Doc Code: TRAN.LET
Document Description: Transmittal Letter

USED IN LIEU OF PTO/SB/21 (07-09)

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	

Application Number	17/347,435-Conf. #4020
Filing Date	June 14, 2021
First Named Inventor	Bruce D. Forrest
Art Unit	1645
Examiner Name	Khatol S. Shahnan Shah
Attorney Docket Number	P1143.70000US05

ENCLOSURES (*Check all that apply*)

- [x] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [x] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please Identify below):

Form PTO-1449

Copies of Cited References

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	WOLF, GREENFIELD & SACKS, P.C.		
Signature	/Jessica A. von Reyn/		
Printed name	Jessica A. von Reyn		
Date	September 27, 2024	Reg. No.	76,839

Certificate of Electronic Filing under 37 C.F.R. § 1.8

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: September 27, 2024 Electronic Signature for Abigail S. Feldman: /Abigail S. Feldman/

13174452.1

FEE TRANSMITTAL

Complete if known	
Application Number	17/347,435-Conf. #4020
Filing Date	June 14, 2021
First Named Inventor	Bruce D. Forrest
Examiner Name	Khatol S. Shahnan Shah
Art Unit	1645
Practitioner Docket No.	P1143.70000US05

[x] Applicant asserts small entity status. See 37 CFR 1.27.

[ ] Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

TOTAL AMOUNT OF PAYMENT ($)104.00

METHOD OF PAYMENT (check all that apply)

[ ] Check [x] Credit Card [ ] Money Order [ ] None [ ] Other (please identify): _____

[x] Deposit Account Deposit Account Number: 23/2825 Deposit Account Name: Wolf, Greenfield & Sacks, P.C.

For the above-identified deposit account, the Director is hereby authorized to (check all that apply):

[ ] Charge fee(s) indicated below

[ ] Charge fee(s) indicated below, **except for the filing fee**

[x] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17, **except for any excess claims fees or multiple dependent claim fee**

[ ] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17

[x] Credit any overpayment of fee(s)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES (U = undiscounted fee; S = small entity fee; M = micro entity fee)

	FILING FEES			SEARCH FEES			EXAMINATION FEES			
Application Type	**U ($)**	**S ($)**	**M ($)**	**U ($)**	**S ($)**	**M ($)**	**U ($)**	**S ($)**	**M ($)**	**Fees Paid ($)**
Utility	320	128*	64	700	280	140	800	320	160	
Design	220	88	44	160	64	32	640	256	128	
Plant	220	88	44	440	176	88	660	264	132	
Reissue	320	128	64	700	280	140	2,320	928	464	
Provisional	300	120	60	0	0	0	0	0	0	

* The $128 small entity status filing fee for a utility application is further reduced to $64 for a small entity applicant who files the application via Patent Center or EFS-Web.

2. EXCESS CLAIM FEES

Fee Description	**Undiscounted Fee ($)**	**Small Entity Fee ($)**	**Micro Entity Fee ($)**
Each claim over 20 (including Reissues)	100	40	20
Each independent claim over 3 (including Reissues)	480	192	96
Multiple dependent claims	860	344	172

Total Claims		**Extra Claims**	**Fee ($)**	**Fee Paid ($)**
_____	- 27 or HP =	_____	x _____	= _____

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims		**Extra Claims**	**Fee ($)**	**Fee Paid ($)**
_____	- 3 or HP =	_____	x _____	= _____

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims	
Fee ($)	**Fee Paid ($)**
_____	_____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $420 ($168 for small entity) ($84 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets		**Extra Sheets**		**Number of each additional 50 or fraction thereof**	**Fee ($)**	**Fee Paid ($)**
_____	- 100 =	_____	/50 =	_____ (round **up** to a whole number)	x _____	= _____

4. OTHER FEE(S)

	Fees Paid ($)
Non-English specification, $140 fee ($56 small entity) ($28 for micro entity)	
Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, $400 fee ($200 small or micro entity)	
Other (e.g., late filing surcharge): 2806 Submission of an Information Disclosure Statement	104.00

SUBMITTED BY

Signature	/Jessica A. von Reyn/	Registration No. (Attorney/Agent)	76,839	Telephone	617.646.8000
Name (Print/Type)	Jessica A. von Reyn			Date	September 27, 2024

Certificate of Electronic Filing under 37 C.F.R. § 1.8

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: September 27, 2024 Electronic Signature for Abigail S. Feldman: /Abigail S. Feldman/

13174450.1

Docket No.: P1143.70000US05
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Bruce D. Forrest
Application No.:	17/347,435
Confirmation No.:	4020
Filed:	June 14, 2021
For:	SACCHARIDE-POLYPEPTIDE CONJUGATE COMPOSITIONS AND METHODS OF USE THEREOF
Examiner:	Khatol S. Shahnan Shah
Art Unit:	1645

Certificate of Electronic Filing under 37 C.F.R. § 1.8
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: September 27, 2024 Signature for Brent M. Persun: /Brent M. Persun/

RESPONSE TO NON-FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.111

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

In response to the Office Action, dated June 27, 2024, Applicant respectfully requests entrance of the following Amendment and consideration of the following Remarks. The deadline for responding to the Office Action is September 27, 2024. Applicant thus submits that the present Response is timely submitted on Friday, September 27, 2024.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 7 of this paper.

AMENDMENTS TO THE CLAIMS

This Listing of Claims will replace all prior versions, and listings, of claims in the Application:

Listing of Claims

1-295. (Canceled)

296. (Currently Amended) A pharmaceutical composition comprising a plurality of at least two[[2]] immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* ~~Streptococcus pneumoniae~~ serotype ~~group~~, wherein a first serotype comprises ~~is selected from the group consisting of 6C, 15A,~~ 16F, 20A, 20B, 24F, or 31, ~~and 34~~ and at least one additional serotype comprises ~~is selected from the group consisting of~~ 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, ~~9V, 14, 18C, 19A, 19F, 23F,~~ 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or[[and]] 38, wherein the at least one additional serotype is not the first serotype; and wherein the fragment of the capsular polysaccharide is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, a hexasaccharide, or an oligosaccharide.

297. (Currently Amended) The pharmaceutical composition of claim 296, wherein the first serotype is 31[[20B]].

298. (Currently Amended) The pharmaceutical composition of claim 296, wherein the first serotype is 24F[[6C]].

299. (Currently Amended) The pharmaceutical composition of claim 296, wherein the first serotype is 20A[[15A]].

300. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 16F.

301. (Previously Presented) The pharmaceutical composition of claim 296, wherein at least one polypeptide comprises a mixture of polypeptides.

302. (Currently Amended) The pharmaceutical composition of claim 296, wherein at least one polypeptide comprises cross-reacting material 197 (~~CRM197~~CRM_{197}), tetanus toxoid, a diphtheria toxoid, cholera toxoid, pertussis toxoid, inactivated or mutant pneumococcal pneumolysin, pneumococcal surface protein A, pneumococcal adhesion protein A, pneumococcal lipoprotein PsaA, C5a peptidase group A or group B *Streptococcus* ~~Streptococcus~~, a non-typable *H. influenzae* ~~H. influenzae~~ P4 protein, a non-typable *H. influenzae* ~~H. influenzae~~ P6 protein, *M. catarrhalis* ~~M. catarrhalis~~ uspA, keyhole limpet haemocyanin (KLH), outer membrane protein complex (OMPC) from *N. meningitidis* ~~N. meningitidis~~, a purified protein derivative of tuberculin(PPD), protein D from *H. influenzae* ~~H. influenzae~~, PspA, any fragment thereof, or any combination thereof.

303. (Previously Presented) The pharmaceutical composition of claim 296, further comprising an adjuvant; a chelating agent; a surfactant; an emulsifier; a buffering agent; a preservative; a salt; an anti-fungal compound; or a combination thereof.

304. (Previously Presented) The pharmaceutical composition of claim 296, wherein the pharmaceutical composition is in the form of an intramuscularly injectable composition, intradermally injectable composition, subcutaneously injectable composition, or an intranasally administrable composition.

305. (Previously Presented) The pharmaceutical composition of claim 296, wherein at least one of the immunogenic saccharide-polypeptide conjugates elicits an opsonophagocytic response.

306. (Previously Presented) The pharmaceutical composition of claim 296, wherein the immunogenic saccharide-polypeptide conjugates are collectively present in an amount of at least 0.001%, by weight, based on the weight of the pharmaceutical composition.

307. (Previously Presented) The pharmaceutical composition of claim 296, wherein the immunogenic saccharide-polypeptide conjugates comprise: (i) the capsular polysaccharide at least partially embedded in the polypeptide, (ii) the capsular polysaccharide chemically cross-linked to the polypeptide, and/or (iii) the capsular polysaccharide at least partially chemically cross-linked to the polypeptide.

308. (Previously Presented) The pharmaceutical composition of claim 296, wherein a toxin activity of at least one of the polypeptides is at least partly mitigated.

309. (Previously Presented) The pharmaceutical composition of claim 296, wherein each of the immunogenic saccharide-polypeptide conjugates is present in an amount of at least 0.001%, by weight, based on the weight of the pharmaceutical composition.

310. (Withdrawn) A method comprising administering to a subject a first composition, wherein the first composition comprises the pharmaceutical composition of claim 296.

311. (Withdrawn) The method of claim 310, wherein the first composition is administered intramuscularly.

312. (Withdrawn) The method of claim 310, wherein the administering to the subject the first composition occurs at least about four weeks before or at least about four weeks after an

administration of a second composition comprising an immunogenic saccharide-polypeptide conjugate.

313. (Withdrawn – Currently Amended) The method of claim 312, wherein the second composition comprises an immunogenic saccharide-polypeptide conjugate comprising a capsular polysaccharide from at least one serotype of *Streptococcus pneumoniae* ~~Streptococcus pneumoniae~~ conjugated to a second polypeptide, wherein the at least one serotype comprises 3, 7F, 8, 10A, 11A, 12F, 22F, or 33F.

314. (Withdrawn) The method of claim 310, wherein the subject is a human.

315. (Withdrawn) A method of making a composition comprising: contacting the plurality of immunogenic saccharide-polypeptide conjugates of claim 296 with an excipient, an adjuvant, or any combination thereof.

316. (New) The pharmaceutical composition of claim 296, wherein the first serotype comprises 16F and the at least one additional serotype comprises 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, and 15A.

317. (New) The pharmaceutical composition of claim 296, wherein the first serotype comprises 20A and the at least one additional serotype comprises 7F, 8, 9N, 15A, 15C, 16F, 19A, 22F, 23A, and 23B.

318. (New) The pharmaceutical composition of claim 296, wherein the first serotype comprises 23B and the at least one additional serotype comprises 16F, 20A, 22F, 23A, 24F, 31, 33F, and 35B.

319. (New) The pharmaceutical composition of claim 296, wherein the first serotype comprises 24F and the at least one additional serotype comprises 3, 7F, 8, 9N, 10A, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, and 31.

320. (New) The pharmaceutical composition of claim 296, wherein the first serotype comprises 16F and the at least one additional serotype comprises 3, 7F, 8, 9N, 10A, 12F, 15A, 15C, 17F, 20A, 22F, 23A, 23B, 31, 33F, and 35B.

321. (New) The pharmaceutical composition of claim 296, wherein the first serotype comprises 24F and the at least one additional serotype comprises 3, 6A, 7F, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 19A, 20A, 22F, 23B, 31, and 35B.

322. (New) The pharmaceutical composition of claim 296, wherein the first serotype comprises 31 and the at least one additional serotype comprises 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 22F, 33F, and 35B.

REMARKS

Claims 296-315 were pending in the Application before entrance of the present Amendment, of which claims 310-315 are withdrawn from consideration by the Examiner at this time. By the present Amendment, claims 296-299, 302, and 313 are amended. Applicant reserves the right to pursue the subject matter canceled from the claims in one or more future applications claiming priority to the present Application. Claim 296 is amended to recite a specific subset of first and additional serotypes, to define the fragment of the capsular polysaccharide, and to correct typographical errors. Support for the amendments to claim 296 can be found throughout the originally filed Application, *e.g.*, in original claim 73. Claims 297 and 298 were amended to recite different serotypes in view of the amendments to claim 296. Claim 299 was amended to recite the serotypes deleted from claim 296 by this Amendment. Claim 302 was amended to define two acronyms and to correct typographical errors. Claim 313 was amended to recite a list of the at least one serotypes. Support for the amendments to claim 313 can be found throughout the originally filed Application, *e.g.*, in paragraphs [0043] and [0070], and Table 1 of the Application.

New claims 316-322 have been added to recite specific combinations of serotypes. Support for new claims 316-322 can be found throughout the originally filed Application, *e.g.*, in paragraphs [0043] and [0070], and Table 1 of the Application.

After entrance of the present Amendment, claims 296-322 will be pending in the Application, with claims 310-315 being withdrawn. Applicant submits that no new matter is added to the Application by this Amendment.

Amendment or cancelation of the claims during prosecution of this Application is not to be construed as acquiescence to any of the objections or rejections set forth in the Office Action and was done solely to expedite prosecution of the Application. Applicant reserves the right to pursue the claims as originally filed or similar claims in this particular Application or one or more continuing patent applications claiming priority to this Application.

Each of the rejections levied by the Examiner is addressed in turn below.

Claim Objection

The Examiner objected to claim 302 for reciting acronyms without their respective meanings. Solely to expedite prosecution of the present Application and without acquiescing to the propriety of this objection, Applicant has amended claim 302 to recite "cross-reacting material 197 (CRM_{197})" and "outer membrane protein complex (OMPC)." Accordingly, withdrawal of this objection is respectfully requested.

Claim Rejections under 35 U.S.C. § 112

The Examiner rejected claims 296-309 under 35 U.S.C. § 112(b) as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor regards as the invention. In particular, the Examiner states that the use of the term "fragment thereof" renders claim 296 vague and indefinite. Solely to expedite prosecution of the present Application and without acquiescing to the propriety of this rejection, Applicant has amended claim 296 to recite that the fragment of the capsular polysaccharide is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, a hexasaccharide, or an oligosaccharide. Accordingly, withdrawal of this rejection is respectfully requested.

Claim Rejections under 35 U.S.C. § 102

The Examiner rejected claims 296, 298, 299, and 301-309 under 35 U.S.C. § 102 as allegedly being anticipated by Porro *et al.* (WO 2014/118201; hereinafter "Porro"). Applicant respectfully disagrees.

Nonetheless, solely to expedite prosecution of the present Application and without acquiescing to the propriety of this rejection, claim 296 has been amended to be directed, *inter alia*, to a pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31; at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38; and wherein the at least one additional serotype is not the first serotype. Porro does not teach at least serotypes 16F, 20A, 20B, 24F, or 31, let alone

the recited combination of serotypes. Applicant respectfully requests that this rejection be withdrawn.

The Examiner rejected claims 296, 298, 299, 301-304, and 307 under 35 U.S.C. § 102 as allegedly being anticipated by Matur *et al.* (WO 2016/207905; hereinafter "Matur"). Applicant respectfully disagrees.

Nonetheless, solely to expedite prosecution of the present Application and without acquiescing to the propriety of this rejection, claim 296 has been amended to be directed, *inter alia*, to a pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31; at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38; and wherein the at least one additional serotype is not the first serotype. Matur does not teach at least serotypes 16F, 20A, 20B, 24F, or 31, let alone the recited combination of serotypes. Applicant respectfully requests that this rejection be withdrawn.

The Examiner rejected claims 296, 298, 301-305, 307, and 308 under 35 U.S.C. § 102 as allegedly being anticipated by Bertaud *et al.* (WO 2017/067962; hereinafter "Bertaud"). Applicant respectfully disagrees.

Nonetheless, solely to expedite prosecution of the present Application and without acquiescing to the propriety of this rejection, claim 296 has been amended to be directed, *inter alia*, to a pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31; at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38; and wherein the at least one additional serotype is not the first serotype. Bertaud does not teach at least serotypes 16F, 20A, 20B, 24F, or 31, let

alone the recited combination of serotypes. Applicant respectfully requests that this rejection be withdrawn.

Claim Rejections under 35 U.S.C. § 103

The Examiner rejected claims 296-309 under 35 U.S.C. § 103 as allegedly being obvious in view of Bertaud in view of del Amo *et al.*, "High invasiveness of pneumococcal serotypes included in the new generation of conjugate vaccines." *Clin Microbiol Infect.* **2013**, 20(7):684-9 (hereinafter "del Amo"). Applicant respectfully disagrees.

Nonetheless, solely to expedite prosecution of the present Application and without acquiescing to the propriety of this rejection, claim 296 has been amended to be directed, *inter alia*, to a pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31; at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38; and wherein the at least one additional serotype is not the first serotype.

At least the recited combination of serotypes is not disclosed or suggested by the cited references. Instead, Bertaud is directed to vaccines comprising *S. pneumoniae* serotype 6A, 6B, 6C, and 6D capsular polysaccharides, as the reference notes "… surprisingly, the present invention provides a sized *Streptococcus pneumoniae* 6A polysaccharide with improved properties …" (Bertaud, page 3, lines 5-6). The reference provides immunogenic compositions comprising numerous combinations of serotype 6A, 6B, 6C, and/or 6D capsular polysaccharides with other serotypes (*e.g.*, pages 9-11); however, none of the combinations include at least serotypes 16F, 20A, 20B, 24F, or 31, as claimed. The Examiner cited del Amo for its purported disclosure of numerous serotypes (*e.g.*, 1, 2, 3, 4, 5, 6A/6B, 6C, 7C/(7B/40), 7F/7A, 8, 9N/9L, 9V/9A, 10A, 10F/(10C/33C), 11A/11D, 12F/(12A/44/46), 13, 14, 15A/15F, 15B/15C, 16F, 17F, 18/(18A/18B/18C/18F), 19A, 19F, 20, 21, 22F/22A, 23A, 23B, 23F, 24/(24A/24B/24F), 31, 33F/(33A/37), 34, 35A/(35C/42), 35B, 35F/47F, 38/25F, and 39); however, the list of serotypes in del Amo are those that may be detected using an assay, not for inclusion in a pharmaceutical composition as claimed. With respect

Petitioner Merck Ex-1015, 1476

to pharmaceutical compositions, del Amo surveyed a number of pediatric samples to conclude that "… serotypes 1, 5, 7F and 19, which became more prevalent in invasive disease in Spain and Portugal during the last decade, have a high invasive disease potential" (del Amo, page 687, left column; internal citations omitted). Therefore, the combined teachings of Bertaud and del Amo would lead the skilled artisan to generate a composition comprising at least one serotype 6 capsular polysaccharide (Bertaud) in combination with serotype 1, 5, 7F, and 19 capsular polysaccharides (del Amo). This is not a combination of the pending claims, which require at least one of the serotypes to be 16F, 20A, 20B, 24F, or 31.

As the cited references do not teach or suggest the pharmaceutical composition of the amended claims, withdrawal of the rejection is respectfully requested.

Double Patenting

Claims 296-309 have been rejected on the ground of non-statutory obviousness-type double patenting as allegedly being unpatentable over claims 1-10 and 12-15 of U.S. Patent No. 11,058,757. Applicant respectfully disagrees. The claims, as amended, are directed a pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31; at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38; and wherein the at least one additional serotype is not the first serotype. The claims, as amended, are patentably distinct from those of U.S. Patent No. 11,058,757. Withdrawal of the rejection is respectfully requested.

Claims 296-309 have been provisionally rejected on the ground of non-statutory obviousness-type double patenting as allegedly being unpatentable over claims 449- 450, 455, 461-466, 470, 471, 473-478, 481, 482-489, and 492-494 of co-pending Application No. 16/753,597. Applicant respectfully disagrees. The claims, as amended, are directed to a pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A,

20B, 24F, or 31; at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38; and wherein the at least one additional serotype is not the first serotype. The claims, as amended, are patentably distinct from those pending in US Application No. 16/753,597. Withdrawal of the rejection is respectfully requested.

General Comments on Dependent Claims

Each of the dependent claims depends from a base claim that is believed to be in condition for allowance, and Applicant therefore believes that it is unnecessary at this time to argue the allowability of each of the dependent claims individually. Applicant does not, however, necessarily concur with the interpretation of the dependent claims as set forth in the Office Action, nor does Applicant concur that the basis for the rejection of any of the dependent claims is proper. Therefore, Applicant reserves the right to specifically address the patentability of the dependent claims in the future.

In view of the foregoing, this Application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this response, the Application is not in condition for allowance, the Examiner is requested to call the undersigned at the telephone number indicated below to discuss any outstanding issues.

If this Response is not considered timely filed, and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time.

Applicant believes no fee is due with this Response. However, if a fee is due with this Amendment, please charge our Deposit Account No. 23/2825, under Docket No. P1143.70000US05, from which the undersigned is authorized to draw.

Dated: September 27, 2024

Respectfully submitted,

Electronic signature: /Jessica A. von Reyn/
Jessica A. von Reyn
Registration Number: 76,839
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/347,435	**09/27/2024 10:05:45 AM Z ET**	**P1143.70000US05**

Title of Invention

SACCHARIDE-POLYPEPTIDE CONJUGATE COMPOSITIONS AND METHODS OF USE THEREOF

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	4020	FILED BY	Brent Persun
PATENT CENTER #	67348526	FILING DATE	06/14/2021
CUSTOMER #	23628	FIRST NAMED INVENTOR	Bruce D. Forrest
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jessica von Reyn

Documents

TOTAL DOCUMENTS: 5

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
P114370000US05-AMN-JXV.pdf		13	-	73 KB
P114370000US05-AMN-JXV-A....pdf	(1-1)	1	Amendment/Request for Reconsideration-After Non-Final Rejection	25 KB
P114370000US05-AMN-JXV-CLM.pdf	(2-6)	5	Claims	38 KB
P114370000US05-AMN-JXV-REM.pdf	(7-13)	7	Applicant Arguments/Remarks Made in an Amendment	49 KB
P114370000US05-TRN-JXV.pdf		1	Miscellaneous Incoming Letter	26 KB
P114370000US05-FEE-JXV.pdf		1	Fee Worksheet (SB06)	34 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
P114370000US05-AMN-JXV.pdf	F18195D3ADF1B2EA0794D067E4EE446DF9B7B293CDA788BE86624FABA0970E04A8FDF1653D4D753506BCC0FFA83C7BA899FB8BD8A71617CB26F3A5E83DC1DFDD
P114370000US05-AMN-JXV-A....pdf	B9D6D362E5422A9571E0D9F0FA161ECC187076B5EBB389DDBAE4142B9EA34E7018FE83431FD3EA2BE7ECA3319FBEB86D9B3A6C235437307B0CC3DC6BBEEE58EA
P114370000US05-AMN-JXV-CLM.pdf	91C43386C12AD9E764E3B3A9BACDA0523F5B1F079FC7460E849A91CB409510CA0BA4955006E8019748843F8AD7BDC41F6DF0302430E0D847FF24E19526D35738
P114370000US05-AMN-JXV-REM.pdf	B118AFF64F1A764A00A5786DE71F535DB7599C19B0D519B944616879B1C7CB0069887A75AFC9FC337367C1BE24D59CE4E3C6EDC7B792EB653753812098B5217B
P114370000US05-TRN-JXV.pdf	6CD96C06E6A3ECFE255026E6FF1A4781CE8723659B8C1433EE9DF133D79C97664BFEB267B79F45E6F08597BC0C7AAB7A7257C4A1BC78C83264D8657A32177D3B
P114370000US05-FEE-JXV.pdf	6337FC7B67A8C93E48AB933E67A6C8B32D035B7B0A0A9160EF32CA09DAA1BB79E8E9AF7BB48FF7172417163225FA1B3DD949150527D9E587CDF5A5D4139B86AB

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: TRAN.LET
Document Description: Transmittal Letter

USED IN LIEU OF PTO/SB/21 (07-09)

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	

Application Number	17/347,435-Conf. #4020
Filing Date	June 14, 2021
First Named Inventor	Bruce D. Forrest
Art Unit	1645
Examiner Name	K. S. Shahnan Shah
Attorney Docket Number	P1143.70000US05

ENCLOSURES (*Check all that apply*)

- [X] Fee Transmittal Form
  - [ ] Fee Attached
- [X] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) (please Identify below):

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	WOLF, GREENFIELD & SACKS, P.C.		
Signature	/Jessica A. von Reyn/		
Printed name	Jessica A. von Reyn		
Date	September 27, 2024	Reg. No.	76,839

Certificate of Electronic Filing under 37 C.F.R. § 1.8

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: September 27, 2024 Electronic Signature for Brent M. Persun: /Brent M. Persun/

13172618.1

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/347,435	**09/27/2024 10:05:45 AM Z ET**	**P1143.70000US05**

Title of Invention

SACCHARIDE-POLYPEPTIDE CONJUGATE COMPOSITIONS AND METHODS OF USE THEREOF

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	4020	FILED BY	Brent Persun
PATENT CENTER #	67348526	AUTHORIZED BY	Jessica von Reyn
CUSTOMER #	23628	FILING DATE	06/14/2021
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Bruce D. Forrest

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 8626	**E20249QA06517004**	**Brent Persun**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2202	EACH CLAIM IN EXCESS OF 20	40.00	7	280.00
			TOTAL AMOUNT:	**$280.00**

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage

submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

FEE TRANSMITTAL

Complete if known	
Application Number	17/347,435-Conf. #4020
Filing Date	June 14, 2021
First Named Inventor	Bruce D. Forrest
Examiner Name	K. S. Shahnan Shah
Art Unit	1645
Practitioner Docket No.	P1143.70000US05

[x] Applicant asserts small entity status. See 37 CFR 1.27.

[ ] Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

TOTAL AMOUNT OF PAYMENT ($)280.00

METHOD OF PAYMENT (check all that apply)

[ ] Check [x] Credit Card [ ] Money Order [ ] None [ ] Other (please identify): _____

[x] Deposit Account Deposit Account Number: 23/2825 Deposit Account Name: Wolf, Greenfield & Sacks, P.C.

For the above-identified deposit account, the Director is hereby authorized to (check all that apply):

[ ] Charge fee(s) indicated below

[ ] Charge fee(s) indicated below, **except for the filing fee**

[ ] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17, **except for any excess claims fees or multiple dependent claim fee**

[x] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17

[x] Credit any overpayment of fee(s)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES (U = undiscounted fee; S = small entity fee; M = micro entity fee)

	FILING FEES			SEARCH FEES			EXAMINATION FEES			
Application Type	**U ($)**	**S ($)**	**M ($)**	**U ($)**	**S ($)**	**M ($)**	**U ($)**	**S ($)**	**M ($)**	**Fees Paid ($)**
Utility	320	128*	64	700	280	140	800	320	160	
Design	220	88	44	160	64	32	640	256	128	
Plant	220	88	44	440	176	88	660	264	132	
Reissue	320	128	64	700	280	140	2,320	928	464	
Provisional	300	120	60	0	0	0	0	0	0	

* The $128 small entity status filing fee for a utility application is further reduced to $64 for a small entity applicant who files the application via Patent Center or EFS-Web.

2. EXCESS CLAIM FEES

Fee Description	**Undiscounted Fee ($)**	**Small Entity Fee ($)**	**Micro Entity Fee ($)**
Each claim over 20 (including Reissues)	100	40	20
Each independent claim over 3 (including Reissues)	480	192	96
Multiple dependent claims	860	344	172

Total Claims		**Extra Claims**	**Fee ($)**		**Fee Paid ($)**
27	- 20 or HP =	7	x 40.00	=	280.00

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims		**Extra Claims**	**Fee ($)**		**Fee Paid ($)**
1	- 3 or HP =		x	=	

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims	
Fee ($)	**Fee Paid ($)**

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $420 ($168 for small entity) ($84 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets		**Extra Sheets**		**Number of each additional 50 or fraction thereof**	**Fee ($)**	**Fee Paid ($)**
	- 100 =		/50 =	(round **up** to a whole number) x		=

4. OTHER FEE(S)

	Fees Paid ($)
Non-English specification, $140 fee ($56 small entity) ($28 for micro entity)	
Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, $400 fee ($200 small or micro entity)	
Other (e.g., late filing surcharge):	

SUBMITTED BY

Signature	/Jessica A. von Reyn/	Registration No. (Attorney/Agent)	76,839	Telephone	617.646.8000
Name (Print/Type)	Jessica A. von Reyn			Date	September 27, 2024

Certificate of Electronic Filing under 37 C.F.R. § 1.8

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: September 27, 2024 Electronic Signature for Brent M. Persun: /Brent M. Persun/

13172617.1

Docket No.: P1143.70000US05
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Bruce D. Forrest
Application No.:	17/347,435
Confirmation No.:	4020
Filed:	June 14, 2021
For:	SACCHARIDE-POLYPEPTIDE CONJUGATE COMPOSITIONS AND METHODS OF USE THEREOF
Examiner:	Khatol S. Shahnan Shah
Art Unit:	1645

Certificate of Electronic Filing under 37 C.F.R. § 1.8
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: September 27, 2024 Signature for Brent M. Persun: /Brent M. Persun/

RESPONSE TO NON-FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.111

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

In response to the Office Action, dated June 27, 2024, Applicant respectfully requests entrance of the following Amendment and consideration of the following Remarks. The deadline for responding to the Office Action is September 27, 2024. Applicant thus submits that the present Response is timely submitted on Friday, September 27, 2024.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 7 of this paper.

AMENDMENTS TO THE CLAIMS

This Listing of Claims will replace all prior versions, and listings, of claims in the Application:

Listing of Claims

1-295. (Canceled)

296. (Currently Amended) A pharmaceutical composition comprising a plurality of at least two[[2]] immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* ~~Streptococcus pneumoniae~~ serotype ~~group~~, wherein a first serotype comprises ~~is selected from the group consisting of 6C, 15A,~~ 16F, 20A, 20B, 24F, or 31, ~~and 34~~ and at least one additional serotype comprises ~~is selected from the group consisting of~~ 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, ~~9V, 14, 18C, 19A, 19F, 23F,~~ 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or[[and]] 38, wherein the at least one additional serotype is not the first serotype; and wherein the fragment of the capsular polysaccharide is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, a hexasaccharide, or an oligosaccharide.

297. (Currently Amended) The pharmaceutical composition of claim 296, wherein the first serotype is 31[[20B]].

298. (Currently Amended) The pharmaceutical composition of claim 296, wherein the first serotype is 24F[[6C]].

299. (Currently Amended) The pharmaceutical composition of claim 296, wherein the first serotype is 20A[[15A]].

300. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 16F.

301. (Previously Presented) The pharmaceutical composition of claim 296, wherein at least one polypeptide comprises a mixture of polypeptides.

302. (Currently Amended) The pharmaceutical composition of claim 296, wherein at least one polypeptide comprises cross-reacting material 197 (~~CRM197~~CRM_{197}), tetanus toxoid, a diphtheria toxoid, cholera toxoid, pertussis toxoid, inactivated or mutant pneumococcal pneumolysin, pneumococcal surface protein A, pneumococcal adhesion protein A, pneumococcal lipoprotein PsaA, C5a peptidase group A or group B *Streptococcus* ~~Streptococcus~~, a non-typable *H. influenzae* ~~H. influenzae~~ P4 protein, a non-typable *H. influenzae* ~~H. influenzae~~ P6 protein, *M. catarrhalis* ~~M. catarrhalis~~ uspA, keyhole limpet haemocyanin (KLH), outer membrane protein complex (OMPC) from *N. meningitidis* ~~N. meningitidis~~, a purified protein derivative of tuberculin(PPD), protein D from *H. influenzae* ~~H. influenzae~~, PspA, any fragment thereof, or any combination thereof.

303. (Previously Presented) The pharmaceutical composition of claim 296, further comprising an adjuvant; a chelating agent; a surfactant; an emulsifier; a buffering agent; a preservative; a salt; an anti-fungal compound; or a combination thereof.

304. (Previously Presented) The pharmaceutical composition of claim 296, wherein the pharmaceutical composition is in the form of an intramuscularly injectable composition, intradermally injectable composition, subcutaneously injectable composition, or an intranasally administrable composition.

Petitioner Merck Ex-1015, 1488

305. (Previously Presented) The pharmaceutical composition of claim 296, wherein at least one of the immunogenic saccharide-polypeptide conjugates elicits an opsonophagocytic response.

306. (Previously Presented) The pharmaceutical composition of claim 296, wherein the immunogenic saccharide-polypeptide conjugates are collectively present in an amount of at least 0.001%, by weight, based on the weight of the pharmaceutical composition.

307. (Previously Presented) The pharmaceutical composition of claim 296, wherein the immunogenic saccharide-polypeptide conjugates comprise: (i) the capsular polysaccharide at least partially embedded in the polypeptide, (ii) the capsular polysaccharide chemically cross-linked to the polypeptide, and/or (iii) the capsular polysaccharide at least partially chemically cross-linked to the polypeptide.

308. (Previously Presented) The pharmaceutical composition of claim 296, wherein a toxin activity of at least one of the polypeptides is at least partly mitigated.

309. (Previously Presented) The pharmaceutical composition of claim 296, wherein each of the immunogenic saccharide-polypeptide conjugates is present in an amount of at least 0.001%, by weight, based on the weight of the pharmaceutical composition.

310. (Withdrawn) A method comprising administering to a subject a first composition, wherein the first composition comprises the pharmaceutical composition of claim 296.

311. (Withdrawn) The method of claim 310, wherein the first composition is administered intramuscularly.

312. (Withdrawn) The method of claim 310, wherein the administering to the subject the first composition occurs at least about four weeks before or at least about four weeks after an

administration of a second composition comprising an immunogenic saccharide-polypeptide conjugate.

313. (Withdrawn – Currently Amended) The method of claim 312, wherein the second composition comprises an immunogenic saccharide-polypeptide conjugate comprising a capsular polysaccharide from at least one serotype of *Streptococcus pneumoniae* ~~Streptococcus pneumoniae~~ conjugated to a second polypeptide, wherein the at least one serotype comprises 3, 7F, 8, 10A, 11A, 12F, 22F, or 33F.

314. (Withdrawn) The method of claim 310, wherein the subject is a human.

315. (Withdrawn) A method of making a composition comprising: contacting the plurality of immunogenic saccharide-polypeptide conjugates of claim 296 with an excipient, an adjuvant, or any combination thereof.

316. (New) The pharmaceutical composition of claim 296, wherein the first serotype comprises 16F and the at least one additional serotype comprises 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, and 15A.

317. (New) The pharmaceutical composition of claim 296, wherein the first serotype comprises 20A and the at least one additional serotype comprises 7F, 8, 9N, 15A, 15C, 16F, 19A, 22F, 23A, and 23B.

318. (New) The pharmaceutical composition of claim 296, wherein the first serotype comprises 23B and the at least one additional serotype comprises 16F, 20A, 22F, 23A, 24F, 31, 33F, and 35B.

319. (New) The pharmaceutical composition of claim 296, wherein the first serotype comprises 24F and the at least one additional serotype comprises 3, 7F, 8, 9N, 10A, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, and 31.

320. (New) The pharmaceutical composition of claim 296, wherein the first serotype comprises 16F and the at least one additional serotype comprises 3, 7F, 8, 9N, 10A, 12F, 15A, 15C, 17F, 20A, 22F, 23A, 23B, 31, 33F, and 35B.

321. (New) The pharmaceutical composition of claim 296, wherein the first serotype comprises 24F and the at least one additional serotype comprises 3, 6A, 7F, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 19A, 20A, 22F, 23B, 31, and 35B.

322. (New) The pharmaceutical composition of claim 296, wherein the first serotype comprises 31 and the at least one additional serotype comprises 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 22F, 33F, and 35B.

REMARKS

Claims 296-315 were pending in the Application before entrance of the present Amendment, of which claims 310-315 are withdrawn from consideration by the Examiner at this time. By the present Amendment, claims 296-299, 302, and 313 are amended. Applicant reserves the right to pursue the subject matter canceled from the claims in one or more future applications claiming priority to the present Application. Claim 296 is amended to recite a specific subset of first and additional serotypes, to define the fragment of the capsular polysaccharide, and to correct typographical errors. Support for the amendments to claim 296 can be found throughout the originally filed Application, *e.g.*, in original claim 73. Claims 297 and 298 were amended to recite different serotypes in view of the amendments to claim 296. Claim 299 was amended to recite the serotypes deleted from claim 296 by this Amendment. Claim 302 was amended to define two acronyms and to correct typographical errors. Claim 313 was amended to recite a list of the at least one serotypes. Support for the amendments to claim 313 can be found throughout the originally filed Application, *e.g.*, in paragraphs [0043] and [0070], and Table 1 of the Application.

New claims 316-322 have been added to recite specific combinations of serotypes. Support for new claims 316-322 can be found throughout the originally filed Application, *e.g.*, in paragraphs [0043] and [0070], and Table 1 of the Application.

After entrance of the present Amendment, claims 296-322 will be pending in the Application, with claims 310-315 being withdrawn. Applicant submits that no new matter is added to the Application by this Amendment.

Amendment or cancelation of the claims during prosecution of this Application is not to be construed as acquiescence to any of the objections or rejections set forth in the Office Action and was done solely to expedite prosecution of the Application. Applicant reserves the right to pursue the claims as originally filed or similar claims in this particular Application or one or more continuing patent applications claiming priority to this Application.

Each of the rejections levied by the Examiner is addressed in turn below.

Claim Objection

The Examiner objected to claim 302 for reciting acronyms without their respective meanings. Solely to expedite prosecution of the present Application and without acquiescing to the propriety of this objection, Applicant has amended claim 302 to recite "cross-reacting material 197 (CRM_{197})" and "outer membrane protein complex (OMPC)." Accordingly, withdrawal of this objection is respectfully requested.

Claim Rejections under 35 U.S.C. § 112

The Examiner rejected claims 296-309 under 35 U.S.C. § 112(b) as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor regards as the invention. In particular, the Examiner states that the use of the term "fragment thereof" renders claim 296 vague and indefinite. Solely to expedite prosecution of the present Application and without acquiescing to the propriety of this rejection, Applicant has amended claim 296 to recite that the fragment of the capsular polysaccharide is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, a hexasaccharide, or an oligosaccharide. Accordingly, withdrawal of this rejection is respectfully requested.

Claim Rejections under 35 U.S.C. § 102

The Examiner rejected claims 296, 298, 299, and 301-309 under 35 U.S.C. § 102 as allegedly being anticipated by Porro *et al.* (WO 2014/118201; hereinafter "Porro"). Applicant respectfully disagrees.

Nonetheless, solely to expedite prosecution of the present Application and without acquiescing to the propriety of this rejection, claim 296 has been amended to be directed, *inter alia*, to a pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31; at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38; and wherein the at least one additional serotype is not the first serotype. Porro does not teach at least serotypes 16F, 20A, 20B, 24F, or 31, let alone

the recited combination of serotypes. Applicant respectfully requests that this rejection be withdrawn.

The Examiner rejected claims 296, 298, 299, 301-304, and 307 under 35 U.S.C. § 102 as allegedly being anticipated by Matur *et al.* (WO 2016/207905; hereinafter "Matur"). Applicant respectfully disagrees.

Nonetheless, solely to expedite prosecution of the present Application and without acquiescing to the propriety of this rejection, claim 296 has been amended to be directed, *inter alia*, to a pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31; at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38; and wherein the at least one additional serotype is not the first serotype. Matur does not teach at least serotypes 16F, 20A, 20B, 24F, or 31, let alone the recited combination of serotypes. Applicant respectfully requests that this rejection be withdrawn.

The Examiner rejected claims 296, 298, 301-305, 307, and 308 under 35 U.S.C. § 102 as allegedly being anticipated by Bertaud *et al.* (WO 2017/067962; hereinafter "Bertaud"). Applicant respectfully disagrees.

Nonetheless, solely to expedite prosecution of the present Application and without acquiescing to the propriety of this rejection, claim 296 has been amended to be directed, *inter alia*, to a pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31; at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38; and wherein the at least one additional serotype is not the first serotype. Bertaud does not teach at least serotypes 16F, 20A, 20B, 24F, or 31, let

Petitioner Merck Ex-1015, 1494

alone the recited combination of serotypes. Applicant respectfully requests that this rejection be withdrawn.

Claim Rejections under 35 U.S.C. § 103

The Examiner rejected claims 296-309 under 35 U.S.C. § 103 as allegedly being obvious in view of Bertaud in view of del Amo *et al.*, "High invasiveness of pneumococcal serotypes included in the new generation of conjugate vaccines." *Clin Microbiol Infect.* **2013**, 20(7):684-9 (hereinafter "del Amo"). Applicant respectfully disagrees.

Nonetheless, solely to expedite prosecution of the present Application and without acquiescing to the propriety of this rejection, claim 296 has been amended to be directed, *inter alia*, to a pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31; at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38; and wherein the at least one additional serotype is not the first serotype.

At least the recited combination of serotypes is not disclosed or suggested by the cited references. Instead, Bertaud is directed to vaccines comprising *S. pneumoniae* serotype 6A, 6B, 6C, and 6D capsular polysaccharides, as the reference notes "… surprisingly, the present invention provides a sized *Streptococcus pneumoniae* 6A polysaccharide with improved properties …" (Bertaud, page 3, lines 5-6). The reference provides immunogenic compositions comprising numerous combinations of serotype 6A, 6B, 6C, and/or 6D capsular polysaccharides with other serotypes (*e.g.*, pages 9-11); however, none of the combinations include at least serotypes 16F, 20A, 20B, 24F, or 31, as claimed. The Examiner cited del Amo for its purported disclosure of numerous serotypes (*e.g.*, 1, 2, 3, 4, 5, 6A/6B, 6C, 7C/(7B/40), 7F/7A, 8, 9N/9L, 9V/9A, 10A, 10F/(10C/33C), 11A/11D, 12F/(12A/44/46), 13, 14, 15A/15F, 15B/15C, 16F, 17F, 18/(18A/18B/18C/18F), 19A, 19F, 20, 21, 22F/22A, 23A, 23B, 23F, 24/(24A/24B/24F), 31, 33F/(33A/37), 34, 35A/(35C/42), 35B, 35F/47F, 38/25F, and 39); however, the list of serotypes in del Amo are those that may be detected using an assay, not for inclusion in a pharmaceutical composition as claimed. With respect

Petitioner Merck Ex-1015, 1495

to pharmaceutical compositions, del Amo surveyed a number of pediatric samples to conclude that "… serotypes 1, 5, 7F and 19, which became more prevalent in invasive disease in Spain and Portugal during the last decade, have a high invasive disease potential" (del Amo, page 687, left column; internal citations omitted). Therefore, the combined teachings of Bertaud and del Amo would lead the skilled artisan to generate a composition comprising at least one serotype 6 capsular polysaccharide (Bertaud) in combination with serotype 1, 5, 7F, and 19 capsular polysaccharides (del Amo). This is not a combination of the pending claims, which require at least one of the serotypes to be 16F, 20A, 20B, 24F, or 31.

As the cited references do not teach or suggest the pharmaceutical composition of the amended claims, withdrawal of the rejection is respectfully requested.

Double Patenting

Claims 296-309 have been rejected on the ground of non-statutory obviousness-type double patenting as allegedly being unpatentable over claims 1-10 and 12-15 of U.S. Patent No. 11,058,757. Applicant respectfully disagrees. The claims, as amended, are directed a pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31; at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38; and wherein the at least one additional serotype is not the first serotype. The claims, as amended, are patentably distinct from those of U.S. Patent No. 11,058,757. Withdrawal of the rejection is respectfully requested.

Claims 296-309 have been provisionally rejected on the ground of non-statutory obviousness-type double patenting as allegedly being unpatentable over claims 449- 450, 455, 461-466, 470, 471, 473-478, 481, 482-489, and 492-494 of co-pending Application No. 16/753,597. Applicant respectfully disagrees. The claims, as amended, are directed to a pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A,

20B, 24F, or 31; at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38; and wherein the at least one additional serotype is not the first serotype. The claims, as amended, are patentably distinct from those pending in US Application No. 16/753,597. Withdrawal of the rejection is respectfully requested.

General Comments on Dependent Claims

Each of the dependent claims depends from a base claim that is believed to be in condition for allowance, and Applicant therefore believes that it is unnecessary at this time to argue the allowability of each of the dependent claims individually. Applicant does not, however, necessarily concur with the interpretation of the dependent claims as set forth in the Office Action, nor does Applicant concur that the basis for the rejection of any of the dependent claims is proper. Therefore, Applicant reserves the right to specifically address the patentability of the dependent claims in the future.

Petitioner Merck Ex-1015, 1497

In view of the foregoing, this Application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this response, the Application is not in condition for allowance, the Examiner is requested to call the undersigned at the telephone number indicated below to discuss any outstanding issues.

If this Response is not considered timely filed, and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time.

Applicant believes no fee is due with this Response. However, if a fee is due with this Amendment, please charge our Deposit Account No. 23/2825, under Docket No. P1143.70000US05, from which the undersigned is authorized to draw.

Dated: September 27, 2024

Respectfully submitted,

Electronic signature: /Jessica A. von Reyn/
Jessica A. von Reyn
Registration Number: 76,839
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

Petitioner Merck Ex-1015, 1498

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 17/347,435	Filing Date 06/14/2021	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $240 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	09/27/2024	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 27	Minus	** 27	= 0		x $40 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $192 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	Examiner
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/YEN NGO/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/347,435	06/14/2021	Bruce D. Forrest	P1143.70000US05	4020

23628 7590 01/31/2025
WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER	
SHAHNAN SHAH, KHATOL S	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
01/31/2025	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents_eOfficeAction@WolfGreenfield.com
WGS_eOfficeAction@WolfGreenfield.com

Petitioner Merck Ex-1015, 1500

Office Action Summary	Application No. 17/347,435	Applicant(s) Forrest et al.	
	Examiner KHATOL S SHAHNAN SHAH	Art Unit 1645	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 9/27/2024.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 296-322 is/are pending in the application.

5a) Of the above claim(s) 310-315 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 296-309 and 316-322 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 9/27/2024.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Petitioner Merck Ex-1015, 1501

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

2. Applicants' amendment and response of 9/27/2024 are acknowledged. Claims 296-299, 302 and 313 have been amended. New claims 316-322 have been added.

Status of Claims

3. Claims 296-322 are pending. Claims 296-299, 302 and 313 have been amended. New claims 316-322 have been added. Claims 1-295 have canceled by previous amended. Claims 310-315 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on May 20, 2024. Claims 296-309 and 316-322 are currently under examination.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on 9/27/2024 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. An initialed copy is attached hereto.

Claim Objections Withdrawn

5. Objection of claim 302, made in paragraph 7 of the office action mailed 6/27/2024 is withdrawn in view of applicants amendment of 9/27/2024.

Claim Rejection Withdrawn

Claim Rejections - 35 USC § 112

6. Rejection of claims 296-309 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, made in paragraph 7 of the office action mailed 6/27/2024 is withdrawn in view of applicants' amendment of 9/27/2024.

