 28, the neoglycoconjugate vaccine or an adaptive immune response-triggering composition produced by the method of claim 29 or 30, or the neoglycoconjugate vaccine of claim 31 or 32, for producing an antibody that specifically binds to the neoglycoconjugate, or for detecting an antibody that specifically binds to the neoglycoconjugate immunogen.~~

~~39. Use of the neoglycoconjugate produced by the method of any one of claims 1 to 23, the synthetic neoglycoconjugate of any one of claims 26 to 28, the neoglycoconjugate vaccine or an adaptive immune response-triggering composition produced by the method of claim 29 or 30, or the neoglycoconjugate vaccine of claim 31 or 32, for detecting or screening for the presence of an antibody that specifically binds to the carbohydrate antigen or a tumor-circulating cell comprising the carbohydrate antigen, or for detecting the presence of antibodies resulting from an immunization or vaccination with the carbohydrate antigen.~~

~~40. The use of claim 39, wherein the detection or screening is performed via any suitable detection method such as an immunosorbent assay, ELISA, microarray, or immunoblot analysis.~~

~~41. A method of treating a subject comprising administering a neoglycoconjugate or neoglycoconjugate immunogen as defined in any preceding claims or produced by a method as defined by any preceding claims, to generate an immune response in said subject to a carbohydrate antigen, and optionally screening a biological sample from said subject for the presence of antibodies that specifically binds to the carbohydrate antigen.~~

~~42.~~ A glycoconjugate for use as a medicament ~~in immunizing a subject against SARS-CoV-2, for use in~~ triggering the production of anti-SARS-CoV-2 antibodies ~~in a subject~~, ~~or for use in detecting the presence of anti-SARS-CoV-2 antibodies in a sample from a subject,~~ the glycoconjugate comprising one or more carbohydrate antigens conjugated to a ~~suitable carrier material (e.g., a~~ carrier protein or peptide~~)~~, wherein the one or more carbohydrate antigens comprise or consist of sialylated Thomsen-Friedenreich (TF) antigen, unsialylated TF antigen, sialylated Tn antigen, unsialylated Tn antigen, or any combination

thereof, wherein said anti-SARS-CoV-2 antibodies bind to the one or more carbohydrate antigens present on glycosylated spike (S) protein expressed on SARS-CoV-2 virions.

[Claim 2~~43~~]. The glycoconjugate for use ~~of~~ according to claim ~~42~~1, wherein the one or more carbohydrate antigens comprise ~~or consist of~~ unsialylated TF antigen ~~(e.g., (2,3)-S-TF and/or disialyl core 1).~~

~~44. The glycoconjugate for use of claim 42 or 43, wherein the carbohydrate antigens comprise or consist of Tn (e.g., sialylated~~ and/or unsialylated Tn~~)~~ antigen.

~~45. The glycoconjugate for use of any one of claims 42 to 44, wherein the carrier material comprises a peptide which is a B cell epitope or T cell epitope.~~

~~46. The glycoconjugate for use of any one of claims 42 to 45, wherein the carbohydrate antigens are covalently conjugated to positions 4 and/or 6 of the peptide of **SEQ ID NO: 3**, or to a variant of the peptide of **SEQ ID NO: 3** comprising a cysteine or lysine at positions 4 and/or 6.~~

~~47. The glycoconjugate for use of claim 46, wherein the peptide or peptide variant of **SEQ ID NO: 3** is comprised in or fused to the carrier material.~~

~~48. The glycoconjugate for use of any one of claims 42 to 47, wherein the carrier material is, is from, or comprises: Tetanus Toxoid (TT), Diphtheria Toxoid (DT), cross-reacting material 197 (CRM197), Meningococcal Outer Membrane Protein Complex (OMPC), H. Influenzae Protein D (HiD), a virus-like particle (VLP), a cytokine, an immunogenic peptide such as Tetanus Toxin 831-844 (**SEQ ID NO: 1 or 2**), albumin (such as bovine serum albumin or human serum albumin), keyhole limpet hemocyanin (KLH), or an immunogenic fragment thereof.~~