Double Patenting Withdrawn

7. Rejection of claims 296-309 on the ground of non-statutory double patenting as being unpatentable over claims 1-10, 12-14 and 15 of U.S. Patent No. 11,058,757 B2, is withdrawn in view of applicants' amendment of 9/27/2024.

Double Patenting Withdrawn

8. Rejection of claims 296-309 provisionally rejected on the ground of non-statutory double patenting as being unpatentable over claims 449- 450, 455, 461- 466, 470, 471, 473- 478, 481, 482-489, 492-494 of co-pending Application No. 16/753,597 (reference application has not been published), is withdrawn in view of applicants' amendment of 9/27/2024.

Claim Rejections - 35 USC § 102 Withdrawn

9. Rejection of claims 296, 298, 299, 301, 302, 303, 304, and 307 are rejected under 35 U.S.C. 102(a)(1)/102(a)(2) as being anticipated by Matur et al., (WO 2016207805 A1, priority to 6/23/2015, is withdrawn in view of applicants' amendment of 9/27/2024.

Claim Rejections - 35 USC § 102 Withdrawn

10. Rejection of claims 296, 298, 301, 302, 303, 304, 305, 307 and 308 are rejected under 35 U.S.C. 102(a)(1)/102(a)(2) as being anticipated by Bertaud et al., (WO 2017/067962 A1, priority to 10/21/2015, submitted on Applicant's IDS), is withdrawn in view of applicants' amendment of 9/27/2024.

Claim Rejections - 35 USC § 103 Withdrawn

11. Rejection of claims 296-309 is rejected under 35 U.S.C. 103 as being unpatentable over Bertaud et al., WO 2017/067962 A1, priority to 10/21/2015 as applied to claims 296, 298, 301, 302, 303, 304, 305, 307 and 308 above, and further in view of del Amo et al. Clinical Microbiology and Infection vol. 20, pp. 684-689, 8 November 2013, is withdrawn in view of applicants' amendment of 9/27/2024.

Claim Rejections - 35 USC § 102 Maintained

12. Rejection of claims 296, 298, 299, 301, 302, 303, 304, 305, 306, 307, 308 and 309 are rejected under 35 U.S.C. 102(a)(1)/102(a)(2) as being anticipated by Porro et al., (WO 2014/118201 A1), priority to 1/31/2013, is maintained.

Amended claim 296 is drawn to a pharmaceutical composition comprising at least 2 immunogenic saccharide- polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique Streptococcus pneumoniae serotype, wherein a first serotype comprises 16, 20A, 20B, 24F or 31 and at least one additional serotype is selected from the group consisting of 1, 2, 3, 4,5, 6A, 6B, 6C, 7F, OV, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 22F, 23A, 23B, 24F, 31, 33F, 34, 35B, and 38, wherein the at least one additional serotype is not the first serotype; and wherein the fragment of the capsular polysaccharide is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, a hexasaccharide or an oligosaccharide.

Porro et al. disclose limitations of claims 296, 298, 299 a pharmaceutical or antigenic multivalent molecular construct consisting of a basic unit comprising a helper-T dependent carrier protein covalently bound to a minimum of three carbohydrate structures of different serological specificity, wherein each carbohydrate structure are at least three capsular polysaccharides selected among type 1, 2, 3, 4, 5, 6A, 6B, 6C, 6D, 7F, 8. 9N, 9V,10A, 11A, 11B, 11C, 11F, 12F, 14, 15A, 15B, 15C, 17F, 18C, 19F, 20, 22F, 23A, 23F, 33F and 35B of Streptococcus pneumoniae (see abs, claims specially claims 1, 2, 4, 5, 8, 9, 11. As to amended claim 296, Porro et al. teach serotype 20 which inherently include serotypes 20A and 20 B (see claim 6, pages 3, 20, 81). Porro et al. teach monosaccharide and oligosaccharide (see pages 5, 6, 8, 9, 12, 48, 80). Porro et al. disclose conjugated polypeptides to capsular polysaccharides (see claims). The invention contains each *S. pneumonia* capsular saccharide (see page 8, 12, 68 and claim 5). Porro et al. disclose that examples of carrier proteins which may be used in the present invention are diphtheria toxoid, tetanus toxoid, CRM197, pneumococcal surface protein (see

claims 4, 7 8). meeting the limitation of claims 301, 302, 307). Porro et al. disclose cross-linked polysaccharide to poly peptide limitations of claim 307 see pages 43, 45 and 47. Porro et al. disclose the immunogenic composition may be adjuvanted (pages 26,31, 60, 63 and tables 5,6 and claims 13-14), and may further comprise a buffering agent (pages 36, 38, 43, 47, 52 and fig 4) and a salt (page 38 (meeting the limitation of claim 303). Moreover, the vaccine preparation (claim 11-12; meeting the limitation of claim 304) containing immunogenic compositions may be administered via the intramuscular, intradermal or subcutaneous routes (see page 31,61 and claim 14). As to limitation of claim 305, Porro et al. teach opsonophagocytic response (see pages 20, 61). As to limitation of claims 306 and 309. Porro et al. teach 0.1 to 1.0 microgram saccharide-polypeptide conjugate amount by weight (see claim 12 , page 62). As it pertains to claim 308, the Office takes the position that the prior art meets this limitation, particularly, the polypeptide that is a toxoid based upon Applicant's definition: paragraph 035- The term "partly mitigated" in reference to the toxin activity of a polypeptide can refer to a decreased toxicity of the polypeptide as compared to a wild type version of the polypeptide. A CRM197 protein or toxoid is inherently, based upon Applicant's definition, 'partly mitigated'.

The prior art anticipates the claimed invention.

Since the Office does not have the facilities for examining and comparing applicants' composition with the composition of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and in re Fitzgerald et al., 205 USPQ 594.

Applicants' Arguments and Office Response

13. Applicant's arguments filed 9/27/2024 have been fully considered but they are not persuasive. Applicants argue:

> The Examiner rejected claims 296,298,299, and 301-309 under 35 U.S.C. § 102 as allegedly being anticipated by Porro *et al.* (WO 014/118201; hereinafter "Porro"). Applicant respectfully disagrees.
>
> Nonetheless, solely to expedite prosecution of the present Application and without acquiescing to the propriety of this rejection, claim 296 has been amended

to be directed, *inter alia,* to a pharmaceutical composition comprising a plurality of at least two immunogenic saccharide- polypeptide conjugates from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31; at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, lOA, 1 lA, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38; and wherein the at least one additional serotype is not the first serotype. Porro does not teach at least serotypes 16F, 20A, 20B, 24F, or 31, let alone the recited combination of serotypes. Applicant respectfully requests that this rejection be withdrawn.

In response to applicants' arguments, it is the examiner's position that Porro teach the limitations of amended claim 296. Porro et al. disclose limitations of claims 296, a pharmaceutical or antigenic multivalent molecular construct consisting of a basic unit comprising a helper-T dependent carrier protein covalently bound to a minimum of three carbohydrate structures of different serological specificity, wherein each carbohydrate structure are at least three capsular polysaccharides selected among type 1, 2, 3, 4, 5, 6A, 6B, 6C, 6D, 7F, 8. 9N, 9V,10A, 11A, 11B, 11C, 11F, 12F, 14, 15A, 15B, 15C, 17F, 18C, 19F, **20**, 22F, 23A, 23F, 33F and 35B of Streptococcus pneumoniae (see abs, claims specially claims 1, 2, 4, 5, 8, 9, 11. As to amended claim 296, Porro et al. teach **serotype 20** which inherently include **serotypes 20A and/or 20 B** (see claim 6, pages 3, 20, 81). Porro et al. teach monosaccharide and oligosaccharide (see pages 5, 6, 8, 9, 12, 48, 80). Porro et al. disclose conjugated polypeptides to capsular polysaccharides (see claims). The invention contains each *S. pneumonia* capsular saccharide (see page 8, 12, 68 and claim 5).

Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

15. Claims 296-309 and new claims 316-322 are rejected under 35 U.S.C. 103 as being unpatentable over Porro et al., (WO 2014/118201 A1), priority to 1/31/2013, in view of John J. Mekalanos US 9533032 B and further in view of del Amo et al. (Clinical Microbiology and Infection vol. 20, pp. 684-689, 8 November 2013).

Amended claim 296 is drawn to a pharmaceutical composition comprising at least 2 immunogenic saccharide- polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique Streptococcus pneumoniae serotype, wherein a first serotype comprises 16, 20A, 20B, 24F or 31 and at least one additional serotype is selected from the group consisting of 1, 2, 3, 4,5, 6A, 6B, 6C, 7F, OV, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 22F, 23A, 23B, 24F, 31, 33F, 34, 35B, and 38, wherein the at least one additional serotype is not the first serotype; and wherein the fragment of the capsular polysaccharide is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, a hexasaccharide or an oligosaccharide.

Porro et al. disclose limitations of claims 296, 298, 299 a pharmaceutical or antigenic multivalent molecular construct consisting of a basic unit comprising a helper-T dependent carrier protein covalently bound to a minimum of three carbohydrate structures of different serological specificity, wherein each carbohydrate structure are at least three capsular polysaccharides selected among type 1, 2, 3, 4, 5, 6A, 6B, 6C, 6D, 7F, 8. 9N, 9V,10A, 11A, 11B, 11C, 11F, 12F, 14, 15A, 15B, 15C, 17F, 18C, 19F, 20, 22F, 23A, 23F, 33F and 35B of Streptococcus pneumoniae (see abs, claims specially claims 1, 2, 4, 5, 8, 9, 11. As to amended claim 296, Porro et al. teach serotype 20 which inherently include serotypes 20A and

20 B (see claim 6, pages 3, 20, 81). Porro et al. teach monosaccharide and oligosaccharide (see pages 5, 6, 8, 9, 12, 48, 80). Porro et al. disclose conjugated polypeptides to capsular polysaccharides (see claims). The invention contains each *S. pneumonia* capsular saccharide (see page 8, 12, 68 and claim 5). Porro et al. disclose that examples of carrier proteins which may be used in the present invention are diphtheria toxoid, tetanus toxoid, CRM197, pneumococcal surface protein (see claims 4, 7 8). meeting the limitation of claims 301, 302, 307). Porro et al. disclose cross-linked polysaccharide to poly peptide limitations of claim 307 see pages 43, 45 and 47. Porro et al. disclose the immunogenic composition may be adjuvanted (pages 26,31, 60, 63 and tables 5,6 and claims 13-14), and may further comprise a buffering agent (pages 36, 38, 43, 47, 52 and fig 4) and a salt (page 38 (meeting the limitation of claim 303). Moreover, the vaccine preparation (claim 11-12; meeting the limitation of claim 304) containing immunogenic compositions may be administered via the intramuscular, intradermal or subcutaneous routes (see page 31,61 and claim 14). As to limitation of claim 305, Porro et al. teach opsonophagocytic response (see pages 20, 61). As to limitation of claims 306 and 309. Porro et al. teach 0.1 to 1.0 microgram saccharide-polypeptide conjugate amount by weight (see claim 12 , page 62). As it pertains to claim 308, the Office takes the position that the prior art meets this limitation, particularly, the polypeptide that is a toxoid based upon Applicant's definition: paragraph 035- The term "partly mitigated" in reference to the toxin activity of a polypeptide can refer to a decreased toxicity of the polypeptide as compared to a wild type version of the polypeptide. A CRM197 protein or toxoid is inherently, based upon Applicant's definition, 'partly mitigated'.

Porro et al. do not teach serotypes 16F, 19A, 23B. 24F or 31.
Mekalanos teaches a vaccine composition comprising at least 2 immunogenic saccharide- polypeptide conjugates each comprising individually a capsular polysaccharide (see claims, abstract and columns 17-18). Mekalanos claim 15 teaches *Streptococcus pneumoniae* polysaccharide is capsular type 1, 2, 3, 4, 5, 6A, 6B, 7A, 7B, 7C, 7F, 8, 9A, 9L, 9N, 9V, 10A, 10B, 10F, 11A, 11B, 11C, 11D, 11F, 12A, 12B, 12F, 13, 14, 15A, 15B, 15C, 15F, 16A, **16F**, 17A, 17F, 18A, 18B, 18C, 18F, **19A**, 19B, 19C, 19F, **20**, 21, 22F, **23B**, 23F, 24A, 24B, **24F**, 25A, 25F, 27, 28A, 28F, 29, **31**, 32A, 32F,

33A, 33B, 33D, 33F, 34, 35A, 35B, 35F, 36, 37, 38, 39, 40, 41A, 41F, 42, 43, 44, 45, 46, 47A, 47F, or 48. The above serotypes include serotypes **16F, 20, 24F and 31**. As to newly added claims 316, 317, 319, 320, 321, 322 the added serotype have been taught by Mekalanos including 19A, 23B and others recited in those claims.

Additionally, del Amo et al. teach plurality of Streptococcal pneumoniae serotypes included in the new generations of conjugate vaccines or pharmaceutical compositions (see title, abstract page 685 and tables 1 and 2). del Amo et al. teach 40 serotypes/serogroups (1, 2, 3, 4, 5, 6A/6B, 6C, 7C/(7B/ 40), 7F/7A, 8, 9N/9L, 9V/9A, 10A, 10F/(10C/33C), 11A/11D, 12F/(12A/44/46), 13, 14, 15A/15F, 15B/15C, **16F**, 17F, 18/(18A/ 18B/18C/18F), **19A**, 19F, **20**, 21, 22F/22A, 23A, **23B**, 23F, 24/ (24A/24B/**24F**), **31**, 33F/(33A/37), 34, 35A/(35C/42), 35B, 35F/ 47F, 38/25F, 39) see page 685.

It would have been obvious before the effective filing date of the presently claimed invention to employ serotypes 16F,19A, 23B, 24F, 31 taught by del Amo et al. and Mekalanos together with the claimed serotypes recited by Porro et al. to obtain the claimed invention. Because the extra serotypes further cover infections associated with that serotype with a reasonable expectation of success. One of skill in the art would be motivated because one can prevent those infections also. There is an expectation of success because Porro et al. specifically teach that you can mix any of the ones listed and the conjugates have been made with various mixtures for a long time. All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. See the recent Board decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396). Accordingly, the subject matter of claims w o u l d have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the presently claimed invention, absent evidence to the contrary.

Additionally, *KSR International Co. v. Teleflex Inc.,* 127 S. Ct. 1727, 1741 (2007), discloses combining prior art elements according to known methods to yield predictable results, thus the combination is obvious unless its application is beyond that

person's skill. *KSR International Co. v. Teleflex Inc.,* 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It is well known to combine known serotypes recited by the claims in a conjugate which function in a predictable manner to yield a reasonable expectation of success along with predictable results to one of ordinary skill in the art at the time of the invention. Thus, it would have been obvious to a person of ordinary skill in the art to combine prior art elements according to known methods that is ready for improvement to yield predictable results. The claimed invention is *prima facie* obvious in view of the teachings of the prior art, absent any convincing evidence to the contrary.

Conclusion

20. No claims are allowed.

21. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KHATOL S SHAHNAN SHAH whose telephone number is (571)272-0863. The examiner can normally be reached on Mon-Tue, Thurs-Fri 12pm-8pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Khatol S Shahnan-Shah/
Examiner, Art Unit 1645
January 25, 2025

/JANA A HINES/
Primary Examiner, Art Unit 1645

Notice of References Cited	Application/Control No. 17/347,435	Applicant(s)/Patent Under Reexamination Forrest	
	Examiner KHATOL S SHAHNAN SHAH	Art Unit 1645	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date YYYY-MM-DD	Name	CPC Classification	US Classification
*	A	US-9533032-B2	2017-01-03	Mekalanos; John J.	A61P31/16	1/1
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date YYYY-MM-DD	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in YYYY-MM-DD format are publication dates. Classifications may be US or foreign.

Petitioner Merck Ex-1015, 1512

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/347,435	Forrest et al.
	Examiner	Art Unit
	KHATOL S SHAHNAN SHAH	1645

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
P2E2 all databases	12/28/2024	KSS
PALM inventor, biotech, continuity, priority	12/28/2024	KSS
Google scholar	12/28/2024	KSS
NPL	12/28/2024	KSS
Checked co pending applications	12/28/2024	KSS
Consulted Primary HInes	01/22/2025	KSS

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/KHATOL S SHAHNAN SHAH/ Examiner, Art Unit 1645	

Petitioner Merck Ex-1015, 1513

Immunogenicity of **conjugate** vaccines consisting of pneumococcal capsular polysaccharide types 6B, 14, 19F, and 23F and a meningococcal outer membrane protein …

PP Vella, S Marburg, JM Staub, PJ Kniskern… - Infection and …, 1992 - Am Soc Microbiol

… reduction by thermal **or** sonication treatment before **conjugation** (26… dependent anti-Ps responses (23, **31**, 43). Mice and nonhu… Studies with additional **serotypes** are ongoing. The use of …

☆ Save 99 Cite Cited by 77 Related articles All 9 versions

Association between **serotype**-specific antibody response and **serotype** characteristics in patients with pneumococcal pneumonia, with special reference to degree of …

S Athlin, M Kalfoff, HC Slotved… - Clinical and Vaccine …, 2014 - Am Soc Microbiol

… **serotype** with respect to sampling site (blood, sputum, **or** … A total of **16 serotypes** were identified in 132 isolates, with … Efficacy of a pneumococcal **conjugate** vaccine against acute …

☆ Save 99 Cite Cited by 24 Related articles All 12 versions

Global **serotype** distribution among Streptococcus pneumoniae isolates causing otitis media in children: potential implications for pneumococcal **conjugate** …

GL Rodgers, A Arguedas, R Cohen, R Dagan - Vaccine, 2009 - Elsevier

… **Serotype 16F**, a frequent **serotype** found in nasopharyngeal … from 10% to **24%** to become the predominant **serotype** in OM in … 19A isolates from nine children with recurrent AOM **or** AOM-…

☆ Save 99 Cite Cited by 186 Related articles All 12 versions

Immunogenicity of PCV24, an expanded pneumococcal **conjugate** vaccine, in adult monkeys and protection in mice

D McGuinness, RM Kaufhold, PM McHugh, MA Winters… - Vaccine, 2021 - Elsevier

… for the remaining **serotypes**: **31** to 43-fold for **serotypes** 4, 2, … with PCV13 **or** V114, for the majority of the common **serotypes**. … **serotype 20A conjugated** polysaccharide, referred to as **20** in …

☆ Save 99 Cite Cited by 18 Related articles All 5 versions

… , genetic, and serological characterization of two capsule subtypes among Streptococcus pneumoniae **serotype 20** strains: discovery of a new pneumococcal **serotype**

JJ Calix, RJ Porambo, AM Brady, TR Larson… - Journal of Biological …, 2012 - ASBMB

… **conjugate** vaccine against vaccine-related **serotypes** 6A and … by the SSI **serotype 20** strain **or** other **serotype 20** clinical … The 1 H- **31** P correlation experiment was a HMBC with transfer …

☆ Save 99 Cite Cited by 220 Related articles All 9 versions

Emergence of Penicillin-Nonsusceptible *Streptococcus pneumoniae* Clones Expressing **Serotypes** Not Present in the Antipneumococcal **Conjugate** Vaccine

N Porat, A Arguedas, BG Spratt, R Trefler… - The Journal of …, 2004 - academic.oup.com

… the world, including in Israel [**31**], and is shared by strains … from southern Israel (**16**/19 [84%]) than among Jews (3/ 19 [**16%**]). … those in developing countries **or** particular groups within …

☆ Save 99 Cite Cited by 110 Related articles All 13 versions »

Comparative genomic analysis of two ST320 *Streptococcus pneumoniae* isolates, representing **serotypes** 19A and 19F

W Puzia, J Gawor, R Gromadka, A Skoczyńska… - BMC Genomic …, 2023 - Springer

… The efficacy of polysaccharide **conjugate** vaccines formulated … PCV7 **or** were introduced de novo into the national **or** local … using the SDS/phenol method [**31**]. In brief, bacteria were …

☆ Save 99 Cite Cited by 2 Related articles All 9 versions

Transplacental transmission of **serotype**-specific pneumococcal antibodies in a Brazilian population

BTC Carvalho, MM Carneiro-Sampaio… - Clinical Diagnostic …, 1999 - Am Soc Microbiol

… **Conjugate** pneumococcal vaccines containing five **or** seven … in several studies (1, 3, **31**). However, these vaccines are still … against **serotype** 3, which is not included in the **conjugate** …

☆ Save 99 Cite Cited by 41 Related articles All 10 versions

Distribution of *Streptococcus pneumoniae* **serotypes** in the northeast macro-region of São Paulo state/Brazil after the introduction of **conjugate** vaccine

MIC Medeiros, SCG Almeida, MLLS Guerra… - BMC Infectious …, 2017 - Springer

… from individuals with IPDs during the **16**-year period from 1998 to … Evaluating all age groups and **serotypes** with 10 **or** more … **Serotype** 1 greatly affected patients from 2 to **20** years old (…

☆ Save 99 Cite Cited by 8 Related articles All 13 versions

Complicated pneumococcal pneumonia with pleural effusion **or** empyema in the 13-valent pneumococcal **conjugate** vaccine era

A Díaz-Conradi, S Hernández… - Pediatric …, 2019 - Wiley Online Library

… (8/**31**, 25.8%) than … **serotypes** causing pneumonia complicated with PE **or** empyema between 2012 and 2015 showed there was a significant decrease in the proportion of **serotype** 1 (**16**/…

☆ Save 99 Cite Cited by 21 Related articles All 4 versions

… , genetic, and serological characterization of two capsule subtypes among **Streptococcus** pneumoniae **serotype 20** strains: discovery of a new pneumococcal **serotype**

JJ Calix, RJ Porambo, AM Brady, TR Larson… - Journal of Biological …, 2012 - ASBMB

… analyses of the **vaccine**-associated **serotype 20** do not agree … noted among strains typed as **serotype 20**. We examined the … 20β capsule structure **20B**, a new pneumococcal **serotype**. …

☆ Save 99 Cite Cited by 220 Related articles All 9 versions

Characteristics of **serogroup 20** *S.pneumoniae* isolates from Brazil

J Caierão, FN Sant'Anna, P Hawkins, GR Cunha… - BMC Infectious …, 2016 - Springer

… Although **serogroup 20** is not part of any conjugate pneumococcal **vaccine**, its **serotype 20A**, but not **20B**, belongs to the polysaccharide 23-valent formula. Little is known about its …

☆ Save 99 Cite Cited by 13 Related articles All 14 versions

New pneumococcal **serotype** 20C is a WciG O-acetyltransferase deficient variant of canonical **serotype 20B**

J Yu, N Ravenscroft, P Davey, R Liyanage… - Microbiology …, 2024 - journals.asm.org

… Since only a limited number of **serotypes** are targeted by the **vaccines**, non-**vaccine** … Structural, genetic, and serological elucidation of **Streptococcus** pneumoniae **serogroup** 24 **serotypes**…

☆ Save 99 Cite Related articles All 4 versions

A New Pneumococcal Capsule Type, 10D, is the 100th **Serotype** and Has a Large *cps* Fragment from an Oral **Streptococcus**

F Gansale, JS Saad, L McGee, AJ van Tonder… - MBio, 2020 - Am Soc Microbiol

… specific, PCVs provide protection only against the **serotypes** included in the **vaccine** (5). Pneumococcus displays one of many structurally diverse capsules, with 99 identified so far (…

☆ Save 99 Cite Cited by 301 Related articles All 12 versions

Whole genome sequencing of **Streptococcus** pneumoniae: development, evaluation and verification of targets for **serogroup** and **serotype** prediction using an …

G Kapatai, CL Sheppard, AAl-Shahib, DJ Litt… - PeerJ, 2016 - peerj.com

… Additional '**serotypes**' (6E, 6F, 6G, 6H, 11E, **20A** and **20B**) have … PCV13-**serotype** reduction and non-**vaccine serotype** increase … of **serotypes** due to the clonal expansion of non-**vaccine** …

☆ Save 99 Cite Cited by 157 Related articles All 13 versions »

Streptococcus *pneumoniae* **serotype** 33G: genetic, serological, and structural analysis of a new capsule type

S Manna, JP Werren, BD Ortika, B Bellich… - Microbiology …, 2024 - Am Soc Microbiol

… **serotype**, which we have named 33G. We detected **serotype** 33G in nasopharyngeal swabs (n = **20**) … Accurate **serotyping** data are essential in evaluating **vaccine** impact in carriage and …

☆ Save 99 Cite Cited by 12 Related articles All 14 versions

… assay for pneumococcal antibodies against additional **serotypes** and discovery of serological subtypes in **Streptococcus** pneumoniae **serotype 20**

RL Burton, MH Nahm - Clinical and Vaccine Immunology, 2012 - Am Soc Microbiol

… we therefore provisionally assigned them to **serotype 20A** and **serotype 20B**, respectively. … 6320 to **serotype 20A** and the remaining type **20** strains tested in this study to **serotype 20B**. …

☆ Save 99 Cite Cited by 82 Related articles All 6 versions

Genomic analysis of ***Streptococcus*** *pneumoniae* **serogroup 20** isolates in Alberta, Canada from 1993–2019

AN Williams, A Ma, MA Croxen… - Microbial …, 2023 - microbiologyresearch.org

… Subtyping of **serogroup 20** genomes as **20A** or **20B** was determined by standalone … **vaccination** in 1997, cases of invasive **serogroup 20**, appearing to be predominantly **serotype 20B**, …

☆ Save 99 Cite Cited by 1 Related articles All 7 versions

Changes in the incidence of **Streptococcus** pneumoniae bacteremia and its **serotypes** over 10 years in one hospital in South Korea

M Park, HS Kim, KS Shin, HS Kim, JY Park, W Song… - Vaccine, 2014 - Elsevier

… Here, we examined the distribution of pneumococcal **serotypes** and the antibiotic susceptibility of **Streptococcus** pneumoniae in clinical blood isolates. The **serotypes** of 91 S. …

☆ Save 99 Cite Cited by 13 Related articles All 9 versions

Genetic diversity of fluoroquinolone-nonsusceptible ***Streptococcus*** *pneumoniae* clinical isolates and the first identification of **serotype 20B** in China

Q Guo, C Zhuo, Y Xu, W Huang, C Wang… - European journal of …, 2014 - Springer

… that **serotype 20** contained two subgroups, **20A** and **20B**. They were … **vaccinated** with the 23-valent pneumococcal polysaccharide **vaccine** (PPV23), since PPV-23 contains **serotype 20A** …

☆ Save 99 Cite Cited by 10 Related articles All 9 versions

Structural, genetic, and serological elucidation of **Streptococcus** pneumoniae **serogroup 24 serotypes**: discovery of a new **serotype**, 24C, with a variable capsule …

F Gamaia, K Maruhn, C Li, RJ Porambo… - Journal of clinical …, 2021 - Am Soc Microbiol

… Although conjugate **vaccines** have brought about a significant reduction in … **vaccine serotypes**, the relative **serotype** prevalence has shifted with the dramatic emergence of **serotype 24F** …

☆ Save 99 Cite Cited by 67 Related articles All 11 versions

Molecular characterization and epidemiology of ***Streptococcus*** *pneumoniae* **serotype 24F** in Denmark

ID Kavalari, K Fuursted, KA Krogfelt, HC Slotved - Scientific Reports, 2019 - nature.com

… of new pneumococcal **serotypes** not included in the **vaccines** 1 . One of the non-PCV **serotypes** that has emerged in recent years is **serotype 24F** 4,5 . The non-**vaccine serotype 24F** is …

☆ Save 99 Cite Cited by 33 Related articles All 14 versions

Bacteriological and molecular characterization of temperature- and CO_2-dependent ***Streptococcus*** *pneumoniae* **serotype 24F** ST162 isolated from Japanese …

J Kobayashi, M Ohkusu, T Matsumoto… - Microbiology …, 2023 - Am Soc Microbiol

… **Streptococcus** pneumoniae **serotype 24F** is one of the most prevalent non-**vaccine serotypes** that causes invasive pneumococcal disease (IPD) in many countries, including Japan. This …

☆ Save 99 Cite Cited by 2 Related articles All 5 versions

Clinical Relevance and Molecular Pathogenesis of the Emerging **Serotypes** 22F and 33F of ***Streptococcus*** *pneumoniae* in Spain

J Sempere, S De Miguel… - Frontiers in …, 2020 - frontiersin.org

… the impact of current **vaccine** strategies in the epidemiology of **serotypes** 22F and 33F during … Finally, **serotypes** 11A and **24F** avoided very efficiently the phagocytosis in comparison to …

☆ Save 99 Cite Cited by 48 Related articles All 12 versions »

Serotype distribution of ***Streptococcus*** *pneumoniae* causing invasive disease in children in the post-PCV era: A systematic review and meta-analysis

E Balsells, L Guillot, H Nair, MH Kyaw - PloS one, 2017 - journals.plos.org

… a limited number of **serotypes** and the potential role of non-**vaccine serotypes**. The first PCV, … Notably, **serotype 24F** appears to be prevalent in Europe and Western Pacific regions, but …

☆ Save 99 Cite Cited by 411 Related articles All 17 versions »

A Novel, Multiple Drug–Resistant, **Serotype 24F** Strain of ***Streptococcus*** *pneumoniae* That Caused Meningitis in Patients in Naples, Italy

A Pantosti, G Gherardi, M Conte, F Faella… - Clinical infectious …, 2002 - academic.oup.com

… express a nonvaccine **serotype** capsule (eg, **serotype 24F**). … the pneumococcal **vaccine**, this **vaccine** could theoretically … of **vaccine serotypes** to switch to new nonvaccine **serotypes** is …

☆ Save 99 Cite Cited by 40 Related articles All 14 versions »

Genetic characteristics of invasive pneumococcal disease-derived **Streptococcus** pneumoniae of **serogroup 24** isolated in Tokyo, Japan

Y Uchitani, R Okuno, T Ariyoshi, H Kubota… - Journal of Infection and …, 2024 - Elsevier

… Since the introduction of the national routine **vaccination** program against **Streptococcus** … non-**vaccine serotypes** has increased. This study focused on non-**vaccine serogroup 24** strains …

☆ Save 99 Cite Related articles All 3 versions

… **serotype** distribution among **Streptococcus** pneumoniae isolates causing otitis media in children: potential implications for pneumococcal conjugate **vaccines**

GL Rodgers, A Arguedas, R Cohen, R Dagan - Vaccine, 2009 - Elsevier

… colonization by certain **serotypes** and their propensity to cause AOM. This review examines the global **serotype** distribution relationship between pneumococcal **serotypes** and AOM in …

☆ Save 99 Cite Cited by 186 Related articles All 12 versions

Prevalence of **Streptococcus** pneumoniae **serotypes** causing invasive and non-invasive disease in South East Asia: a review

E Jauneikaite, JM Jefferies, ML Hibberd, SC Clarke - Vaccine, 2012 - Elsevier

… Using the Quellung reaction (with full antisera set and factor), **24%** of all Malaysian isolates were **serotype** 19F and 7.8% were 6B (data not shown). Studies from Thailand reported data …

☆ Save 99 Cite Cited by 113 Related articles All 13 versions

Impact of the Conjugation Method on the Immunogenicity of ***Streptococcus*** *pneumoniae* **Serotype** 19F Polysaccharide in Conjugate **Vaccines**

J Poolman, C Frasch, A Nurkka… - Clinical and Vaccine …, 2011 - Am Soc Microbiol

… Biologicals) are two pneumococcal conjugate **vaccines** licensed for the prevention of … by the **vaccine serotypes** of **Streptococcus** pneumoniae. Neither **vaccine** contains **serotype** 19A, …

☆ Save 99 Cite Cited by 118 Related articles All 7 versions

Related searches

pneumococcal conjugate vaccine serotypes

7 valent conjugate vaccine serotype **19a**

streptococcus **pneumoniae** serotype **distribution**

streptococcus **pneumoniae** serotype **19a**

streptococcus **pneumoniae** serotype **12f**

streptococcus **pneumoniae** serotype **22f**

serotype **23f** streptococcus **pneumoniae**

prevalence of streptococcus **pneumoniae** serotypes

streptococcus **pneumoniae** serotype **11a**

capsular genes streptococcus **pneumoniae** serogroup

eight children's hospitals streptococcus **pneumoniae** serotype

recombinant clone streptococcus **pneumoniae** serotype

conjugate vaccine serotypes streptococcus **pneumoniae clones**

conjugate vaccine serotypes **southern israel**

conjugate vaccine serotypes **acute otitis media**

sequence diversity streptococcus **pneumoniae** serogroup

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L3206	44	forrest ADJ bruce	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/01/21 04:56 PM
L3207	21	L3206 AND (saccharide-polypeptide)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/01/21 04:56 PM
L3208	10	L3207 AND (streptococcus ADJ pneumoniae)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/01/21 04:57 PM
L3209	149	love ADJ jack	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB,	OR	ON	ON	2025/01/21 04:58 PM

Petitioner Merck Ex-1015, 1520

			HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)				
L3210	14	L3209 AND (saccharide-polypeptide)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/01/21 04:59 PM
L3211	8	L3210 AND streptococcus	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/01/21 04:59 PM
L3212	867	saccharide ADJ polypeptide	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/01/21 05:01 PM
L3213	8	L3211 AND conjugate	(US-PGPUB; USPAT; USOCR; FIT (AP, AT,	OR	ON	ON	2025/01/21 05:01 PM

Petitioner Merck Ex-1015, 1521

			AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)				
L3214	8	L3213 AND (16F OR 20A OR 20B OR 24F OR "31")	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/01/21 05:03 PM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

Petitioner Merck Ex-1015, 1522

Impact of molecular methods in the analysis of the invasiveness of **Streptococcus pneumoniae**

E Arno Moran - 2016 - diposit.ub.edu

... is a good method to determine the capsular **serotype** of **Streptococcus pneumoniae**. ... **pneumococcal serotypes** from isolate sets (**20**, 29) and also from clinical specimens (3, 23, **31**, 33, ...

☆ Save 99 Cite Related articles All 2 versions »

Novel synthetic antimicrobial peptides with In-Vivo and In-Vitro activity against **Streptococcus Pneumoniae**/Le Cheng Foh

CF Le - 2013 - studentsrepo.um.edu.my

... **Serotypes** 19F and 23F were the two prevailing **serotypes** ... di mana kadar pelindungan sebanyak **20** – 50% lebih tinggi ... differs in their chemical **compositions** which give rise to the ...

☆ Save 99 Cite Related articles All 2 versions »

Multiplex PCR assay for detection of **pneumococcal serotypes** in nasopharyngeal samples of healthy children; Tehran, 2009-2010

SR Tabatabaei, F Fallah, F Shiva... - ... & Review in ..., 2014 - library.go4manuaub.com

... , widely different rates have been reported by various researchers [2,8,**20**-26]. Eleven ... by PCR in the different **serotypes** of **Streptococcus pneumoniae** isolated from ... 2006;44(1):124-**31**. ...

☆ Save 99 Cite Cited by 9 Related articles All 3 versions »

Molecular identification and detection of **streptococcus pneumoniae serotypes** isolated from selected hospitals in tehran using multiplex PCR method

S RafieiTabatabaei, F Fallah, D Afshar... - Journal of Babol ..., 2019 - jbums.org

... **Serotype** distribution of **Streptococcus pneumoniae** causing invasive disease in children in the post-... of capsular types and **drug** resistance patterns of invasive pediatric **Streptococcus** ...

☆ Save 99 Cite Cited by 3 Related articles All 7 versions »

Serotype Distribution of **Streptococcus pneumoniae** Carriage in Six-Month-Old Infants: A Cross-sectional Study During 2017-18, Tehran, Iran

S Sayyahfar, A Esteghamati, SA Fahimzad... - Archives of Pediatric ..., 2022 - briefiands.com

... in concordance with those of the present study (**24**). Accordingly, the researchers concluded ... **Serotype** 23F as the most frequent **serotype** inducing invasive **pneumococcal** diseases (**16**). ...

☆ Save 99 Cite Cited by 2 Related articles All 9 versions »

Pectic Polysaccharides Isolated from Malian **Medicinal** Plants Protect against ***Streptococcus pneumoniae*** in a Mouse **Pneumococcal** Infection Model

KT Inngjerdingen, BK Langerud... - Scandinavian ..., 2013 - Wiley Online Library

... in Mali has been reported to be about **20**% 3. Worldwide, an ... A strain of **Streptococcus pneumoniae serotype** 6B was ... the expression of TLR4 on macrophages **31**. The ability of the ...

☆ Save 99 Cite Cited by 25 Related articles All 5 versions

PI3Kδ hyper-activation promotes development of B cells that exacerbate ***Streptococcus pneumoniae*** infection in an antibody-independent manner

AK Stark, A Chandra, K Chakraborty, R Alam... - Nature ..., 2018 - nature.com

... **pneumoniae** (TIGR4 **serotype** 4) and followed their survival ... with inhaled nemiralisib **24** h prior to infection led to a **20%** ... produce high levels of IL-10 **31**,32 . We obtained blood samples ...

☆ Save 99 Cite Cited by 79 Related articles All 21 versions

Novel Synthetic Antimicrobial Peptides with In-Vivo and In-Vitro Activity Against **Streptococcus Pneumoniae**

FOH LE CHENG - 2013 - search.proquest.com

… **Serotypes** 19F and 23F were the two prevailing **serotypes** … di mana kadar pelindungan sebanyak **20** – 50% lebih tinggi … differs in their chemical **compositions** which give rise to the …

☆ Save 99 Cite Related articles All 2 versions

Pneumococcal vaccines: WHO position paper—2012

World Health Organization - Weekly Epidemiological Record …, 2012 - apps.who.int

… L'agent étiologique, à savoir **Streptococcus pneumoniae**, … IPD in **20** of the world's poorest countries; **serotypes** 23F and … immunization a reduction in the circulation of **drug**-resistant …

☆ Save 99 Cite Cited by 360 Related articles All 3 versions »

CCDR 50th Anniversary: Invasive **pneumococcal** disease surveillance in Canada, 2021–2022

A Griffith, AR Golden, B Lefebvre… - Canada …, 2024 - ncbi.nlm.nih.gov

… 12F and **20**, is increasing in prevalence. Surveillance of IPD … -19 lockdown (26–**31**). A comprehensive interrupted time … **Serotype** distribution of invasive **Streptococcus pneumoniae** …

☆ Save 99 Cite Cited by 2 Related articles All 8 versions

Molecular characterisation of pneumococcal **serotype 16F**: Established predominant carriage and otitis media **serotype** in the 7vPCV era

RL Marsh, H Smith-Vaughan, J Beissbarth, K Hare… - Vaccine, 2007 - Elsevier

… switching from a **vaccine serotype** 4 to a **serotype 16F**. Capsular switching is thought to be a potential mechanism for pneumococci to evade high levels of **vaccine**-induced antibody, …

☆ Save 99 Cite Cited by 21 Related articles All 13 versions »

Serotypes of Streptococcus pneumoniae isolated from blood and cerebrospinal fluid related to **vaccine serotypes** and to clinical characteristics

S Berg, B Trollfors, E Persson, E Backhaus… - … journal of infectious …, 2006 - Taylor & Francis

… **serotypes** which are not included in the 23-valent **vaccine** were 23A (10 strains) and **16F** (7 … To date, no drastic increases in **serotypes** not covered by the 23-valent **vaccine** have, to our …

☆ Save 99 Cite Cited by 56 Related articles All 5 versions

… **serotypes** and clones circulating in Portugal before widespread use of conjugate **vaccines** reveals heterogeneous behavior of clones expressing the same **serotype**

R Sá-Leao, F Pinto, S Aguiar, S Nunes… - Journal of clinical …, 2011 - Am Soc Microbiol

To estimate the invasive disease potential of **serotypes** and clones circulating in Portugal before extensive use of the seven-valent pneumococcal conjugate **vaccine**, we analyzed 475 …

☆ Save 99 Cite Cited by 130 Related articles All 12 versions

Evaluating post-**vaccine** expansion patterns of pneumococcal **serotypes**

MT Phillips, JL Warren, N Givon-Lavi, A Tothpal… - Vaccine, 2020 - Elsevier

… non-**vaccine serotypes** increase by the same proportion overestimates changes in **serotype** … **Serotype 16F** was highly ranked among cases gained only among adults 18 years and older…

☆ Save 99 Cite Cited by 17 Related articles All 12 versions

Genomic epidemiology of *Streptococcus pneumoniae* **serotype 16F** lineages

J Mokaya, KC Mellor, GGR Murray… - Microbial …, 2023 - microbiologyresearch.org

… to inform **vaccine** strategies [16]. We show that **serotype 16F** remains a dominant non-**vaccine** type … Our results show that not only is **serotype 16F** the predominant non-**vaccine serotype** …

☆ Save 99 Cite Cited by 4 Related articles All 11 versions

Serotype changes and drug resistance in invasive pneumococcal diseases in adults after **vaccinations** in children, Japan, 2010–2013

K Ubukata, N Chiba, S Hanada… - Emerging infectious …, 2015 - ncbi.nlm.nih.gov

… **vaccine** (PCV) for children was introduced in Japan in November 2010, we examined changes in Streptococcus pneumoniae **serotypes** … in gPRSP, **serotypes** 15C, **16F**, and 23A, appear …

☆ Save 99 Cite Cited by 71 Related articles All 14 versions

Changes in pneumococcal **serotypes** and antibiotypes carried by **vaccinated** and unvaccinated day-care centre attendees in Portugal, a country with …

R Sa-Leao, S Nunes, A Brito-Avô, N Frazao… - Clinical microbiology …, 2009 - Elsevier

… of the most dramatic **serotype** shifts is not clear. Still, it is of interest to note that, as in our study, after introduction of PCV7 an increase in **serotype 16F** was noted among young …

☆ Save 99 Cite Cited by 159 Related articles All 13 versions »

Differences in serious clinical outcomes of infection caused by specific pneumococcal **serotypes** among adults

JD Grabenstein, LK Musey - Vaccine, 2014 - Elsevier

… were evaluated in terms of **serotypes** included in licensed adult pneumococcal **vaccines** (ie, 23… **serotypes** not represented in either **vaccine** formulation (notably **16F**). The pneumococcal …

☆ Save 99 Cite Cited by 122 Related articles All 9 versions

Pneumococcal **serotype** distribution: a snapshot of recent data in pediatric and adult populations around the world

YA Cui, H Patel, WM O'Neil, S Li… - Human Vaccines & …, 2017 - Taylor & Francis

… Most often ranking in the top 3 among non-**vaccine serotypes** in IPD-related pneumococcal

… **Serotypes** 6C and **16F** were the most prevalent among non-**vaccine serotypes** in a US and …

☆ Save 99 Cite Cited by 62 Related articles All 6 versions

Preclinical evaluation of an investigational 21-valent pneumococcal conjugate **vaccine**, V116, in adult-rhesus monkey, rabbit, and mouse models

S Curry, RM Kaufhold, MA Monslow, Y Zhang… - Vaccine, 2023 - Elsevier

… non-**vaccine serotypes**, thus highlighting the need for **vaccines** with expanded disease coverage. To address these needs, we have developed V116, an investigational 21-valent non-…

☆ Save 99 Cite Cited by 2 Related articles All 4 versions

Related searches

pneumococcal conjugate vaccine **on** serotype **distribution**

non-vaccine serotypes **high nasopharyngeal carriage**

vaccine serotype **streptococcus pneumoniae colonization**

cerebrospinal fluid vaccine serotypes

infant pneumococcal vaccination serotype **prevalence**

non-vaccine **pneumococcal** serotypes

vaccine **failures streptococcus pneumoniae** serotype **19a**

vaccinations **in children** serotype **changes**

carriage serotypes **23 valent polysaccharide** vaccine

serotype **distribution** vaccination **programme**

serotype **distribution 7 valent conjugate** vaccine

serotype **diversity** vaccination **uptake**

non-vaccine serotypes **western australian aboriginal people**

clinical characteristics vaccine serotypes

pneumococcal conjugate vaccines serotype **prevalence**

pneumococcal conjugate vaccines serotype **19a**

FORM PTO-1449/A and B (modified PTO/SB/08)	APPLICATION NO.: 17/347,435	ATTY. DOCKET NO.: P1143.70000US05
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	FILING DATE: June 14, 2021	CONFIRMATION NO.: 4020
	FIRST NAMED INVENTOR: Bruce D. Forrest	
Sheet 1 of 1	GROUP ART UNIT: 1645	EXAMINER: Khatol S. Shahnan Shah

U.S. PATENT DOCUMENTS

Examiner's Initials #	Cite No.	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication or Issue of Cited Document MM-DD-YYYY
		Number	Kind Code		

FOREIGN PATENT DOCUMENTS

Examiner's Initials #	Cite No.	Foreign Patent Document			Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Translation (Y/N)
		Office/ Country	Number	Kind Code			

OTHER ART – NON PATENT LITERATURE DOCUMENTS

Examiner's Initials #	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	Translation (Y/N)
/K.S.S/		[NO AUTHOR LISTED], Pneumococcal polysaccharide vaccine. Wikipedia. 2015. Accessed from <https://web.archive.org/web/20150227211129/https://en.wikipedia.org/wiki/Pneumococcal_polysaccharide_vaccine>. 4 pages.	
/K.S.S/		CURRY *et al*., Preclinical evaluation of an investigational 21-valent pneumococcal conjugate vaccine, V116, in adult-rhesus monkey, rabbit, and mouse models. Vaccine. 2023 Jan 23;41(4):903-913. doi: 10.1016/j.vaccine.2022.12.017. Epub 2022 Dec 22.	
/K.S.S/		HENRICHSEN, J., Six newly recognized types of *Streptococcus pneumoniae*. J Clin Microbiol. 1995 Oct;33(10):2759-62. doi: 10.1128/jcm.33.10.2759-2762.1995.	
/K.S.S/		ROBBINS *et al*., Considerations for formulating the second-generation pneumococcal capsular polysaccharide vaccine with emphasis on the cross-reactive types within groups. J Infect Dis. 1983 Dec;148(6):1136-59. doi: 10.1093/infdis/148.6.1136.	
/K.S.S/		SCHIFFMAN, G., Chemistry and immunochemistry of the pneumococcal polysaccharide vaccine with special reference to cross-reactions and immunologic factors. Rev Infect Dis. 1981 Mar-Apr;3 Suppl:S18-30. doi: 10.1093/clinids/3.supplement_1.s18.	
/K.S.S/		SIH, T.M., Acute otitis media in Brazilian children: analysis of microbiology and antimicrobial susceptibility. Ann Otol Rhinol Laryngol. 2001 Jul;110(7 Pt 1):662-6. doi: 10.1177/000348940111000712.	