~~49. The glycoconjugate as defined in any one of claims 42 to 48, wherein the glycoconjugate is: (i) the neoglycoconjugate produced by or as defined in the method of any one of claims 1 to 23; (ii) the neocarbohydrate antigen of claim 24 or 25; (iii) the synthetic neoglycoconjugate of claim 27 or 28; or (iv) the neoglycoconjugate vaccine or an adaptive immune response-triggering composition as defined in or produced by the method of claim 29 or 30 or as defined in claim 31 or 32.~~

~~50. The glycoconjugate as defined in any one of claims 42 to 48, which is produced by a method comprising: (a) providing a water-soluble carbohydrate antigen covalently linked to a terminal alkene (alkenyl carbohydrate antigen), the terminal alkene being directly conjugatable to a thiol group via a thiol-ene reaction and wherein the alkenyl carbohydrate antigen is an unprotected, water-soluble alkenyl carbohydrate antigen; (b) providing a carrier material having one or more free thiol groups; and (c) performing a photocatalytic thiol-ene reaction to directly conjugate the carbohydrate antigen to the material at the one or more free thiol groups, thereby producing the glycoconjugate.~~

[Claim 3~~51~~]. The glycoconjugate ~~of~~ for use according to claim ~~50~~1 or 2, wherein:

- ~~the photocatalytic thiol-ene reaction is performed under reaction conditions that avoid carrier material denaturation, and/or that retain the carrier material's activity, antigenicity, and/or structure;~~
- ~~the photocatalytic thiol-ene reaction is performed is performed in the absence of any organic solvent, or wherein said photocatalytic thiol-ene reaction is performed in the presence of an organic solvent at a concentration sufficiently low to avoid carrier material denaturation;~~
- ~~the photocatalytic thiol-ene reaction is performed in the presence of a catalyst, wherein the catalyst is: a water-soluble catalyst, such as a water-soluble free radical-generating azo compound; 2,2'-azobis[2-(2-imidazolin-2-yl)propane]dihydrochloride (Vazo-44 or VA-044); 2,2'-azobis(2-amidinopropane) dihydrochloride (AAPH); lithium phenyl-2,4,6-trimethylbenzoylphosphinate (LAP); metals or metal ions having photoinitiator activity; a peroxide; *tert*-butyl hydroperoxide; benzoylperoxide; ammonium persulfate; or any derivative thereof having photoinitiator activity; or a water-insoluble catalyst, such as a water-insoluble free radical-generating azo compound, 2,2-dimethoxy-2-phenylacetophenone (DMPA), azobisisobutyronitrile (AIBN), 2,2′-azobis(2-methylpropionitrile), 4,4′-Azobis(4-cyanopentanoic acid) (ACVA), 1,1′-azobis(cyanocyclohexane) (ACHN), diazenedicarboxylic acid bis(*N*,*N*-dimethylamide) (TMAD); azodicarboxylic acid dipiperidide (ADD), or any derivative thereof having photoinitiator activity;~~
- ~~the photocatalytic thiol-ene reaction comprises irradiation under ultraviolet light;~~
- ~~the photocatalytic thiol-ene reaction comprises reacting between 1 to 200 molar equivalents of the alkenyl carbohydrate antigen per free thiol group of the carrier material; and/or wherein said photocatalytic thiol-ene reaction is performed for 10 to 300, 10 to 270, 10 to 240, 10 to 210, 10 to 180, 10 to 150, 10 to 120, 10 to 90, 10 to 60, or 10 to 30 minutes, and/or for a sufficient time to achieve at least a 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50-fold reduction in total free thiol concentration in the carrier material;~~

– ~~the photocatalytic thiol-ene reaction is performed at a pH that avoids carrier material denaturation;~~

~~the photocatalytic thiol-ene reaction, following conjugation to the carrier material, produces a carbohydrate antigen that is not cleavable from the carrier material by an endogenous enzyme of the subject;~~

~~the alkenyl carbohydrate antigen is covalently linked to the terminal alkene, and/or the carbohydrate antigen is conjugated to the carrier material, via an O-glycosidic bond, an S-glycosidic bond, an N-glycosidic bond, or a C-glycosidic bond, or a bond obtained by reductive amination between an allyl amine and a reducing sugar;~~

~~the photocatalytic thiol-ene reaction conjugates more than~~ one or more ~~type of~~ carbohydrate antigen are conjugated to the carrier ~~material;~~protein or peptide under non-denaturing conditions such that