[NOTE – No copies of U.S. patents, published U.S. patent applications, or pending, unpublished patent applications stored in the USPTO's Image File Wrapper (IFW) system, are included. See 37 CFR § 1.98 and 1287 OG 163. Copies of all other patent(s), publication(s), unpublished, pending U.S. patent applications, or other information listed are provided as required by 37 CFR § 1.98 unless 1) such copies were provided in an IDS in an earlier application that complies with 37 CFR § 1.98, and 2) the earlier application is relied upon for an earlier filing date under 35 U.S.C. § 120.]

EXAMINER:	DATE CONSIDERED:
/KHATOL S SHAHNAN SHAH/	12/28/2024

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

13174455.1

Conjugate of structurally reassigned pneumococcal **serotype 31** polysaccharide with CRM197 elicited potent immune response

T Sun, S Mai, H Mao, H Li, Y Duan, S Meng, J Bao… - Carbohydrate …, 2022 - Elsevier

… **Serotype 31** is a non-vaccine **serotype** and has increased in … , we report the revised **serotype 31** polysaccharide (s-**31**-ps) … -conjugate of **serotype 31** polysaccharide and cross reacting …

☆ Save 99 Cite Cited by 8 Related articles All 5 versions

Doc Code: TRAN.LET
Document Description: Transmittal Letter

USED IN LIEU OF PTO/SB/21 (07-09)

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	

Application Number	17/347,435-Conf. #4020
Filing Date	June 14, 2021
First Named Inventor	Bruce D. Forrest
Art Unit	1645
Examiner Name	Khatol S. Shahnan Shah
Attorney Docket Number	P1143.70000US05

ENCLOSURES (*Check all that apply*)

- [x] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [x] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please Identify below):

  Form PTO-1449
  Copies of Cited References

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	WOLF, GREENFIELD & SACKS, P.C.		
Signature	/Jessica A. von Reyn/		
Printed name	Jessica A. von Reyn		
Date	April 22, 2025	Reg. No.	76,839

Certificate of Electronic Filing under 37 C.F.R. § 1.8

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: April 22, 2025 Electronic Signature for Abigail S. Feldman: /Abigail S. Feldman/

13839916

FORM PTO-1449/A and B (modified PTO/SB/08)				APPLICATION NO.: 17/347,435	ATTY. DOCKET NO.: P1143.70000US05
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				FILING DATE: June 14, 2021	CONFIRMATION NO.: 4020
				FIRST NAMED INVENTOR: Bruce D. Forrest	
Sheet	1	of	1	GROUP ART UNIT: 1645	EXAMINER: Khatol S. Shahnan Shah

U.S. PATENT DOCUMENTS

Examiner's Initials #	Cite No.	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication or Issue of Cited Document MM-DD-YYYY
		Number	Kind Code		

FOREIGN PATENT DOCUMENTS

Examiner's Initials #	Cite No.	Foreign Patent Document			Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Translation (Y/N)
		Office/ Country	Number	Kind Code			
		WO	2018/064444	A1	Biological E Ltd.	04-05-2018	
		WO	2019/070994	A1	Liffey Biotech Ltd.	04-11-2019	

OTHER ART – NON PATENT LITERATURE DOCUMENTS

Examiner's Initials #	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	Translation (Y/N)
		Extended European Search Report, mailed March 5, 2025, in connection with Application No. EP 24193141.9 (P1143.70000EP01).	

[NOTE – No copies of U.S. patents, published U.S. patent applications, or pending, unpublished patent applications stored in the USPTO's Image File Wrapper (IFW) system, are included. See 37 CFR § 1.98 and 1287 OG 163. Copies of all other patent(s), publication(s), unpublished, pending U.S. patent applications, or other information listed are provided as required by 37 CFR § 1.98 unless 1) such copies were provided in an IDS in an earlier application that complies with 37 CFR § 1.98, and 2) the earlier application is relied upon for an earlier filing date under 35 U.S.C. § 120.]

EXAMINER:	DATE CONSIDERED:

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

FEE TRANSMITTAL

(page 1 of 2)

Complete if known	
Application Number	17/347,435-Conf. #4020
Filing Date	June 14, 2021
First Named Inventor	Bruce D. Forrest
Examiner Name	Khatol S. Shahnan Shah
Art Unit	1645
Practitioner Docket No.	P1143.70000US05

[X] Applicant asserts small entity status. See 37 CFR 1.27.

[ ] Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

TOTAL AMOUNT OF PAYMENT ($) 112.00

METHOD OF PAYMENT (check all that apply)

[ ] Check [X] Credit Card [ ] Money Order [ ] None [ ] Other (please identify): _____

[X] Deposit Account Deposit Account Number: 23/2825 Deposit Account Name: Wolf, Greenfield & Sacks, P.C.

For the above-identified deposit account, the Director is hereby authorized to (check all that apply):

[ ] Charge fee(s) indicated below

[ ] Charge fee(s) indicated below, **except for the filing fee**

[X] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17, **except for any excess claims fees or multiple dependent claims fees**

[ ] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17

[X] Credit any overpayment of fee(s)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES (U = undiscounted fee; S = small entity fee; M = micro entity fee)

	FILING FEES			SEARCH FEES			EXAMINATION FEES			
Application Type	**U ($)**	**S ($)**	**M ($)**	**U ($)**	**S ($)**	**M ($)**	**U ($)**	**S ($)**	**M ($)**	**Fees Paid ($)**
Utility	350	140*	70	770	308	154	880	352	176	
Design	300	120	60	300	120	60	700	280	140	
Plant	240	96	48	485	194	97	725	290	145	
Reissue	350	140	70	770	308	154	2,550	1,020	510	
Provisional	325	130	65	0	0	0	0	0	0	

* The $140 small entity filing fee for a utility application is further reduced to $70 for a small entity applicant who files the application via Patent Center.

2. EXCESS CLAIM FEES

Fee Description	**Undiscounted Fee ($)**	**Small Entity Fee ($)**	**Micro Entity Fee ($)**
Each claim over 20 (including Reissues)	200	80	40
Each independent claim over 3 (including Reissues)	600	240	120
Multiple dependent claims	925	370	185

Total Claims **Extra Claims** **Fee ($)** **Fee Paid ($)**

_____ - 27 or HP = _____ x _____ = _____

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims **Extra Claims** **Fee ($)** **Fee Paid ($)**

_____ - 3 or HP = _____ x _____ = _____

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims **Fee ($)** **Fee Paid ($)**

_____ _____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $450 ($180 for small entity) ($90 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets **Extra Sheets** **Number of each additional 50 or fraction thereof** **Fee ($)** **Fee Paid ($)**

_____ - 100 = _____ /50 = _____ (round **up** to a whole number) x _____ = _____

Certificate of Electronic Filing under 37 C.F.R. § 1.8

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: April 22, 2025 Electronic Signature for Abigail S. Feldman: /Abigail S. Feldman/

13877106

FEE TRANSMITTAL

(page 2 of 2)

4. CONTINUING APPLICATION FEE

If the actual filing date of the application is more than six years after the earliest benefit date, a continuing application fee is due. The earliest benefit date is the earliest filing date for which benefit is claimed under 35 U.S.C. 120, 121, 365(c), or 386(c) and § 1.78(d).

Choose only one of the following:

If the actual filing date is more than six years, and is less than or equal to nine years, after the earliest benefit date, the continuing application fee is $2,700 ($1,080 for small entity or $540 for micro entity). See 37 CFR 1.17(w)(1).

or

If the actual filing date is more than nine years after the earliest benefit date, the continuing application fee is $4,000 ($1,600 for small entity or $800 for micro entity), less any amount previously paid under 37 CFR 1.17(w)(1). See 37 CFR 1.17(w)(2).

Fees Paid ($)

5. OTHER FEE(S)

Fees Paid ($)

Non-English specification, $150 fee ($60 for small entity) ($30 for micro entity)

Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, $400 fee ($200 small or micro entity)

Other (e.g., late filing surcharge): 2806 Submission of an Information Disclosure Statement 112.00

SUBMITTED BY					
Signature	/Jessica A. von Reyn/	Registration No. (Attorney/Agent)	76,839	Telephone	617.646.8000
Name (Print/Type)	Jessica A. von Reyn			Date	April 22, 2025

13877106

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/347,435	**04/22/2025 10:18:32 AM Z ET**	**P1143.70000US05**

Title of Invention

SACCHARIDE-POLYPEPTIDE CONJUGATE COMPOSITIONS AND METHODS OF USE THEREOF

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	4020	FILED BY	Abigail Feldman
PATENT CENTER #	70102426	FILING DATE	06/14/2021
CUSTOMER #	23628	FIRST NAMED INVENTOR	Bruce D. Forrest
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jessica von Reyn

Documents

TOTAL DOCUMENTS: 7

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
P114370000US05-TRN-JXV.pdf	1	Miscellaneous Incoming Letter	26 KB
P114370000US05-FEE-JXV.pdf	2	Fee Worksheet (SB06)	83 KB
P114370000US05-IDSBODY-JXV.pdf	3	Letter specifying the conditions for filing under 37 CFR 1.97	35 KB
P114370000US05-IDS1449-JXV.pdf	1	Information Disclosure Statement (IDS) Form (SB08)	21 KB
Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.			
WO2018064444A1_FOR.pdf	75	Foreign Reference	3753 KB
WO2019070994A1_FOR.pdf	195	Foreign Reference	10412 KB

P114370000EP01_EESR_mailed_03-05-2025.pdf	11	Other reference-Patent/Application/Search Documents	232 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
P114370000US05-TRN-JXV.pdf	531FD57776FDA45F2BCE39C8C6817FEBAE693FD4057256A9A865F09580E0EDE9EEDB6C197AC9C36F9FD7E1FB9307F12BBF6D6D82BAE6E36B405F5C7C41D6E30A
P114370000US05-FEE-JXV.pdf	A2D222B292E645BB1F4436670AF0835DBA0E1D7091BCFE64F9357C4EEA23588945B0FAEA4B3C0CD5296A390D3553FE6DFEACC8002090B2A21F852456EB339F85
P114370000US05-IDSBODY-JXV.pdf	03EA436779545C32F1CF9EFEECDBE6397137627CDA3D03BFA1EF7FF32EA779419BFC411CF300FA5CF9F483800A8BA39FA47EDAE6032AF9EC7AFE4ACBB922CEA8
P114370000US05-IDS1449-JXV.pdf	74DAEEE9145F49A5FC81611DCB3B8E0AD923DFCF30246A2B7F07B90DFF10107A581702C5C9BA274E17F6A5E515BA0F3842F1E00DC233A58359F8C0ADC5CEA060
WO2018064444A1_FOR.pdf	F546E890B0E2C2D15316F9D28E31407F8A55E4F1D46ED0A3788D5A1C6140DC98ABF4C2E820F1D2FFE24BB588205B5110369BD47D4185A610C08E95467626E487
WO2019070994A1_FOR.pdf	106540E58AC9265A05E97C00EE183CE4D63CA2767C56A5A27E09985AEF3D8D15796905CE309C570A7534B17DA98D29D853FF4F2D0700409C6F8B5B2B610183FE
P114370000EP01_EESR_mailed_03-05-2025.pdf	D2C8E38A9707F021C5A425E5019FB89A90AC7E4254EB633146EFAF54FDBB3B67455E32832FE14AD3C2A9541FF7DFC358820F0B422A353179AEFF6CF4FE4C5AF8

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an

international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/347,435	**04/22/2025 10:18:32 AM Z ET**	**P1143.70000US05**

Title of Invention

SACCHARIDE-POLYPEPTIDE CONJUGATE COMPOSITIONS AND METHODS OF USE THEREOF

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	4020	FILED BY	Abigail Feldman
PATENT CENTER #	70102426	AUTHORIZED BY	Jessica von Reyn
CUSTOMER #	23628	FILING DATE	06/14/2021
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Bruce D. Forrest

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 8543	**E20254LA19448800**	**Abigail Feldman**

PRE-AUTHORIZED ACCOUNT	PRE-AUTHORIZED CATEGORY
232825	**37 CFR 1.17 (Patent application and reexamination processing fees)**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2806	SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT	112.00	1	112.00
			TOTAL AMOUNT:	**$112.00**

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 April 2019 (11.04.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/070994 A1

(51) International Patent Classification:
A61K 39/09 (2006.01) *A61K 39/00* (2006.01)

(21) International Application Number:
PCT/US2018/054391

(22) International Filing Date:
04 October 2018 (04.10.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/568,164 04 October 2017 (04.10.2017) US
62/732,260 17 September 2018 (17.09.2018) US

(71) Applicant: **LIFFEY BIOTECH LIMITED** [IE/IE]; c/o Mathesons, 70 Sir John Rogerson's Quay, Dublin 2, D02 R296 (IE).

(72) Inventors; and
(71) Applicants: **FORREST, Bruce D.** [US/US]; 135 Piermont Avenue, South Nyack, New York 10960 (US). **LOVE, Jack D.** [US/US]; 4111 W. Inman Avenue, Tampa, Florida 33609 (US).

(74) Agent: **HOLZAPFEL, Keli**; Wilson Sonsini goodrich & Rosati, 650 Page Mill road, Palo Alto, California 94304 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2019/070994 A1

(54) Title: SACCHARIDE-POLYPEPTIDE CONJUGATE COMPOSITIONS AND METHODS OF USE THEREOF

(57) Abstract: Saccharide-polypeptide conjugates, compositions containing these, methods of making and using the conjugates and compositions, and kits containing these, are disclosed.

Petitioner Merck Ex-1015, 1538

SACCHARIDE-POLYPEPTIDE CONJUGATE COMPOSITIONS AND METHODS OF USE THEREOF

CROSS REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/568,164, filed October 4, 2017, and United States Provisional Application No. 62/732,260, filed September 17, 2018, all of which are incorporated herein by reference in their entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on October 1, 2018, is named 50308-706_601_SL.txt and is 5,037 bytes in size.

SUMMARY

[0003] Provided herein is a brief summary. This summary can be used to provide an understanding of the embodiments provided herein, but the embodiments are not limited to what is provided in this summary.

[0004] Provided herein is a pharmaceutical composition in unit dose form that can comprise a plurality of at least eight unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 2, 6C, 7C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 20B, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35B, 35F, and 38, and wherein a total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in the pharmaceutical composition in unit dose form, ranges from about 0.5 μg to about 5 μg. A pharmaceutical composition in unit dose form can comprises a plurality of at least 29 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 1, 2, 3, 4, 5, 6A, 6B, 7F,

Petitioner Merck Ex-1015, 1539

7C, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 20B, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 35F, 34, 35B, and 38, and wherein a total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in the pharmaceutical composition in unit dose form, ranges from about 0.5 μg to about 5 μg. A pharmaceutical composition in unit dose form can comprise at least 2 immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype group, wherein one serotype is 6C and at least one additional serotype is selected from the group consisting of 1, 2, 3, 4, 5, 6A, 6B, 7F, 7C, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 20B, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35B, and 38, and wherein a total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in the pharmaceutical composition in unit dose form, ranges from about 0.5 μg to about 5 μg. A pharmaceutical composition in unit dose form can comprise at least 2 immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype group, wherein one serotype is 20B and at least one additional serotype is selected from the group consisting of 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 7C, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35B, and 38, and wherein a total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in the pharmaceutical composition in unit dose form, ranges from about 0.5 μg to about 5 μg. A pharmaceutical composition can comprise an immunogenic saccharide-polypeptide conjugate comprising, individually, at least two unique capsular polysaccharides, fragments thereof, or combinations thereof conjugated to a polypeptide, wherein the at least two unique capsular polysaccharides, fragments thereof, or combinations thereof are from a *Streptococcus pneumoniae* serotype selected from a group consisting of 1, 2, 3, 4, 5, 6A, 6B, 7F, 7C, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 20B, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35F, 35B, and 38. A vaccine in unit dose form can comprise at

Petitioner Merck Ex-1015, 1540

least one immunogenic saccharide-polypeptide conjugate comprising a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a *Streptococcus pneumoniae* serotype selected from a group consisting of 23A and 23B, or a combination thereof.

[0005] Provided herein is a method that can comprise administering to a subject a first composition, wherein the first composition is one of any pharmaceutical composition or vaccine as described herein. Further provided herein is a method that can comprise administering to the subject the first composition occurs at least about four weeks before or at least about four weeks after an administration of a second composition comprising an immunogenic saccharide-polypeptide conjugate comprising a second polypeptide to the subject, wherein the second polypeptide has at least about 70% length homology, at least about 70% sequence homology, or a combination thereof, to the polypeptide of the first composition.

[0006] Provided herein is a method that can comprise: administering a second immunogenic saccharide-polypeptide conjugate composition to a subject at least four weeks after a first immunogenic saccharide-polypeptide conjugate composition was administered; wherein the second immunogenic saccharide-polypeptide conjugate composition comprises a first polypeptide that has at least about 70% length homology, at least about 70% sequence homology, or a combination thereof, to a second polypeptide of the second immunogenic saccharide-polypeptide conjugate composition; and wherein the first immunogenic saccharide-polypeptide conjugate composition comprises a first serotype; wherein the second immunogenic saccharide-polypeptide conjugate composition comprises a second serotype, and wherein the first serotype and the second serotype are different; wherein the first immunogenic saccharide-polypeptide conjugate composition or the second immunogenic saccharide-polypeptide conjugate composition is the vaccine of any one of claims 159-249.

[0007] Further provided herein is a method of making a composition that can comprise: contacting the immunogenic saccharide-polypeptide conjugate of any one of the described pharmaceutical compositions or vaccines with an excipient, an adjuvant, or any combination thereof.

[0008] Provided herein is a kit that can comprise any pharmaceutical composition or vaccine described herein contained in a container described herein.

Petitioner Merck Ex-1015, 1541

[0009] Provided herein are methods of making pharmaceutical compositions or vaccines, methods of immunizing with pharmaceutical compositions or vaccines, and methods of vaccinating with pharmaceutical compositions or vaccines.

INCORPORATION BY REFERENCE

[0010] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE FIGURES

[0011] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings of which:

[0012] FIG. 1 illustrates a flow diagram of the general process for manufacture of a saccharide peptide conjugate vaccine.

[0013] FIG. 2 illustrates a flow diagram of a process for cell banking of a bacterial strain.

[0014] FIG. 3 illustrates a flow diagram of a process for producing, isolating, and purifying CRM_{197}.

[0015] FIG. 4 illustrates a flow diagram of a fermentation process for isolating a polysaccharide from a strain of *Streptococcus pneumoniae*.

[0016] FIG. 5 illustrates a flow diagram of a conjugation process for conjugating a polysaccharide and CRM_{197}.

[0017] FIG. 6 illustrates a flow diagram for a process for formulating a polysaccharide polypeptide conjugate vaccine.

[0018] FIG. 7 illustrates the projected expanded coverage provided by a *Streptococcus pneumoniae* polypeptide conjugate vaccine comprising *Streptococcus pneumoniae* serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F, and 35B (ePCV; LiffeyVax Serotypes) against invasive pneumococcal disease (IPD) in United States and Canada when this vaccine is administered in a vaccination regime with Prevnar 13 (PCV13). Prevnar 13 alone only covers about 46.1% of IPD compared to an overall coverage of 90% when administered in a vaccination regime with ePCV.

Petitioner Merck Ex-1015, 1542

[0019] FIG. 8 illustrates the projected expanded coverage provided by a *Streptococcus pneumoniae* polypeptide conjugate vaccine comprising *Streptococcus pneumoniae* serotypes 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B (Liffey/Vax ePCV8) against invasive pneumococcal disease (IPD) in United States and Canada when this vaccine is administered in a vaccination regime with Prevnar 13 (PCV13) or a vaccine comprising the Prevnar 13 serotypes plus seven additional serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) (PCV20). Prevnar 13 alone only covers about 46.1% of IPD, but the addition of the seven serotypes in the PCV20 is predicted to cover about 21% more of IPD. The further addition of the eight serotypes in the Liffey/Vax ePCV8 is predicted to cover about 23% more of IPD when administered in a vaccination regime with PCV20.

[0020] FIG. 9 illustrates the projected expanded coverage provided by a *Streptococcus pneumoniae* polypeptide conjugate vaccine comprising *Streptococcus pneumoniae* serotypes 6C, 9N, 15A, 15C, 16F, 20B, 23A, 23B, 24F, 31, 34, 35F, 35B, and 38 (ePCV8+7) against invasive pneumococcal disease (IPD) in United States and Canada when this vaccine is administered in a vaccination regime with Prevnar 13 (PCV13) or a vaccine comprising the Prevnar 13 serotypes plus seven additional serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) (PCV20). Prevnar 13 alone only covers about 46.1% of IPD, but the addition of the seven serotypes in the PCV20 is predicted to cover about 21% more of IPD. The further addition of seven serotypes in the Liffey/Vax ePCV8 (Liffey/Vax ePCV8+7) (see **FIG. 8** for ePCV8) is predicted to cover about 29% more of IPD when administered in a vaccination regime with PCV20.

[0021] FIGS. 10A, 10B, 10C, 10D, 10E, and 10F illustrate the annotated capsular polysaccharide (*cps*) locus for various *S. pneumoniae* serotypes (Bentley et al., Genetic Analysis of the Capsular Biosynthetic Locus from all 90 Pneumococcal Serotypes. *PloS Genet* 2(3): 31 (2006)).

DETAILED DESCRIPTION

[0022] Several aspects are described below with reference to example applications for illustration. It should be understood that numerous specific details, relationships, and methods are set forth to provide a full understanding of the features described herein. One having ordinary skill in the relevant art, however, will readily recognizes that the features described herein can be practiced without one or more of the specific details or with other methods. The features described herein are not limited by the illustrated ordering of acts or events, as some acts can

Petitioner Merck Ex-1015, 1543

occur in different orders and/or concurrently with other acts or events. Furthermore, not all illustrated acts or events are required to implement a methodology in accordance with the features described herein.

[0023] The terminology used herein is for the purpose of describing particular cases only and is not intended to be limiting. As used herein, the singular forms "a", "an" and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise. Furthermore, to the extent that the terms "including", "includes", "having", "has", "with", or variants thereof are used in either the detailed description and/or the claims, such terms are intended to be inclusive in a manner similar to the term "comprising".

[0024] The term "about" or "approximately" can mean within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, *i.e.*, the limitations of the measurement system. For example, "about" can mean within 1 or more than 1 standard deviation, per the practice in the art. Alternatively, "about" can mean a range covering plus or minus up to 20%, up to 10%, up to 5%, or up to 1% of a given value. Where particular values are described in the application and claims, unless otherwise stated the term "about" can mean within an acceptable error range for the particular value should be assumed. When a conjugate is present in μg, "about" can mean +/- 0.5 μg, 0.75 μg, 1.0 μg, 1.25 μg, 1.5 μg, 1.75 μg, or 2 μg for each conjugate.

[0025] A "unit dose" when used in reference to a pharmaceutical composition or vaccine can refer to units suitable as unitary dosage for humans, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect. In some instance the unit dose can contain a diluent; *i.e.*, carrier, or vehicle. In some instances, the unit dose can be a physically discrete.

[0026] The term "saccharide" can refer to a saccharide, oligosaccharide or polysaccharide. For example, saccharide can mean a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, a hexasaccharide, a heptasaccharide, an octasaccharide, a nonasaccharide, or a decasaccharide. An oligosaccharide can refer to two to ten saccharides. A polysaccharide can refer to more than ten saccharides.

[0027] The term "polypeptide" can refer to a single linear chain of amino acids held together by amide bonds. A polypeptide can refer to at least two amino acids. A polypeptide can be an oligopeptide, wherein the term "oligopeptide" can refer to a single chain of from two to twenty

Petitioner Merck Ex-1015, 1544

amino acids joined by amide bonds. A polypeptide can be a protein, wherein the term "protein" can refer to a single chain of fifty or more amino acids held together by amide bonds.