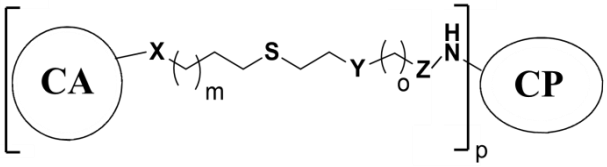
– ~~the carbohydrate antigen in (a) is linked to the terminal alkene via a linker; and/or~~

– the carrier protein or peptide in the glycoconjugate has a native or non-denatured conformation~~material provided in step (b) is: (i) a carrier material comprising one or more cysteine residues having the one or more free thiol groups, (ii) a carrier material engineered to add one or more further cysteine residues at a solvent-accessible position of the carrier material; (iii) a carrier material treated with a thiolating agent; (iv) a carrier material treated with a reducing agent; or (v) any combination of (i) to (iv)~~.

[Claim 4]. The glycoconjugate for use according to any one of claims 1 to 3, wherein the one or more carbohydrate antigens are conjugated to the carrier protein or peptide at one or more amine groups on the carrier protein or peptide.

[Claim 5]. The glycoconjugate for use according to claim 4, wherein at least some of the one or more amine groups are epsilon amino groups of lysine residues comprised in the carrier protein or peptide.

[Claim 6]. The glycoconjugate for use according to claim 4 or 5, wherein the glycoconjugate has the structure:

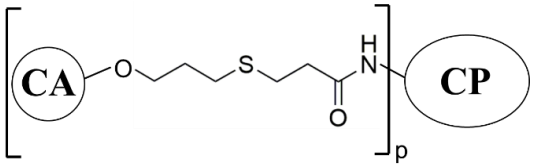


wherein:

- CA is the carbohydrate antigen;
- CP-NH is the carrier protein or peptide having one or more amine groups;
- X is O, S, NR_1, or CH_2 ;
- R_1 is H, COH (formamide), COMe, or COEt ;
- m is 1, 2, 3, 4, or 5 ;
- Y is $-(CH_2)_n-$ or $-(OCH_2CH_2O)_n-$ and n is 0, 1, 2, 3, 4, or 5 ;
- o is 0, 1, 2, 3, 4, or 5 ; or o is 0 and Z is -CO- and Y is $-(OCH_2CH_2O)_n-$; or o is 0 and Z is $-SO_2-$ and Y is $-(OCH_2CH_2O)_n-$;

- Z is -CO- , -NR_2SO_2- , -OCO- , -NR_2CO- , or -NR_2CS- ;
- R_2 is H, Me, or Et ; and
- p is an integer corresponding to the total number of carbohydrate antigens conjugated to the carrier protein or peptide at said one or more amine groups.

[Claim 7]. The glycoconjugate for use according to claim 6, wherein the glycoconjugate has the structure:



.

[Claim 8]. The glycoconjugate for use according to any one of claims 1 to 3, wherein the one or more carbohydrate antigens are conjugated to the carrier protein or peptide at one or more thiol groups on the carrier protein or peptide.

[Claim 9]. The glycoconjugate for use according to claim 8, wherein at least some of the one or more thiol groups are found on cysteine residues comprised in the carrier protein or peptide.

[Claim 10]. The glycoconjugate for use according to any one of claims 1 to 9, wherein the carrier protein or peptide is, is from, or comprises: Tetanus Toxoid (TT), Diphtheria Toxoid (DT), cross-reacting material 197 (CRM197), Meningococcal Outer Membrane Protein Complex (OMPC), H. Influenzae Protein D (HiD), a cytokine, an immunogenic peptide, Tetanus Toxin 831-844 (**SEQ ID NO: 1 or 2**), albumin, keyhole limpet hemocyanin (KLH), or an immunogenic fragment thereof.

[Claim 11]. The glycoconjugate for use according to any one of claims 1 to 9, wherein the carrier protein or peptide is, is from, or comprises TT or CRM197, or an immunogenic fragment thereof.