[0028] The term an "immune response" can refer to the production of cytokines and/or antibodies with a degree of specificity for an antigen after administering the antigen to a subject. In some instances, the term "immune response" can refer to any change in immune cells or change caused by immune cells after administering the antigen to a subject. An immune response can be T cell independent, T cell dependent, or both.

[0029] The term "homology" can mean percent sequence identity between a particular nucleic acid or amino acid sequence and another nucleic acid or amino acid sequence. First, a nucleic acid or amino acid sequence can be compared another sequence using the BLAST 2 Sequences (Bl2seq) program from the stand- alone version of BLASTZ containing BLASTN version 2.0.14 and BLASTP version 2.0.14. BLASTN can be used to compare nucleic acid sequences, while BLASTP can be used to compare amino acid sequences. Once aligned, the number of matches is determined by counting the number of positions where an identical nucleotide or amino acid residue is presented in both sequences. The percent sequence identity or homology can be determined by dividing the number of matches either by the length of the sequence set forth in the identified sequence, or by an articulated length (*e.g.*, 100 consecutive nucleotides or amino acid residues from a sequence set forth in an identified sequence), followed by multiplying the resulting value by 100%.

[0030] The term "length homology" can mean percent length identity between the length of a particular polypeptide and the length of another polypeptide. "Length homology" can in some instances be calculated by dividing the number of amino acids in a first peptide chain by the number of amino acids in a second peptide chain and multiplying the result by 100%. Chain amino acids can be those forming the backbone of the peptide.

[0031] The term "length" in reference to a polypeptide can refer to counting the number of amino acids along the amino acid chain.

[0032] The term "immunogenic fragment" can be a fragment that is conjugated to a polypeptide, administered to a subject, and which elicits an immune response. In some instances, the fragment can be a fragment of a capsular polysaccharide. In other instances, the polypeptide can be CRM_{197}.

Petitioner Merck Ex-1015, 1545

[0033] Immunogenic, which can but need not be obligated to be preceded any term herein, can mean that which, when administered to a subject, which can be a human or an animal, for example a dog, cat, rat, mouse, sheep, or monkey, produces an immune response in the animal. For example, a dog can be *Canis lupis familiarius*, a cat can be *Felis catus*, a rat can be *Rattus norvegicus*, a mouse can be *Mus musculus*, a sheep can be *Ovis aries*, or a monkey can be *Simia imus*. The administration can be, for example, subcutaneous, intramuscular, or rectal, for example in the form of a suppository.

[0034] In some embodiments, a unique immunogenic saccharide-polypeptide conjugate can be one that differs from other unique immunogenic saccharide-polypeptide conjugates, for example in a plurality of these, by at least one aspect. For example, the unique immunogenic saccharide-polypeptide conjugate can differ by the saccharide or fragment thereof it contains - in that this can render the unique immunogenic saccharide-polypeptide conjugate unique, or by the polypeptide it contains, or both. In some instances, unique immunogenic saccharide-polypeptide conjugates, to be unique, simply need not be 100% identical.

[0035] The term "partly mitigated" in reference to the toxin activity of a polypeptide can refer to a decreased toxicity of the polypeptide as compared to a wild type version of the polypeptide.

[0036] The term "molecular weight" can be a number average molecular weight or a weight average molecular weight.

[0037] The term "plurality" can mean two or more.

[0038] The term "subject" can refer to a human or an animal. The subject can be a subject in need thereof.

[0039] Bacteria can incorporate saccharides into their surface structure. For example, *Streptococcus pneumoniae* (*S. pneumoniae*) can contain saccharides in its surface structure. The saccharides can be antigens that can induce an immune response in host, such as an animal or human. For example, B cells can produce antibodies against a saccharide. This response can be a T cell independent immune response. An immune response can be induced with full-length, native form polysaccharides, oligosaccharides, or fragments thereof. An immune response can be induced with full-length, native form capsular polysaccharides, or fragments thereof. Other bacteria that can contain saccharides are *Neisseria meningitidis (N. meningitidis)*, *Salmonella enterica (S. enterica)*, and *Haemophilus influenzae (H. influenzae)*.

Petitioner Merck Ex-1015, 1546

[0040] The saccharides on bacteria can be used to classify the bacteria into a subclass or serotype. More specifically, a serotype can refer to the type of a microorganism determined by its constituent antigens. The constituent antigens can be different saccharides, such as different capsular polysaccharides or immunogenic fragments thereof. Some non-limiting examples of *S. pneumoniae* serotypes can include, but are not limited to 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 7C, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 22F, 23F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35F, 35B, 38, and Serogroup 20 (comprising serotypes 20A and 20B).

[0041] By conjugating a saccharide to a polypeptide, the immune response to the saccharide can be enhanced by inducing a T cell dependent response. A saccharide alone may not stimulate T cells because, for example, a saccharide may not be loaded onto the Major Histocompatibility Complex (MHC) of antigen presenting cells. However, peptides can be loaded onto MHC. Therefore, by conjugating a saccharide to a polypeptide, the saccharide-polypeptide conjugate can then be loaded onto the MHC, recognized by the T cell, and stimulate a T cell response. T cells can then stimulate a more vigorous immune response and also promote a more rapid and long-lasting immunologic memory. Provided herein are saccharide-polypeptide conjugates that can be used to induce an immune response, which can be referred to as immunogenic saccharide-polypeptide conjugates. In some instances, the immunogenic saccharide-polypeptide conjugates can provide immune protection against a saccharide or organism containing the saccharides. In other instances, the immunogenic saccharide-polypeptide conjugates can be part of a vaccine.

Compositions of Saccharide-Polypeptide Conjugate

[0042] An immunogenic saccharide-polypeptide conjugate composition can be a saccharide conjugated to a polypeptide. An immunogenic saccharide-polypeptide conjugate composition can be a capsular polysaccharide conjugated to a polypeptide. An immunogenic saccharide-polypeptide conjugate composition can be a capsular polysaccharide or fragment of the capsular polysaccharide conjugated to a polypeptide. An immunogenic saccharide-polypeptide conjugate can comprise a saccharide antigen coupled to one or more polypeptides. An immunogenic saccharide-polypeptide conjugate can comprise one unique saccharide antigen coupled a polypeptide. An immunogenic saccharide-polypeptide conjugate can comprise two or more unique saccharide antigens coupled a polypeptide. A saccharide antigen can elicit an immune response.

Petitioner Merck Ex-1015, 1547

[0043] A saccharide can be from any bacteria and fungi that can incorporate saccharides into their surface structure. For example, saccharides can be from *S. pneumoniae*. Further examples include saccharides from *N. meningitidis*, *S. enterica*, or *H. influenzae*. A saccharide can be a full-length, native form polysaccharide, oligosaccharide, or fragments thereof. A saccharide can be in any form that induces an immune response. A saccharide can be a capsular polysaccharide or fragment thereof. A saccharide can be from a subclass or serotype. Some non-limiting examples of saccharides from a *S. pneumoniae* serotype include, but are not limited to 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 7C, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 22F, 23F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35F, 35B, 38, and Serogroup 20. Serogroup 20 can comprise serotype 20A and serotype 20B. *S. pneumoniae* that can produce serotype 20A polysaccharide can be identified by a mutated *whaF* allele as compared to the intact *whaF* allele of *S. pneumoniae* that can produce serotype 20B polysaccharide. **TABLE 1** depicts exemplary repeat unit polysaccharide structures of various *S. pneumoniae* serotypes. **FIGS. 10A, 10B, 10C, 10D**, **10E**, and **10F** depict annotated the capsular polysaccharide (*cps*) locus for various *S. pneumoniae* serotypes (Bentley *et al.* Genetic Analysis of the Capsular Biosynthetic Locus from all 90 Pneumococcal Serotypes. *PloS Genet* 2(3): 31 (2006)).

Petitioner Merck Ex-1015, 1548

TABLE 1. Exemplary *S. pneumoniae* Polysaccharide Serotypes

Serotype	Polysaccharide Structure (Repeat Unit)
1	→3)-α-Sug*p*-(1→4)-α-D-Gal*p*A-(1→3)-α-D-Gal*p*A-(1→]$_n$ Sug*p*: 2-acetamido-2,6-dideoxy-D-*xylo*-hexos-4-ulose
2	→4)-β-D-Glc*p*-(1→3)-α-L-Rha*p*-(1→3)-α-L-Rha*p*-(1→3)-β-L-Rha*p*-(1→]$_n$ 2 ↓ 1 α-D-Glc*p*A-(1→6)-α-D-Glc*p*
3	→3)-β-D-GlcA*p*-(1→4)-β-D-Glc*p*-(1→]$_n$
4	→3)-β-D-Man*p*NAc-(1→3)-α-L-Fuc*p*NAc-(1→3)-α-D-Gal*p*NAc-(1→4)-α-Gal*p*2,3(S)Pyr-(1→]$_n$
5	→4)-β-D-Glc*p*-(1→4)- α -L-Fuc*p*NAc-(1→3)-β-D-Sug*p*-(1→]$_n$ 3 ↑ 1 α-L-Pne*p*NAc-(1-2)-β-D-Glc*p*A L-PneNAc: 2-acetamido-2,6-dideoxy-l-talose (pneumosamine) Sug*p*: 2-acetamido-2,6-dideoxy-D-*xylo*-hexos-4-ulose
6A	→2)-α-D-Gal*p*-(1→3)-α-D-Glc*p*-(1→3)-α-L-Rha*p*-(1→3)-D-Ribitool-(5→P→]$_n$
6B	→2)-α-D-Gal*p*-(1→3)-α-D-Glc*p*-(1→3)-α-L-Rha*p*-(1→4)-D-Ribitol-(5→P→]$_n$
6C	→2)-α-D-Glc*p*-(1→3)-α-D-Glc*p*-(1→3)-α-L-Rha*p*-(1→3)-D-Ribitol-(5→P→]$_n$

Petitioner Merck Ex-1015, 1549

Serotype	Polysaccharide Structure (Repeat Unit)
7F	→6)-α-D-Gal*p*-(1→3)-β-L-Rha*p*2Ac-(1→4)-β-D-Glc*p*-(1→3)-β-D-Gal*p*NAc-(1→ 4 ↖ 1 β-D-Gal*p* α-D-Gal*p*NAc-(1→2)-α-L-Rha*p*
7C	→6)-α-D-Glc*p*NAc-(1→2)-α-L-Rha*p*-(1→2)-β-L-Rha*p*-(1→4)-β-D-Glc*p*-(1→4)-α-D-Gal*p*NAc-(1→ 3 ↖ 1 β-D-Rib*f*-(1→4)-α-L-Rha*p*
8	→4)-β-D-Glc*p*-(1→4)-α-D-Gal*p*-(1→4)-α-D-GlcA*p*-(1→4)-β-D-Glc*p*-(1→]$_n$
9N	→4)-α-D-Glc*p*NAc-(1→4)-α-D-Glc*p*A-(1→3)-α-D-Glc*p*-(1→3)-β-D-Man*p*NAc-(1→4)-β-D-Glc*p*-(1→]$_n$
9V	→4)-α-D-Glc*p*A-(1→3)-α-D-Glc*p*-(1→3)-β-D-Man*p*NAc-(1→4)-β-D-Glc*p*-(1→4)-α-D-Glc*p*-(1→]$_n$ ↖ 2Ac (17%) 4Ac (6%) 2Ac (3%) 3Ac (25%) 6Ac (55%) 3Ac (4%)
10A	Galβ1 ↘ 6 →4)-GalNAc-β-(1→3)-Gal-α-(1→2)-ribitol-5-PO4$^-$-5Gal*f*β-(1→3)-Galβ-(1→]$_n$ 3 ↖ Gal*f*β1

Petitioner Merck Ex-1015, 1550

Serotype	Polysaccharide Structure (Repeat Unit)
11A	
12F	
14	
15A	

Petitioner Merck Ex-1015, 1551

Serotype	Polysaccharide Structure (Repeat Unit)
15B	→6)-β-D-Glc*p*NAc-(1→3)-β-D-Gal*p*-(1→4)-β-D-Glc*p*-(1→]$_n$ 4 ↑ 1 α -D-Gal*p*-(1→2)-β-D-Gal*p*-3-PO_4—R 80% R = H 20% R = choline Note: On average 70% of the repeating units is O acetylated. The site of the O acetylation is unknown (Jansson *et al.* Carbohydr. Res. (1987) 162:111-116), although Venkateswaran *et al.* Infect. Dis. (1983) 147:1041-1054 suggested that it is linked to a galactose moiety.
15C	→6)-β-D-Glc*p*NAc-(1→3)-β-D-Gal*p*-(1→4)-β-D-Glc*p*-(1→]$_n$ 4 ↑ 1 α-D-Gal*p*-(1→2)-β-D-Gal*p*-3-PO_4—R 80% R = H 20% R = choline
17F	OAc ↓ 2 -[3)-L-Rha*p*-β-(1→4)-D-Glc*p*-β-(1→3)-D-Gal*p*-α-(1→3)-L-Rha*p*-β-(1→4)-L-Rha*p*-α-(1→2)-D-Arabinitol-1-PO_4→]$_n$ 4 ↑ 4 β-D-Gal*p* and

Petitioner Merck Ex-1015, 1552

Serotype	Polysaccharide Structure (Repeat Unit)
	OAc ↓ 2 -[3)-L-Rha*p*-β-(1→4)-D-Glc*p*-β-(1→3)-D-Gal*p*-α-(1→3)-L-Rha*p*-β-(1→4)-L-Rha*p*-α-(1→2)-D-Arabinitol-1-PO_4→]$_n$ 1 ↑ 4 β-D-Gal*p*
18C	α-D-Glc*p* 1 ↓ 2 -[4)-β-D-Glc*p*-(1→4)-β-D-Gal*p*-(1→4)-α-D-Glc*p*-(1→3)-α-L-Rha*p*-(1→]n 3 ↑ PO4-1-glycerol
19F	→2)-α-L-Rha-(1→5-PO4$^-$-5→4)-β-D-ManNAc-(1→4)-β-D-Glc-(1→]$_n$
19A	→3)-α-L-Rha-(1→5-PO_4^--5→4)-β-D-ManNAc-(1→4)-β-D-Glc-(1→]$_n$

Petitioner Merck Ex-1015, 1553

Serotype	Polysaccharide Structure (Repeat Unit)
20A	β-Gal*f* 1 ↓ 4 →3)-α-GlcNA*cp*-(1→PO_4→6)-α-Glc*p*-(1→6)-β-Glc*p*-(1→3)-β-Gal*f*-(1→3)-β-Glc*p*-(1→]$_n$
20B	$OAc_{0.90}$ ↓ 2 β-Gal*f* 1 ↓ 4 →3)-α-GlcNA*cp*-(1→PO_4→6)-α-Glc*p*-(1→6)-β-Glc*p*-(1→3)-β-Gal*f*-(1→3)-β-Glc*p*-(1→]$_n$ 6 ↑ 1 α-Glc*p* $OAc_{0.90}$ ↓ 5
22F	Ac ↓ 2 →4)-β-D-Glc*p*A-(1→4)-β-L-Rha*p*-(1→4)-α-D-Glc*p*-(1→3)-α-D-Gal*f*-(1→2)-α-L-Rha*p*)-1→]$_n$ 3 ↑ α-D-Glc*p*

Petitioner Merck Ex-1015, 1554

Serotype	Polysaccharide Structure (Repeat Unit)
23F	α-L-Rha*p* 1 ↓ 2 →4)-β-D-Glc*p*-(1→4)-β-D-Gal*p*-(1→4)-β-L-Rha*p*-(1→]$_n$ 3 ↑ PO_4-1-glycerol
23A	α-L-Rha*p* 1 ↓ 2 PO_4-1-glycerol-(2→P→3)-β-D-Gal*p*-(1 ↓ 4 →4)-β-D-Glc*p*-(1→3)-β-L-Rha*p*-(1→]$_n$
23B	→4)-β-D-Glc*p*-(1→4)-β-D-Gal*p*-(1→4)-β-L-Rha*p*-(1→]$_n$ 3 ↑ PO_4-1-glycerol
31	→2)-β-L-Rha*p*-(1→3)-β-D-Gal*f*-(1→3)-β-Rha*p*-(1→4)-β-D-Glc*p*A-(1→3)-β-D-Gal*f*-(1→]$_n$
33F	→3)-β-D-Gal*p*-(1→3)-α-D-Gal*p*-(1→3)– β-D-Gal*f*-(1→3)-β-D-Glc*p*-(1→5)-β-D-Gal*f*-(1→]$_n$ 2 2 ↑ ↑ 1 $OAc_{0.4}$ α-D-Gal*p*

Petitioner Merck Ex-1015, 1555

Serotype	Polysaccharide Structure (Repeat Unit)
33B	Ac 2 ↓ 5)-β-D-Gal*f*-(1→3)-β-D-Gal*p*-NAc-(1→3)-α-D-Gal*p*-(1→4)-Ribitol-5-P→2)- α-D-Glc*p*-(1→3)-β-D-Glc*p*-(1→]$_n$ 2 ↑ 1 α-D-Gal*p*
34	→6)-Gal-β-(1→3)-Gal-α-(1→2)-Rib-5-PO_4^--6-Gal*f*-β-(1→3)-Gal-β-1→]$_n$ ↓ 2OAc ↓ 3,5OAc
34	→3)-β-D-Gal*f*-(1→3)-α-D-Glc*p*-(1→2)-β-D-Gal*f*6$Ac_{0.5}$-(1→3)-α-D-Gal*p*-(1→2)-D-Rib-ol-(5→*P*→
35F	→6)-Gal*f*-β-(1→3)-Gal-α-(1→2)-Rib-5-PO_4^--3-Gal*f*-β-(1→3)-Gal-β-1→]$_n$ ↓ 2OAc
35B	$OAc_{0.7}$ ↓ 2 →4)-β-D-Gal*p*NAc-(1→6)-β-D-Gal*f*-(1→3)-β-D-Glc*p*-(1→6)-β-D-Gal*f*-(1→1)-Rib-(5-PO_4→]$_n$

Petitioner Merck Ex-1015, 1556

[0044] Saccharides can be isolated from bacteria. Saccharides can be isolated from bacteria and then conjugated to a polypeptide to form a saccharide-polypeptide conjugate. Any method for isolating the unconjugated polysaccharide can be used. For example, a polysaccharide serotype can be grown in a soy-based medium. The individual polysaccharides can then be purified by steps including centrifugation, precipitation, and ultra-filtration. *See* U.S. Patent Application Publication No. 2008/028638 and U.S. Pat. No. 5,847,112. Other processes for purifying polysaccharides are described in U.S. Pat. No. 4,686,102; 4,242,501; 4221,906; 5623,057; and 5,847,112. Alternatively or additionally, polysaccharides may be isolated simultaneously from more than one serotype, which can produce a mixture of polysaccharide serotypes with the desired polysaccharide already combined. Furthermore, these isolated polysaccharides can be sized by microfluidization. The polysaccharides can be sized in order to reduce viscosity in polysaccharide samples and/or to improve filterability for conjugated sample. A saccharide-polypeptide conjugate can include a saccharide or a fragment thereof which is at least partially embedded in one or more polypeptides. The one or more polypeptides can have one or more crosslinks. The at least partially embedded saccharide or fragment thereof can, but need not be, covalently bound to at least one of the polypeptides when at least partially embedded therein.

[0045] Any of the *S. pneumoniae* strains for isolating and purifying the polysaccharides as described herein can be provided by either the CDC, United States or CCUG, Gothenburg. Alternatively, any of the polysaccharides described herein can be isolated and purified from any source (e.g., any laboratory) in which serotyping or other genetic sequencing is used to identify the unique strain from which the polysaccharides are isolated and purified. A vial of a strain of *S. pneumoniae* can be seeded and then can be grown overnight on an agar plate. A single colony can be picked from this plate and streaked onto a new agar plate for overnight growth. This process can be repeated three times to purify the strain before a flask can be seeded and incubated. After allowing the seeded flask sufficient time for growth, the flask contents can be harvested by centrifugation. The centrifugation product can be resuspended in a medium of about 20% glycerol and then can be dispensed into cryogenic vials. The cell bank can be contained in the cryogenic vials, which can be stored at -70°C until use. The cell bank of the strain can then be used for isolation and purification of the polysaccharides of that strain using a fermentation process.

[0046] Polysaccharides of a *S. pneumoniae* strain can be isolated and purified from a cell bank of a strain. The strain can be provided by either the CDC, United States or CCUG, Gothenburg, and then can be used to produce a cell bank as described above. Alternatively,

Petitioner Merck Ex-1015, 1557

strain can be provided by any source (e.g., any laboratory) in which serotyping or other genetic sequencing is used to identify the serotype of the strain. A vial of a cell bank can be produced as described above is used to inoculate a flask, which is allowed to grow overnight. This culture is used to seed a new culture for fermentation in a fermenter. The culture is allowed to grow under the appropriate conditions for that strain. After fermentation, the cells are inactivated and then are treated with deoxycholate to break open the cells and release the capsular polysaccharide. Subsequently, debris is removed by centrifugation, which is followed by a depth filter step through a 0.45 μm filter and the cell free broth is collected. The product is then purified and the polysaccharide size is determined. Quality control tests are performed on the product, such as a purity assay and confirmation of strain inactivation (no growth after plating). Any polysaccharides described herein can be isolated and purified using this method.

[0047] The saccharides or polysaccharides of the invention are depolymerized (sized) to a final range from 100-500 kDa.

[0048] Saccharides that can be used in the saccharide-polypeptide conjugate can also be obtained from commercial sources. For example, individual polysaccharide serotypes can be obtained in a powder form. These polysaccharides can be dissolved in water and incubated with a salt to dissociate residual impurities, which can then be removed by a filtration step. The purified polysaccharides serotypes can then be conjugated to a polypeptide.

[0049] A polypeptide of an immunogenic saccharide-polypeptide conjugate can be an oligopeptide. A polypeptide of can be a carrier protein. A polypeptide can be any polypeptide that allows for conjugation or coupling of saccharide and results in the display of the conjugate or coupling in a way that induces a protective immune response against the saccharide. A polypeptide can be any polypeptide that allows for conjugation or coupling of a capsular polysaccharide or fragment of the capsular polysaccharide and can result in the display of the conjugate or coupling in a way that can induce a protective immune response against the capsular polysaccharide or fragment of the capsular polysaccharide. A polypeptide can be CRM_{197}, tetanus toxoid, a diphtheria toxoid, a cholera toxoid, pertussis toxoid, inactivated or mutant pneumococcal pneumolysin, pneumococcal surface protein A, pneumococcal adhesion protein A, pneumococcal lipoprotein PsaA, C5a peptidase group A or group B streptococcus, a non-typable *H. influenzae* P4 protein, a non-typable *H. influenzae* P6 protein, *M catarrhalis* uspA, a keyhole limpet haemocyanin (KLH), OMPC from *N. meningitidis*, the purified protein derivative of tuberculin(PPD), protein D from *H. influenzae*, PspA, or any fragment thereof. The polypeptide can be a polypeptide in which the

Petitioner Merck Ex-1015, 1558

toxin activity of the polypeptide can be at least partially mitigated. Examples of suitable polypeptides for use as in a saccharide-polypeptide conjugate are described in U.S. patent 8,808,707 and can include: polylysine, polyglutamic acid, polyaspartic acid, co-polymers thereof, and mixed polymers of these amino acids and others, *e.g.*, serines, threonines, or tyrosines, to confer desirable solubility properties on the resultant loaded carrier and conjugate. A polypeptide can be a CRM_{197} with 100% sequence homology with GADDVVDSSKSFVMENFSSYHGTKPGYVDSIQKGIQKPKSGTQGNYDDDWKEFYST DNKYDAAGYSVDNENPLSGKAGGVVKVTYPGLTKVLALKVDNAETIKKELGLSLTE PLMEQVGTEEFIKRFGDGASRVVLSLPFAEGSSSVEYINNWEQAKALSVELEINFETR GKRGQDAMYEYMAQACAGNRVRRSVGSSLSCINLDWDVIRDKTKTKIESLKEHGPI KNKMSESPNKTVSEEKAKQYLEEFHQTALEHPELSELKTVTGTNPVFAGANYAAWA VNVAQVIDSETADNLEKTTAALSILPGIGSVMGIADGAVHHNTEEIVAQSIALSSLMV AQAIPLVGELVDIGFAAYNFVESIINLFQVVHNSYNRPAYSPGHKTQPFLHDGYAVS WNTVEDSIIRTGFQGESGHDIKITAENTPLPIAGVLLPTIPGKLDVNKSKTHISVNGRKI RMRCRAIDGDVTFCRPKSPVYVGNGVHANLHVAFHRSSSEKIHSNEISSDSIGVLGYQ KTVDHTKVNSKLSLFFEIKS (SEQ ID NO: 1). A polypeptide can be a CRM_{197} with at least 80%, 90%, 95%, or 98% sequence homology with SEQ ID NO: 1. A polypeptide can be a modified CRM_{197} as disclosed in US Patent No. 9,359,400. A polypeptide can be CRM_{197} with non-natural amino acid substitutions as disclosed in US Patent No.9,764,039.