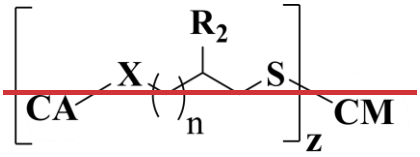
[Claim 12]. The glycoconjugate for use according to any one of claims 1 to 3, wherein the one or more carbohydrate antigens are covalently conjugated to positions 4 and/or 6 of the peptide of **SEQ ID NO: 3**, or to a variant of the peptide of **SEQ ID NO: 3** comprising a cysteine or lysine at positions 4 and/or 6.

[Claim 13]. The glycoconjugate for use according to any one of claims 1 to 3, wherein the carrier protein or peptide comprises an immunogenic fragment of the SARS-CoV-2 S protein sequence of **SEQ ID NO: 4**, the fragment comprising one or more carbohydrate antigens conjugated to position 323, 325, and/or 678 of **SEQ ID NO: 4**.

[Claim 14]. The glycoconjugate for use according to any one of claims 1 to 3, wherein the carrier protein or peptide comprises an immunogenic fragment of a variant of the SARS-CoV-2 S protein sequence of **SEQ ID NO: 4** having a lysine or cysteine at positions 323, 325, and/or 678, the fragment comprising one or more carbohydrate antigens conjugated to the lysine or cysteine residues at position 323, 325, and/or 678 of **SEQ ID NO: 4**.

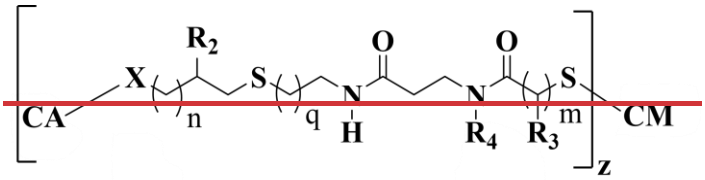
~~52. The glycoconjugate as defined in any one of claims 42 to 48, which is:~~

~~(a) a synthetic glycoconjugate having the structure:~~



wherein: **CA** is the carbohydrate antigen; **S-CM** is the carrier material having **z** sulfur atoms available for conjugation, wherein **z** is at least 1; **X** is O, S, NR_1, or CH_2; R1 is -H, -COH, -$COCH_3$, or -COEt; **n** is 0, 1, 2, 3, 4, or 5; and $\mathbf{R_2}$ is H or Me; or a stereoisomer thereof; or

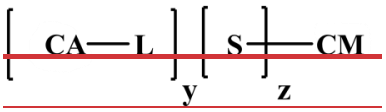
(b) a synthetic glycoconjugate having the structure:



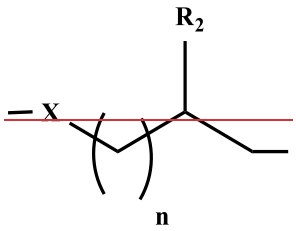
wherein: **CA** is the carbohydrate antigen; **S-CM** is the carrier material having **z** sulfur atoms available for conjugation, wherein **z** is at least 1; **X** is S, NR_1, CH_2 or O; $\mathbf{R_1}$ is -H, -COH, -

~~COMe, or -COEt; **n** is 0, 1, 2, 3, 4, or 5; **R_2** is H or Me; **q** is 1, 2, 3, 4, or 5; **R_3** and **R_4** are each a hydrogen atom and **m** is 1, 2, 3, 4 or 5, or **R_3** and **R_4** form together a radical -CO-CH_2- or a radical -CO-CH_2-CH_2- with the carbonyl linked to the nitrogen atom, and **m** is 1; or a stereoisomer thereof; or~~

~~(c) a synthetic glycoconjugate having the structure:~~

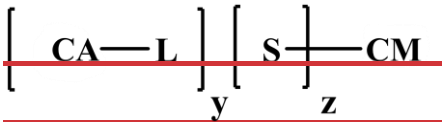


~~wherein: **CA** is the carbohydrate antigen; **y** is at least 1; and when y is more than 1, **CA** are identical or different; **$[S]_z$-CM** is the carrier material having **z** sulfur atoms available for conjugation, wherein **z** is at least equal to **y**; and **L** is a linker selected from the group consisting of linkers having the structure:~~