[0050] Moreover, suitable polypeptide carriers can include bacterial toxins, toxoids, or inactivated toxin. A toxoid can be a bacterial toxin whose toxicity has been weakened or suppressed while other properties, typically immunogenicity, are maintained. As a class, bacterial toxins and derivatives thereof can to be highly immunogenic. Polypeptides derived from bacterial toxins can be effective at eliciting an immune response to saccharides of the conjugate. Steps can be taken (*e.g.*, by chemical and/or genetic means) to render the toxins non-toxic and safe for administration to mammals. Examples of such bacterial toxin-derived polypeptides which may currently commonly used in vaccine compositions, and can be used in the immunogenic saccharide-polypeptide conjugate described herein, include the diphtheria and tetanus toxoids, and variants thereof (*e.g.*, DT, CRM_{197},TT), cholera toxoid, pertussis toxoid, inactivated or mutant pneumococcal pneumolysin, pneumococcal surface protein A, pneumococcal adhesion protein A, pneumococcal lipoprotein PsaA, C5a peptidase group A or group B streptococcus, non-typable *H. influenzae* P4 protein, non-typable *H. influenzae* P6 protein, *M catarrhalis* uspA, keyhole limpet haemocyanin (KLH), OMPC from *N. meningitidis*, the purified protein derivative of tuberculin(PPD), protein D from *H.*

Petitioner Merck Ex-1015, 1559

influenzae, PspA, or any fragment thereof. Polypeptide fragments can be used to elicit a protective immune response against the capsular polysaccharide or fragment of the capsular polysaccharide of the immunogenic saccharide-polypeptide conjugate. These fragments can encompass T-helper epitopes.

[0051] CRM_{197} is a non-toxic mutant of diphtheria toxin with a single amino acid substitution of glutamic acid for glycine at position 52, with the amino acid sequence of GADDVVDSSKSFVMENFSSYHGTKPGYVDSIQKGIQKPKSGTQGNYDDDWKEFYST DNKYDAAGYSVDNENPLSGKAGGVVKVTYPGLTKVLALKVDNAETIKKELGLSLTE PLMEQVGTEEFIKRFGDGASRVVLSLPFAEGSSSVEYINNWEQAKALSVELEINFETR GKRGQDAMYEYMAQACAGNRVRRSVGSSLSCINLDWDVIRDKTKTKIESLKEHGPI KNKMSESPNKTVSEEKAKQYLEEFHQTALEHPELSELKTVTGTNPVFAGANYAAWA VNVAQVIDSETADNLEKTTAALSILPGIGSVMGIADGAVHHNTEEIVAQSIALSSLMV AQAIPLVGELVDIGFAAYNFVESIINLFQVVHNSYNRPAYSPGHKTQPFLHDGYAVS WNTVEDSIIRTGFQGESGHDIKITAENTPLPIAGVLLPTIPGKLDVNKSKTHISVNGRKI RMRCRAIDGDVTFCRPKSPVYVGNGVHANLHVAFHRSSSEKIHSNEISSDSIGVLGYQ KTVDHTKVNSKLSLFFEIKS (SEQ ID NO: 1). CRM_{197} can be from 58-59 kDa in size. CRM_{197} can be 58.4 kDa in size. CRM_{197} can be produced, isolated, and purified from a cell bank. A vial from a cell bank of CRM_{197} can be used to seed a new flask and allowed to ferment. The fermentation culture can be centrifuged and the contents can be harvested, clarified, and filtered using a 0.2 μm filter. The filtrate can then be concentrated and diafiltered. The CRM_{197} can be further purified by filtration using microtubes or membranes of the appropriate pore size. Then anion exchange chromatography can be used in the isolation and purification of the CRM_{197}, which can be followed by ammonium sulfate precipitation, and another filtration using a 0.45 μm filter. CRM_{197} can be further isolated and purified from this product by hydrophobic interaction chromatography, after which CRM_{197} can be concentrated and diafiltered into the desired buffer. A final step can be filtration with 0.2 μm filter. The isolated and purified CRM_{197} can be stored at ≤ -70°C until use in conjugation with a saccharide or polysaccharide. Quality control tests can be performed on the isolated and purified CRM_{197}.

[0052] A polypeptide can be conjugated to an immunogenic serotype 1 capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 2 capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 3 capsular polysaccharide, fragment thereof, or

Petitioner Merck Ex-1015, 1560

combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 4 capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 5 capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 6A capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 6B capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 6C capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 7F capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 7C capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 8 capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 9N capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 9V capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 10A capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 11A capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 12F capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 14 capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 15A capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 15B capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 15C capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 16F capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 17F capsular polysaccharide,

Petitioner Merck Ex-1015, 1561

fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 18C capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 19A capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 19F capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 20A capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 20B capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 22F capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 23A capsular polysaccharide or fragment thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 23B capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 23F capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 24F capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 24B capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 31 capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 33F capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 33B capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 34 capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 35F capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 35B capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. A polypeptide can be conjugated to an immunogenic serotype 38 capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*.

Petitioner Merck Ex-1015, 1562

[0053] In some embodiments, CRM_{197} can be conjugated to an immunogenic serotype 1 capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 2 capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 3 capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 4 capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 5 capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 6A capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 6B capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 6C capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 7F capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 7C capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*.CRM_{197} can be conjugated to an immunogenic serotype 8 capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 9N capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 9V capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 10A capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 11A capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 12F capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 14 capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 15A capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 15B capsular polysaccharide, fragment thereof, or combination thereof isolated from *S.*

Petitioner Merck Ex-1015, 1563

pneumoniae. CRM_{197} can be conjugated to an immunogenic serotype 15C capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 16F capsular polysaccharide, fragment thereof, or combination thereof from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 17F capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 18C capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 19A capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 19F capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 20A capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 20B capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 22F capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 23A capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 23B capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 23F capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 24F capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 24B capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 31 capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 33F capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 33B capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 34 capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 35F capsular polysaccharide, fragment thereof, or combination thereof isolated from *S.*

Petitioner Merck Ex-1015, 1564

pneumoniae. CRM_{197} can be conjugated to an immunogenic serotype 35B capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*. CRM_{197} can be conjugated to an immunogenic serotype 38 capsular polysaccharide, fragment thereof, or combination thereof isolated from *S. pneumoniae*.

[0054] In further embodiments, any of the saccharides as described herein can be conjugated to any polypeptides described herein. Any of the immunogenic saccharide-polypeptide conjugates described herein can be isolated and purified.

Methods of Conjugating a Saccharide and Polypeptide to Produce a Saccharide-Polypeptide Conjugate

[0055] The saccharides can be conjugated to the polypeptide by, *e.g.*, chemical or biological synthesis. A saccharide can be a polysaccharide, a capsular polysaccharide, or an immunogenic fragment thereof. A capsular polysaccharide or fragment of the capsular polysaccharide can be conjugated to the polypeptide by chemical or biological synthesis.

[0056] For example, the capsular polysaccharide or immunogenic fragment thereof can be chemically activated and then reacted with the polypeptide. For example, capsular polysaccharides or fragments of the capsular polysaccharides can be reacted with either ammonia or diaminoethane to generate a free terminal amino group. The amino group can then be reacted with an excess of disuccinimidyl ester of adipic acid, which can introduce an active succininmidyl ester group. This can then be reacted to a free amino group on the polypeptide to form covalent amide bonds.

[0057] A polysaccharide and polypeptide can be conjugated using 1-cyano-dimethylaminopyridinium tetrafluoroborate (CDAP) chemistry. CDAP can be used to activate a broad range of acidic, neutral, and other classes of polysaccharides, which can then be derivatized with diamines, dihydrazides or other functional groups in preparation for coupling to proteins. In CDAP, the cynanylating reagent 1-cyano-dimethylaminopyridinium tetrafluoroborate can be used for the synthesis of polysaccharide-protein conjugates. The cyanilation reaction can be performed under relatively mild conditions, which can avoid hydrolysis of the alkaline sensitive polysaccharides. This synthesis can allow for direct coupling to a carrier. The polysaccharide can be solubilized in water or a saline solution. CDAP can be dissolved in acetonitrile and can be added immediately to the polysaccharide solution. The CDAP can reacts with the hydroxyl groups of the polysaccharide to form a cyanate ester. This cyanate ester can be highly reactive, which can result in an activated polysaccharide. This can be done at a pH of 9–10. After this activation step, the polypeptide

Petitioner Merck Ex-1015, 1565

can be added. Amino groups of lysine of a polypeptide can react with the activated polysaccharide to form an isourea covalent link. This conjugation step can occur under mildly alkaline conditions, such as a pH of 7–9. In some cases, there can be a strong pH dependence on the epsilon amines of lysine to form a stable O-alkyl-isourea linkage. After the coupling reaction, a large excess of an amino-containing reagent such as glycine can then be added to quench the residual activated functional groups. The CDAP activation can take only a few minutes and conjugation can be completed in a few hours. The conjugate can then be passed through a gel permeation column to remove unreacted polypeptide and residual reagents.

[0058] In some embodiments, CDAP can be made up at 100 mg/ml in acetonitrile and stored at -20°C for up to 1 month. CDAP can be slowly pipetted into a vortexed solution of polysaccharide in water (rapid addition of the organic co-solvent precipitates the polysaccharide) and 20 s later a volume of aqueous 0.2M triethylamine (TEA) equal to volume of CDAP used can be added. At 2.5 min, a large molar excess of a 0.5 M hexanediamine solution in either 0.1 M sodium borate at pH 9.3 or 0.75 M HEPES at pH 7.5, can be added. The reaction mixture can be allowed to stand overnight at 4°C, can be desalted on either a P-6 DG or a P-6 cartridge, can be equilibrated with saline and then can be further dialyzed into saline. The extent of derivatization with hexanediamine can be determined using a TNBS assay for primary amines; absorbance can be measured at 366nm, using an extinction coefficient of 11000 M^{-1}. Polysaccharide concentrations can be determined as described by Monsigny et al., using the corresponding polysaccharide as the standard.

[0059] In some embodiments, polysaccharide can be solubilized in saline at 10 mg/ml. At t = 0, CDAP (100 mg/ml in acetonitrile) can be added (1 mg CDAP/ mg polysaccharide) while vortexing. At 30 s, 0.2 M TEA can be added (10 µl/mg polysaccharide) to raise the pH. At 2.5 min the pH can be readjusted to the coupling pH and the amine or hydrazide reagent or the polypeptide can be added, in the appropriate buffer. After an overnight reaction, the solution can be dialyzed and/or desalted on a P6DG column. Polysaccharide polypeptide conjugates can be fractionated on an S400HR column, which can be equilibrated with either saline or PBS. HPLC can be performed on HPLC size exclusion columns using a Waters 626 pump, monitored at 280 nm and with a refractive index detector. Samples can be filtered before chromatography using a Millex Ultrafree MC device.

[0060] In some embodiments, for low pH coupling, amines on polypeptide can be functionalized with hydrazides using the two-step method as follows. Five mg of polypeptide at 12.5 mg/ml in 0.19 M HEPES, 2.5 mM EDTA, pH 7.3 can be iodoacetylated by the addition of a 15-fold molar excess of SIA over moles of polypeptide. After 2 h reaction in the

Petitioner Merck Ex-1015, 1566

dark, the solution can be desalted on a 1 x 15 cm P6DG column, can be equilibrated with 2 mM MES, 0.2 M NaCl, pH 5.9 and the void volume fractions, which can be concentrated with a Centricon 50 device. DTPH (30 µl) at 0.1 M in water, can be reduced to 3-mercapto-propionyl hydrazide by addition of 25 µl 0.1 M TCEP in water, and can then be added to the iodoacetylated polypeptide with a pH that can be adjusted to about 5. After a 2 h reaction, reagent can be removed by desalting again and concentrating with a Centricon 50 device to 10 mg/ml. TNBS can be used to determined number of hydrazide per moles of polypeptide. To couple the hydrazide-derivatized polypeptide, 3 mg of polysaccharide at 10 mg/ml in saline can be activated by the addition of 15 µl CDAP at 100 mg/ml in acetonitrile, followed 30 s later by 30 µl of 0.2 M TEA. At 2.5 min, the pH can be reduced to 5.5 by the addition of 100 µl 1 M MES, pH 5.5 and the activated polysaccharide can be added to 3.8 mg of the polypeptide-hydrazide. After an overnight reaction at 4°C, the reaction can be quenched by the addition of 50 µl 1 M ethanolamine. The solution can be applied to an S400HR column, which can be equilibrated with PBS, and the void volume fractions can be pooled. Sterile filtration can be done by passage through a Millex GB 0.2 µm filter.

[0061] In some embodiments, CDAP can be used to conjugate a polysaccharide and CRM_{197}. The polysaccharide (10 mg) can be dissolved in 1.0 mL of 0.1M sodium borate buffer pH 9.0 and can be activated by addition of 50 µl of a solution of CDAP dissolved in acetone:water (6:4). Immediately, the pH can be adjusted and maintained at 9.0 by continuous dropwise addition of a 0.1 M NaOH solution. The mixture can be stirred for 5 min and then a volume of 1.4 mL of 0.05 M HCl can be added, stirred for a while and then left to rest during 1 ½ min more. The mixture can be rapidly passed through a PD-10 column equilibrated in 0.1 M sodium bicarbonate buffer pH 8.3. An aliquot of this can be used to determine cyanate ester formation and the rest of the preparation can be immediately used for coupling purposes. Polypeptide (15 mg) can be dissolved in 1.0 mL of 0.1 M $NaHCO_3$ buffer pH 8.3 and added to the activated polysaccharide solution. The mixture can be gently stirred during 8 h at room temperature. A volume of 1.0 mL 0.1 M Tris-HCl buffer pH 8.6 can be added to block any remaining activation sites on the unreacted polysaccharide and incubated during 1 h more. The final solution can be lyophilized and stored until used for the purification procedure. The progress of the conjugation can be analyzed by high-performance size exclusion chromatography (HPSEC) using a Zorbax GF-250 column and monitored at 280 nm and 210 nm. For example, aliquots of the reaction mixture can be taken at 10 min and at every hour up to 4 h. The column can be equilibrated in 0.025 M phosphate buffer pH 7.0 supplemented with 0.13 M NaCl and be calibrated with the following proteins: thyroglobulin(669 kDa),

Petitioner Merck Ex-1015, 1567

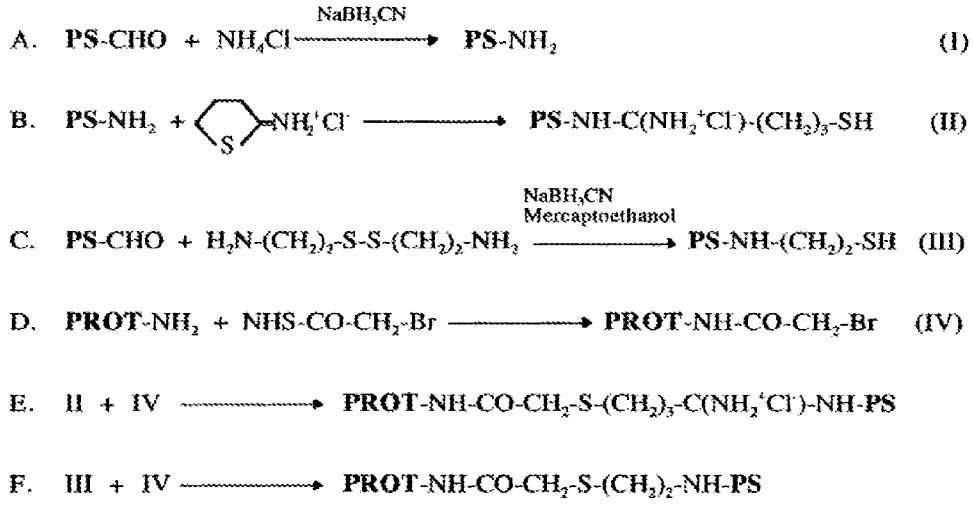
ferritin (440 kDa), catalase (232 kDa), aldolase (158 kDa), BSA (67 kDa), ovalbumin (43 kDa), and ribonuclease (13.7 kDa). The void volume can be determined with Blue dextran. Samples (10 µl aliquots) can be injected into the column and a flow rate of 0.5 mL/min can be used. Prior and after the analysis the column can be washed with the equilibration buffer. The conjugation reaction progress (%) can be measured by comparing the conjugate peak area related to the free protein peak area using detection at wavelength 280 nm according to the following equation: (conjugate peak area/(conjugate peak area + free protein peak area)) x 100.

[0062] In some embodiments, the polysaccharide can be activated via CDAP chemistry in a CDAP solution. The polysaccharide can be mixed with CDAP solution, which can then be incubated at the appropriate temperature for polysaccharide activation. A calculated amount of CRM_{197} can be added to the activated polysaccharides. The reaction can then be quenched using glycine or any other suitable quenching reagent. The conjugation reaction mixture can be filtered, diafiltered, and concentrated for the polysaccharide-CRM_{197} conjugates. The polysaccharide-CRM_{197} conjugates can then be purified by gel filtration chromatography. The fractions containing the polysaccharide-CRM_{197} conjugates can be pooled, concentrated, and then filtered through a 0.2 µm filter. The product can be stored at 2-8°C.

[0063] As another example, the capsular polysaccharide or immunogenic fragment thereof can activated by periodate oxidation. Sodium periodate oxidizes diols (two adjacent carbons with hydroxyl groups) can be converted into aldehydes (C=O) and in the process breaks C-C bonds. Thus, depending upon the structure, periodate activation can fragment a capsular polysaccharide or immunogenic fragment thereof and open the ring structures of sugars. When the diol is within a ring, the ring sugar can be opened possibly altering the polysaccharide conformation. When the diol is in a glycerol or ribitol side chain, the side chain can disappear. The reactive aldehyde groups can then condense with free amino groups on the polypeptide in the presence of sodium cyanoborohydride to form a stable secondary amine. Condensation of the aldehyde with the epsilon amino group on lysine can be a slow process and can take a few days. The remaining aldehyde groups can then be quenched using sodium borohydride, which can convert them back to hydroxyls.

[0064] Another example of coupling a polypeptide to a polysaccharide is based on thioether bonding of polysaccharides activated with 2-iminothiolane (2-IT), or alternatively, with cystamine, to bromoacetylated polypeptides such as tetanus toxoid.

Petitioner Merck Ex-1015, 1568



Schematic I

[0065] The above Schematic I represents end-point coupling of polysaccharides (PS) to proteins (PROT) through thioether bond. (A) Amination of polysaccharide through reducing terminal using ammonium chloride in the presence of cyanoborohydride ion. (B) Thiolation of aminated polysaccharide (I) with 2-iminothiolane (2-IT). (C) Alternative thiolation of polysaccharide through reductive amination with cystamine with concomitant cleavage of disulfide bond. (D) Bromoacetylation of amino groups of protein using N-hydroxysuccimidyl bromoacetate. (E) Coupling of polysaccharide derivatized with 2-IT (II) to bromoacetylated protein (IV). (F) Alternative coupling of polysaccharide derivatized with cystamine (III) to bromocacetylated protein (IV).

[0066] As another example, the immunogenic saccharide-polypeptide conjugate can be produced using bacteria, such as *Escherichia coli* (*E. coli*). The immunogenic saccharide-polypeptide can comprise the capsular polysaccharide at least partially embedded in the polypeptide. The immunogenic saccharide-polypeptide can comprise the capsular polysaccharide chemically cross-linked to the polypeptide. The immunogenic saccharide-polypeptide can comprise the capsular polysaccharide at least partially chemically cross-linked to the polypeptide. A capsular polysaccharide or fragment of the capsular polysaccharide of a serotype from *S. pneumoniae* can be conjugated to a polypeptide by chemical or biological synthesis. One saccharide can be conjugated to one polypeptide. Two or more saccharides can be conjugated to one polypeptide. The saccharides can be the same serotype. The saccharides can be different serotypes. One capsular polysaccharide or immunogenic fragment thereof can be conjugated to one polypeptide. Two or more capsular polysaccharides or fragments thereof can be conjugated to one polypeptide. The capsular

Petitioner Merck Ex-1015, 1569

polysaccharides or fragments thereof can be the same serotype. The capsular polysaccharides or fragments thereof can be different serotypes.

[0067] After conjugation, the polysaccharide polypeptide conjugate can be purified. For example, different chromatographic strategies can be used to purify a polysaccharide-polypeptide conjugate: SEC (using a column packed with Sepharose CL-6B), a combination of ion-exchange chromatography (DEAE-Sepharose) can be followed by HPSEC (Sepharose CL-6B and hydrophobic interaction chromatography (HIC) (column packed with Sephadex LH-20). For HPSEC purification on a Sepharose CL-6B column, an amount of 4.0 mg of the lyophilized mixture containing the polysaccharide polypeptide conjugate, free polysaccharide and free polypeptide, can be dissolved in 0.1 M formic acid buffer (ammonium salt) pH 6.0 and can be applied to the column (60 cm x 4.0 cm) equilibrated with the same buffer, at a flow of 0.5 mL/min. Isocratic elution can be performed with the buffer, and the process can be continuously monitored using a differential refractometric detector. Fractions can be collected, can be lyophilized, and can be used for further analysis. For the second strategy, an amount of 4.0 mg of the lyophilized reaction mixture can be dissolved in 500 µL of 0.1 M phosphate-buffered saline (PBS) pH 7.0 and can be applied to the DEAE-Sepharose column, previously equilibrated in the same buffer. The pass-through of the column can be collected and after washing with the buffer, elution can be performed using a gradient (0.25-1.0 M) of NaCl. The presence of the polysaccharide can be analyzed in each fraction by the Phenol sulfuric technique. The eluted fractions can be pooled, can be lyophilized, can be resuspended in 0.1 M ammonium formate buffer pH 6.0, and can be applied to a Sepharose CL-6B column. Fractions of 5 mL can be collected, can be dialyzed, can be lyophilized, and can be analyzed for protein and carbohydrate contents. In a third chromatographic approach, an amount of 4.0 mg of the lyophilized reaction mixture can be dissolved in 1.0 mL of distilled water and applied to a column packed with Sephadex LH-20 previously equilibrated with distilled water, at a flow rate of 0.5 mL/min. Elution can be performed isocratically with distilled water, and the process can be monitored as described above. Fractions can be collected, can be lyophilized, and can be used for further analysis.