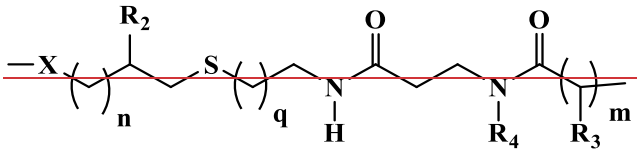


~~wherein: **X** is O, S, NR_1, or CH_2; **R_1** is -H, -COH, -$COCH_3$, or -COEt; **n** is 0, 1, 2, 3, 4, or 5; and **R_2** is H or Me; and when y is more than 1, **L** are identical or different; or a stereoisomer thereof; or~~

~~(d) a synthetic glycoconjugate having the structure:~~

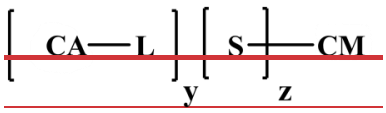


~~wherein: **CA** is the carbohydrate antigen; **y** is at least 1; and when y is more than 1, **CA** are identical or different; **S-CM** is the carrier material having **z** sulfur atoms available for conjugation, wherein **z** is at least 1 and is at least equal to **y**; and **L** is a linker selected from the group consisting of linkers having the structure:~~

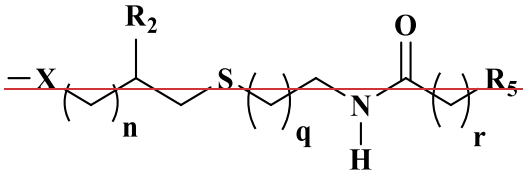


wherein: **X** is S, NR_1, CH_2 or O; R_1 is -H, -COH, -COMe, or -COEt; **n** is 0, 1, 2, 3, 4, or 5; R_2 is H or Me; **q** is 1, 2, 3, 4, or 5; R_3 and R_4 are each a hydrogen atom and **m** is 1, 2, 3, 4 or 5, or R_3 and R_4 form together a radical -CO-CH_2- or a radical -CO-CH_2-CH_2- with the carbonyl linked to the nitrogen atom, and **m** is 1; and when y is more than 1, **L** are identical or different; or a stereoisomer thereof; or

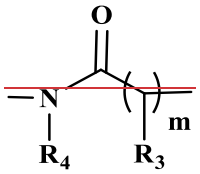
(e) a synthetic glycoconjugate having the structure:



wherein: **CA** is the carbohydrate antigen; **y** is at least 1; and when y is more than 1, **CA** are identical or different; **[S]$_z$-CM** is the carrier material having z sulfur atoms available for conjugation, wherein **z** is at least equal to **y**; and **L** is a linker selected from the group consisting of linkers having the structure:



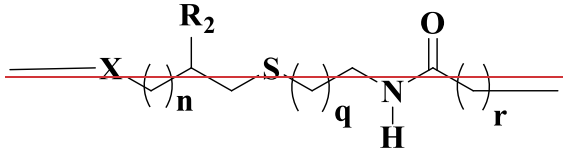
wherein: **X** is S, NR_1, CH_2 or O; R_1 is -H, -COH, -COMe, or -COEt; **n** is 0, 1, 2, 3, 4, or 5; R_2 is H or Me; **q** is 1, 2, 3, 4, or 5; **r** is 1, 2, 3, 4 or 5; R_5 is S-CM, a covalent bond, or a radical of structure:



wherein R_3 and R_4 are each a hydrogen atom and **m** is 1, 2, 3, 4 or 5, or R_3 and R_4 form together a radical -CO-CH_2- or a radical -CO-CH_2-CH_2- with the carbonyl linked to the nitrogen atom, and **m** is 1; and when y is more than 1, **L** are identical or different; or a stereoisomer thereof.

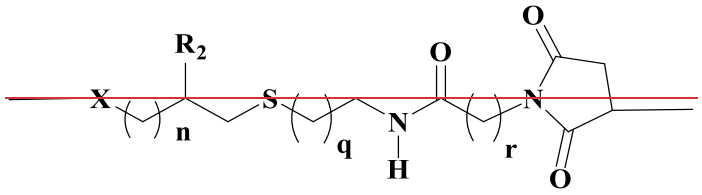
53. The glycoconjugate of claim 52:

– having the structure as defined in (e), wherein the linker has the structure:

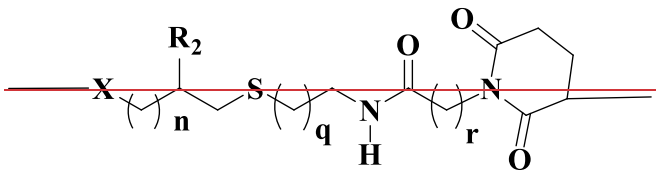


wherein: **X** is S, NR_1, CH_2 or O; $\mathbf{R_1}$ is –H, –COH, –COMe, or –COEt; **n** is 0, 1, 2, 3, 4, or 5; $\mathbf{R_2}$ is H or Me; **q** is 1, 2, 3, 4, or 5; and **r** is 1, 2, 3, 4 or 5;

– having the structure as defined in (e), wherein the linker has the structure:



or



wherein: **X** is S, NR_1, CH_2 or O; $\mathbf{R_1}$ is –H, –COH, –COMe, or –COEt; **n** is 0, 1, 2, 3, 4, or 5; $\mathbf{R_2}$ is H or Me; **q** is 1, 2, 3, 4, or 5; and **r** is 1 or 2;

– wherein the carrier material is or comprises a polymer, a polypeptide, a carrier protein, a solid support, a particle, or any other material having at least one or more a free thiol group suitable for conjugation to the carbohydrate antigen via a photocatalytic thiol-ene reaction;

– wherein the conjugate material is coupled to at least two of the same carbohydrate antigen or to more than one type of carbohydrate antigen, thereby producing a multi-valent synthetic glycoconjugate;

– wherein the carbohydrate antigen is not cleavable from the carrier protein by an endogenous enzyme of the subject; or

– any combination thereof.

[Claim 154]. A SARS-CoV-2 vaccine comprising one or morethe glycoconjugates as defined in any one of claims 42 1 to 5314, and a pharmaceutically acceptable excipient and/or an adjuvant.

55. The SARS-CoV-2 vaccine of claim 54 comprising at least two different glycoconjugates, each glycoconjugate comprising a carrier material conjugated to a at least two different carbohydrate antigens selected from sialylated TF antigen (mono- or di-sialylated TF antigen), unsialylated TF antigen, sialylated Tn antigen, and unsialylated Tn antigen.

~~56. The glycoconjugate as defined in any one of claims 42 to 53, or the SARS-CoV-2 vaccine of claim 54 or 55, wherein the glycoconjugate or vaccine induces the production of antibodies that bind to SARS-CoV-2 virion particles, and preferably have neutralizing activity.~~

~~57. A method for vaccinating a subject for SARS-CoV-2 or for triggering the production of anti-SARS-CoV-2 antibodies in a subject, the method comprising administering the glycoconjugates of any one of claims 42 to 53 or 56, or the SARS-CoV-2 vaccine of any one of claims 54 to 56.~~

~~58. A composition for protecting a subject from infection by a SARS-CoV-2 virus, or for treating COVID-19, the composition comprising one or more ligands (e.g., an antibody, antibody fragment, or lectin) that bind to an O-linked glycan expressed on the SARS-CoV-2 S protein, the O-linked glycan comprising sialylated TF antigen (mono- or di-sialylated TF antigen), unsialylated TF antigen, sialylated Tn antigen, unsialylated Tn antigen, or any combination thereof.~~

~~59. The composition for use of claim 58, wherein the one or more ligands comprise a recombinant monoclonal antibody (e.g., JAA-F11 or humanized JAA-F11).~~

~~60. The composition for use of claim 58, wherein the one or more ligands comprise a lectin (e.g., that binds to both sialylated and unsialylated TF antigen forms).~~

~~61. The composition for use of any one of claims 58 to 60, wherein the lectin is Jacalin or is a Jacalin-related lectin.~~

~~62. The composition for us of any one of claims 58 to 61, which is formulated as an intranasal composition.~~

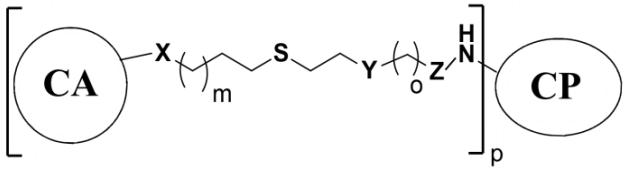
[Claim 16]. Use of a ligand in the manufacture of a medicament for treating or reducing the risk of SARS-CoV-2 viral infection in a subject, the one or more ligands having binding specificity for an O-linked glycan expressed on the SARS-CoV-2 S protein, wherein the O-linked glycan is sialylated TF antigen, unsialylated TF antigen, sialylated Tn antigen, or unsialylated Tn antigen, and wherein the ligand is an antibody, an antibody fragment, or a lectin.

[Claim 17~~63~~]. An immune complex comprising~~: (a)~~ a SARS-CoV-2 S protein, or fragment thereof, expressing an O-linked glycan bound to a ligand having binding specificity for said O-linked glycan, wherein the O-linked glycan is ~~comprising~~ sialylated TF antigen ~~(mono- or di-sialylated TF antigen)~~, unsialylated TF antigen, sialylated Tn antigen, or unsialylated Tn antigen~~, or any combination thereof~~;

and ~~(b)~~wherein the~~a~~ ligand is an antibody, an antibody fragment, or a lectin~~as defined in any one of claims 58 to 61 that is bound to the SARS-CoV-2 S protein, or fragment thereof, at the O-linked glycan~~.

~~64. The complex of claim 63, wherein the SARS-CoV-2 S protein, or fragment thereof, is comprised in an intact SARS-CoV-2 virion particle.~~

[Claim 18]. A synthetic neoglycoconjugate comprising one or more carbohydrate antigens (CA) conjugated to one or more amine groups of a carrier protein or peptide (CP-NH) via a linker, the synthetic neoglycoconjugate having the structure:



wherein:

- X is O, S, NR_1, or CH_2 ;
- R_1 is H, COH (formamide), COMe, or COEt ;
- m is 1, 2, 3, 4, or 5 ;
- Y is $-(CH_2)_n-$ or $-(OCH_2CH_2O)_n-$ and n is 0, 1, 2, 3, 4, or 5 ;
- o is 0, 1, 2, 3, 4, or 5 ; or o is 0 and Z is -CO- and Y is $-(OCH_2CH_2O)_n-$; or o is 0 and Z is $-SO_2-$ and Y is $-(OCH_2CH_2O)_n-$;
- Z is -CO- , $-NR_2SO_2-$, -OCO- , $-NR_2CO-$, or $-NR_2CS-$;
- R_2 is H, Me, or Et ; and
- p is an integer corresponding to the total number of carbohydrate antigens conjugated to the carrier protein or peptide at said one or more amine groups, and

wherein the carrier protein or peptide in the synthetic neoglycoconjugate has a native or non-denatured conformation, and conjugation of the carbohydrate antigen to the carrier protein or peptide increases the immunogenicity of the carbohydrate antigen upon administration to the subject as compared to a corresponding administration of the unconjugated carbohydrate antigen.

[Claim 19]. The synthetic neoglycoconjugate of claim 18, wherein the one or more carbohydrate antigens comprise a tumor associated carbohydrate antigen (TACA), a viral polysaccharide antigen, or a bacterial capsular polysaccharide (CPS).

[Claim 20]. The synthetic neoglycoconjugate of claim 18 or 19, wherein the one or more carbohydrate antigens comprise sialylated TF antigen, unsialylated TF antigen, sialylated Tn antigen, unsialylated Tn antigen, or any combination thereof.

[Claim 21]. The synthetic neoglycoconjugate of any one of claims 18 to 20, wherein the carrier protein or peptide is, is from, or comprises: Tetanus Toxoid (TT), Diphtheria Toxoid (DT), cross-reacting material 197 (CRM197), Meningococcal Outer Membrane Protein Complex (OMPC), H. Influenzae Protein D (HiD), a cytokine, an immunogenic peptide, Tetanus Toxin 831-844 (**SEQ ID NO: 1 or 2**), albumin, keyhole limpet hemocyanin (KLH), or an immunogenic fragment thereof.

[Claim 22]. The synthetic neoglycoconjugate of any one of claims 18 to 21, wherein p is 1 to 50.

[Claim 23]. A vaccine composition comprising the synthetic neoglycoconjugate of any one of claims 18 to 22, and a pharmaceutically acceptable excipient and/or an adjuvant.

[Claim 24]. Use of the synthetic neoglycoconjugate as defined in any one of claims 18 to 21 for the manufacture of a vaccine composition for immunizing a subject against a TACA-expressing cancer.