[0068] Furthermore, 'click' chemistry can be used to conjugate a saccharide with a polypeptide as disclosed in US Patent No. 8,753,645 and in Hu et al., Towards the next generation of biomedicines by site selective conjugation, *Chem. Soc. Rev.*, 2016, 45, 1691. 'Click' chemistry can be used to conjugate modified CRM_{197} or CRM_{197} with non-natural amino acids to polysaccharides.

Petitioner Merck Ex-1015, 1570

Pharmaceutical Compositions and Vaccines

[0069] The saccharide-polypeptide conjugates described herein can be in the form of a pharmaceutical composition. The saccharide-polypeptide conjugates described herein can be in the form of a pharmaceutical composition in unit dose form. The saccharide-polypeptide conjugates described herein can be in the form of a vaccine. The saccharide-polypeptide conjugates described herein can be in the form of a vaccine in unit dose form. A pharmaceutical composition or vaccine can comprise an immunogenic saccharide-polypeptide conjugate. A pharmaceutical composition or vaccine can comprise an immunogenic capsular polysaccharide-polypeptide conjugate. A pharmaceutical composition or vaccine can be in unit dose form and can comprise an immunogenic capsular polysaccharide-polypeptide conjugate. A pharmaceutical composition or vaccine can comprise an immunogenic saccharide-polypeptide conjugate wherein the capsular polysaccharide or immunogenic fragment thereof of the saccharide-polypeptide conjugate can be one serotype. In another embodiment, a pharmaceutical composition or vaccine can comprise an immunogenic saccharide-polypeptide conjugates wherein the capsular polysaccharides or immunogenic fragments thereof can be from different serotypes, creating a mixture of different immunogenic saccharide-polypeptide conjugates. A pharmaceutical composition or vaccine can comprise an immunogenic saccharide-polypeptide conjugates wherein the polypeptide is the same polypeptide in all the immunogenic saccharide-polypeptide conjugates. In other embodiments, a pharmaceutical composition or vaccine can comprise immunogenic saccharide-polypeptide conjugates wherein the polypeptide(s) in the saccharide-polypeptide conjugates are a mixture of different polypeptide(s).

[0070] For example, a pharmaceutical composition or vaccine can comprise an immunogenic saccharide-polypeptide conjugate comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *S. pneumoniae* selected from the group comprising 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35F, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise an immunogenic saccharide-polypeptide conjugate comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *S. pneumoniae* selected from the group comprising 2, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35F, 35B, 38, and Serogroup 20

Petitioner Merck Ex-1015, 1571

(comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of at least two immunogenic saccharide-polypeptide conjugate comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *S. pneumoniae* selected from the group comprising 2, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35F, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of at least two immunogenic saccharide-polypeptide conjugate comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *S. pneumoniae* selected from the group comprising 2, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35F, 35B, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of at least eight immunogenic saccharide-polypeptide conjugate comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *S. pneumoniae* selected from the group comprising 2, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35F, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of at least 20 immunogenic saccharide-polypeptide conjugate comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *S. pneumoniae* selected from the group comprising 3, 6C, 7C, 8, 9N, 10A, 11A, 12F, 15A, 16F, 19A, 19F, 22F, 23A, 23B, 31, 33F, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of at least 20 immunogenic saccharide-polypeptide conjugate comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *S. pneumoniae* selected from the group comprising 3, 6C, 7F, 7C, 8, 9N, 11A, 12F, 15A, 16F, 19A, 19F, 22F, 23A, 23B, 31, 33F, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of at least 15 immunogenic saccharide-polypeptide conjugate comprising individually a capsular polysaccharide, fragment thereof,

Petitioner Merck Ex-1015, 1572

or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *S. pneumoniae* selected from the group comprising 3, 6C, 7F, 7C, 8, 9N, 10A, 11A, 12F, 15A, 16F, 19A, 19F, 22F, 23A, 23B, 31, 33F, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of at least 16 immunogenic saccharide-polypeptide conjugate comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *S. pneumoniae* selected from the group comprising 3, 6C, 7F, 7C, 8, 9N, 10A, 11A, 12F, 15A, 16F, 19A, 19F, 22F, 23A, 23B, 31, 33F, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of at least 20 immunogenic saccharide-polypeptide conjugate comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *S. pneumoniae* selected from the group comprising 3, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 19A, 19F, 22F, 23A, 23B, 31, 33F, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of at least 20 immunogenic saccharide-polypeptide conjugate comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *S. pneumoniae* selected from the group comprising 3, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 19A, 22F, 23A, 23B, 24F, 33F, 35B, and 38. A pharmaceutical composition or vaccine can comprise a plurality of at least 10 immunogenic saccharide-polypeptide conjugate comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *S. pneumoniae* selected from the group comprising 3, 8, 9N, 12F, 15A, 19A, 22F, 23A, 23B, and 24F. A pharmaceutical composition or vaccine can comprise a plurality of at least 11 immunogenic saccharide-polypeptide conjugate comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *S. pneumoniae* selected from the group comprising 3, 8, 9N, 10A, 12F, 15A, 19A, 22F, 23A, 23B, and 24F. A pharmaceutical composition or vaccine can comprise a plurality of at least 24 immunogenic saccharide-polypeptide conjugate comprising individually a capsular polysaccharide, fragment thereof,

Petitioner Merck Ex-1015, 1573

or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *S. pneumoniae* selected from the group comprising 3, 4, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 19A, 22F, 23A, 23B, 24F, 31, 33F, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of at least 20 immunogenic saccharide-polypeptide conjugate comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *S. pneumoniae* selected from the group comprising 3, 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 19A, 19F, 22F, 23A, 23B, 31, 33F, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of at least 20, 21, 22, 23, 24, 25, 26, or 27 immunogenic saccharide-polypeptide conjugate comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *S. pneumoniae* selected from the group comprising 3, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 19F, 22F, 23A, 23B, 24F, 31, 33F, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a saccharide-polypeptide conjugate comprising a capsular polysaccharide or immunogenic fragment thereof from a serotype of *S. pneumoniae* conjugated to a polypeptide, and wherein the serotype is not any one of, or not at least any one of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F; and the serotype is at least one of 2, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35F, 35B, 38, and Serogroup 20 (comprising serotypes 20A and 20B); or a combination thereof. A pharmaceutical composition or vaccine can comprise a saccharide-polypeptide conjugate comprising a capsular polysaccharide or immunogenic fragment thereof from a serotype of *S. pneumoniae* conjugated to a polypeptide, and wherein the serotype is not any one of, or not at least any one of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F; and the serotype is at least one of 2, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35F, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B); or a combination thereof. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae*

Petitioner Merck Ex-1015, 1574

serotype selected from a group consisting of at least 1, 2, 3, 4, 5, 6, 7, 8, or 9 serotypes selected from the group consisting of 2, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of at least 1, 2, 3, 4, 5, 6, 7, 8, or 9 serotypes selected from the group consisting of 2, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise at least 10, 11, 12, 13, 14, 15, or 16 serotypes selected from the group consisting of 2, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35F, 35B, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise at least 17, 18, 19, 20, 21, 22, 23, or 24 serotypes selected from the group consisting of 2, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35F, 35B, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise at least 10, 11, 12, 13, 14, 15, or 16 serotypes selected from the group consisting of 2, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35F, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise at least 17, 18, 19, 20, 21, 22, 23, or 24 serotypes selected from the group consisting of 2, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35F, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 22F, 23A, 23B, 33F, and 35B. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 22F, 23A, 23B, 24F, 33F, and 35B. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 22F, 23A, 23B, 24F, 33F, and 35B. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F, and 35B. A pharmaceutical composition or

Petitioner Merck Ex-1015, 1575

vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20B, 22F, 23A, 23B, 33F, and 35B. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 10A, 11A, 15A, 15B, 15C, 22F, 23A, 24B, 33F, 35B, and 38. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 22F, 23A, 23B, 33F, and 35B. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 22F, 23A, 23B, 33F, and 35B. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 22F, 23A, 23B, 24F, 33F, and 35B. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising 6C, 10A, 11A, 15A, 15B, 15C, 22F, 23A, 24B, 33F, 35B and 38. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 22F, 23A, 23B, 33F, and 35B. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 22F, 23A, 23B, 33F, and 35B. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 23A, 23B, and 35B. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 23A, 23B, 24F, and 35B. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 23A, 23B, 24F, and 35B. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 10A, 11A, 15A, 15B, 15C, 23A, 24B, 35B, and 38. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 23A, 23B, and 35B. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 23A, 23B, and 35B. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 23A, 23B, 24F, and 35B. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising 6C, 10A, 11A, 15A, 15B, 15C, 23A, 24B, 35B and 38. A pharmaceutical composition or vaccine can comprise a plurality of

Petitioner Merck Ex-1015, 1576

saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 23A, 23B, and 35B. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 23A, 23B, and 35B. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 15A, 15C, 16F, 23A, 23B, and 35B. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 9N, 15A, 15C, 16F, 17F, 20B, 23A, 23B, 24F, 31, 33F, 34, 35F, and 35B. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20A, 22F, 23A, 23B, 33F, and 35B. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 15A, 15C, 16F, 20B, 23A, 23B, 34F, 31, 33F, 34, 35F, and 35B. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 15A, 15B, 15C, 16F, 20A, 22F, 23A, 23B, 33F, and 35B. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising at least 13 of the serotypes 1, 2, 3, 4, 5, 6A, 6B, 7C, 7F, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising at least 15 of the serotypes 1, 2, 3, 4, 5, 6A, 6B, 7C, 7F, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising at least 16 of the serotypes 1, 2, 3, 4, 5, 6A, 6B, 7C, 7F, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B 31, 33F, 33B, 35B, 34, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least one additional serotype comprising 1, 2, 3, 4, 5, 6A, 6B, 7C, 7F, 9V, 14, 18C, 19A, 19F, 20B, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide

Petitioner Merck Ex-1015, 1577

conjugates comprising the serotype 6C and at least one additional serotype comprising 2, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 22F, 23A, 23B, 24B, 31, 33F, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least one additional serotype comprising 1, 3, 4, 6A, 6B, 7F, 8, 9N, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 19F, 19A, 22F, 23A, 23B, 24F, 33F, 35F, 35B, 38 or Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least one additional serotype selected from 1, 3, 4, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 19F, 19A, 22F, 23A, 23B, 23F, 24F, 33F, 35F, 35B, 38 or Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising at least 13 of the serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising at least 15 of the serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 35B, 34, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising at least 16 of the serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least one additional serotype comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least one additional serotype comprising 2, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 22F, 23A, 23B, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least one additional serotype comprising 1, 3, 4, 6A, 6B, 7F, 8, 9N, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 19F, 19A, 22F, 23A, 23B, 24F, 33F, 34, 35F, 35B, 38, and Serogroup

Petitioner Merck Ex-1015, 1578

20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least one additional serotype selected from 1, 3, 4, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 19F, 19A, 22F, 23A, 23B, 23F, 24F, 33F, 34, 35F, 35B, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least one additional serotype selected from 3, 4, 7F, 8, 9N, 11A, 12F, 15A, 15B, 15C, 16F, 19A, 22F, 23A, 23B, and 35B. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least one additional serotype selected from 1, 3, 4, 6A, 7F, 8, 9N, 10A, 11A, 12F, 14, 19A, 19F, 22F, 23A, 23B, 23F, 24F, and 33F. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least one additional serotype selected from 3, 4, 6B, 10A, 15A, 15B, 19A, 19F, 22F, 23F, 24F, 35B. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least two additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least three additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least four additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least five additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least six additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F,

Petitioner Merck Ex-1015, 1579

17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least seven additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least eight additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least nine additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least ten additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least eleven additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least twelve additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 35B, 34, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least thirteen additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 35B, 34, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least fourteen additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F,

Petitioner Merck Ex-1015, 1580

9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least fifteen additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least sixteen additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least seventeen additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least eighteen additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least nineteen additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least twenty additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least twenty-one additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide

Petitioner Merck Ex-1015, 1581

conjugates comprising the serotype 6C and at least twenty-two additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 35B, 34, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least twenty-three additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least twenty-four additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 35B, 34, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least twenty-five additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, or 37 additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 7C, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35F, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B), or a combination thereof. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least two additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least three additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least four additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A,

Petitioner Merck Ex-1015, 1582

19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least five additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least six additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least seven additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least eight additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least nine additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least ten additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least eleven additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least

Petitioner Merck Ex-1015, 1583

twelve additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least thirteen additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least fourteen additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least fifteen additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least sixteen additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least seventeen additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least eighteen additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least nineteen additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and

Petitioner Merck Ex-1015, 1584

20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least twenty additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least twenty-one additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least twenty-two additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least twenty-three additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least twenty-four additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least twenty-five additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, or 37 additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 7C, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35F, 35B, 38, and Serogroup 20 (comprising serotypes 20A and 20B), or a combination thereof.

Petitioner Merck Ex-1015, 1585

[0071] A vaccine can comprise immunogenic saccharide-polypeptide conjugates that can each comprise a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof can be from a *Streptococcus pneumoniae* serotype selected from a group consisting of 23A and 23B. A vaccine can comprise at least 2 immunogenic saccharide-polypeptide conjugates that can each comprise a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof can be from a *Streptococcus pneumoniae* serotype group, wherein one serotype can be 23A and at least one additional serotype can be selected from the group consisting of 1, 2, 3, 4, 5, 6A, 6B, 6C, 7C, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 20B, 22F, 23B, 24F, 24B, 31, 33F, 33B, 34, 35B, 35F, and 38. A vaccine can comprising at least 2 immunogenic saccharide-polypeptide conjugates that can each comprise a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof can be from a *Streptococcus pneumoniae* serotype group, wherein one serotype can be 23B and at least one additional serotype can be selected from the group consisting of 1, 2, 3, 4, 5, 6A, 6B, 6C, 7C, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 20B, 22F, 23A, 24F, 24B, 31, 33F, 33B, 34, 35B, 35F, and 38.

[0072] The immunogenic saccharide-polypeptide conjugate(s) can be individually, respectively, or collectively present in an amount of about: 0.001, 0.01, 0.1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 95, or 100%, by weight, based on the weight of the pharmaceutical composition or vaccine. The immunogenic saccharide-polypeptide conjugate(s) can include excipients that can be individually, respectively, or collectively present in an amount of about: 0.001, 0.01, 0.1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 95, or 100%, by weight, based on the weight of the pharmaceutical composition or vaccine. The immunogenic saccharide-polypeptide conjugate(s) can include adjuvants that can be individually, respectively, or collectively present in an amount of about: 0.001, 0.01, 0.1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 95, or 100%, by weight, based on the weight of the pharmaceutical composition or vaccine. The pharmaceutical composition or vaccine can be administered to one of a plurality of humans, which elicits at least one of the following side effects in less than about 5%, 10%, 20% or 30% of the plurality of humans: fatigue, headache, muscle pain, joint pain, decreased appetite, chills, or rash.

Petitioner Merck Ex-1015, 1586

[0073] In other embodiments, a pharmaceutical composition or vaccine can comprise a saccharide-polypeptide conjugate wherein the saccharide is from *N. meningitidis*. A pharmaceutical composition can comprise a saccharide-polypeptide conjugate wherein the saccharide can be from *S. enterica*. A pharmaceutical composition or vaccine can comprise a saccharide-polypeptide conjugate wherein the saccharide can be from *H. influenzae*. A pharmaceutical composition can comprise a plurality of saccharide-polypeptide conjugates comprising saccharides from *Neisseria meningitidis*. A pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising saccharides from *S. enterica*. A pharmaceutical composition or vaccine can comprise can comprise a plurality of saccharide-polypeptide conjugates comprising saccharides from *H. influenzae*.

[0074] The polypeptide of any of the plurality of saccharide-polypeptide conjugates can be the same polypeptide. For example, the polypeptide of any of the plurality of saccharide-polypeptide conjugates can be CRM_{197}. The plurality of saccharide-polypeptide conjugates can comprise a mixture of different polypeptides. For example, the plurality of saccharide-polypeptide conjugates can comprise a mixture of CRM_{197}, tetanus toxoid, a diphtheria toxoid, or any fragment thereof.

[0075] Any pharmaceutical composition or vaccine described herein can be in unit dose form. Additionally, the pharmaceutical composition or vaccine can further comprise an adjuvant. In some embodiments, the adjuvant can be an aluminum-cation comprises adjuvant. In other embodiments, the adjuvant can be aluminum phosphate, aluminum sulfate, or aluminum hydroxide. More examples of suitable adjuvants for use in the pharmaceutical composition or vaccine include: aluminum-based salts and variants thereof; emulsions (either water-in-oil or oil-in-water) and variants thereof, *e.g.*, Freund's Incomplete Adjuvant, MF59® (Glaxosmithkline plc); PRR ligands and variants thereof, *e.g.*, pathogen associated molecular patterns (PAMPs); TLR3 and RLR ligands or variants thereof, *e.g.*, Synthetic analogs of dsRNA, poly(I:C), etc.; TLR4 ligands or variants thereof, *e.g.*, bacterial flagellin, Glucopyranosyl Lipid Adjuvant (GLA), monophosphoryl lipid A, etc.; TLR5 ligands or variants thereof, *e.g.*, imiquimod, gardiquimod, R848, etc.; TLR9 ligands or variants thereof, *e.g.*, Oxydeoxynucleotides containing CpG motifs (CpG ODNs such as ODN1826 and ODN2006); NOD2 ligands or variants thereof, *e.g.*, fragments of bacterial cell walls (such as muramyl dipeptide [MDP]); saponins including synthetic derivatives or variants thereof, e.g., QS21, TQL1055, etc.; or any combination of above. An adjuvant can be 3M-052.

Petitioner Merck Ex-1015, 1587

[0076] A pharmaceutical composition or vaccine can further comprise an excipient. An excipient can be Acacia, Acesulfame Potassium, Acetic Acid, Glacial Acetone, Acetyltributyl Citrate, Acetyltriethyl Citrate, Agar, Albumin, Alcohol, Alginic Acid, Aliphatic Polyesters, Alitame, Almond Oil, Alpha Tocopherol, Aluminum Hydroxide Adjuvant, Aluminum Oxide, Aluminum Phosphate Adjuvant, Aluminum Stearate, Ammonia Solution, Ammonium Alginate, Ascorbic Acid, Ascorbyl Palmitate, Aspartame, Attapulgite, Bentonite, Benzalkonium Chloride, Benzethonium Chloride, Benzoic Acid, Benzyl Alcohol, Benzyl Benzoate, Boric Acid, Bronopol, Butylated Hydroxyanisole, Butylated Hydroxytoluene, Butylparaben, Calcium Alginate, Calcium Carbonate, Dibasic Anhydrous Calcium Phosphate, Dibasic Dihydrate Calcium Phosphate, Tribasic Calcium Phosphate, Calcium Stearate, Calcium Sulfate, Canola Oil, Carbomer, Carbon Dioxide, Carboxymethylcellulose Calcium, Carboxymethylcellulose Sodium, Carrageenan, Castor Oil, Hydrogenated Castor Oil, Microcrystalline Cellulose, Powdered Cellulose, Silicified Microcrystalline Cellulose, Cellulose Acetate, Cellulose Acetate Phthalate, Ceratonia, Cetostearyl Alcohol, Cetrimide, Cetyl Alcohol, Cetylpyridinium Chloride, Chitosan, Chlorhexidine, Chlorobutanol, Chlorocresol, Chlorodifluoroethane (HCFC), Chlorofluorocarbons (CFC), Chloroxylenol, Cholesterol, Citric Acid Monohydrate, Colloidal Silicon Dioxide, Coloring Agents, Copovidone, Corn Oil, Cottonseed Oil, Cresol, Croscarmellose Sodium, Crospovidone, Cyclodextrins, Cyclomethicone, Denatonium Benzoate, Dextrates, Dextrin, Dextrose, Dibutyl Phthalate, Dibutyl Sebacate, Diethanolamine, Diethyl Phthalate, Difluoroethane (HFC), Dimethicone, Dimethyl Ether, Dimethyl Phthalate, Dimethyl Sulfoxide, Dimethylacetamide, Disodium Edetate, Docusate Sodium, Edetic Acid, Erythorbic Acid, Erythritol, Ethyl Acetate, Ethyl Lactate, Ethyl Maltol, Ethyl Oleate, Ethyl Vanillin, Ethylcellulose, Ethylene Glycol Palmitostearate, Ethylene Vinyl Acetate, Ethylparaben, Fructose, Fumaric Acid, Gelatin, Glucose, Liquid, Glycerin, Glyceryl Behenate, Glyceryl Monooleate, Glyceryl Monostearate, Glyceryl Palmitostearate, Glycofurol, Guar Gum, Hectorite, Heptafluoropropane (HFC), Hexetidine, Hydrocarbons (HC), Hydrochloric Acid, Hydroxyethyl Cellulose, Hydroxyethylmethyl Cellulose, Hydroxypropyl Cellulose, Low-substituted Hydroxypropyl Cellulose, Hydroxypropyl Starch, Hypromellose, Hypromellose Acetate Succinate, Hypromellose Phthalate, Imidurea, Inulin, Iron Oxides, Isomalt, Isopropyl Alcohol, Isopropyl Myristate, Isopropyl Palmitate, Kaolin, Lactic Acid, Lactitol, Anhydrous Lactose, Monohydrate Lactose, Spray-Dried Lactose, Lanolin, Lanolin Alcohols, Hydrous Lanolin, Lauric Acid, Lecithin, Leucine, Linoleic Acid, Macrogol, Hydroxystearate Magnesium Aluminum Silicate, Magnesium Carbonate, Magnesium Oxide, Magnesium

Petitioner Merck Ex-1015, 1588

Silicate, Magnesium Stearate, Magnesium Trisilicate, Malic Acid, Maltitol, Maltitol Solution, Maltodextrin, Maltol, Maltose, Mannitol, Medium-chain Triglycerides, Meglumine, Menthol, Methylcellulose, Methylparaben, Mineral Oil, Light Mineral Oil, Mineral Oil and Lanolin Alcohols, Monoethanolamine, Monosodium Glutamate, Monothioglycerol, Myristic Acid, Neohesperidin Dihydrochalcone, Nitrogen, Nitrous Oxide, Octyldodecanol, Oleic Acid, Oleyl Alcohol, Olive Oil, Palmitic Acid, Paraffin, Peanut Oil, Pectin, Petrolatum, Petrolatum and Lanolin Alcohols, Phenol, Phenoxyethanol, Phenylethyl Alcohol, Phenylmercuric Acetate, Phenylmercuric Borate, Phenylmercuric Nitrate, Phosphoric Acid, Polacrilin Potassium, Poloxamer, Polycarbophil, Polydextrose, Polyethylene Glycol, Polyethylene Oxide, Polymethacrylates, Poly(methyl vinyl ether/maleic anhydride), Polyoxyethylene Alkyl Ethers, Polyoxyethylene Castor Oil Derivatives, Polyoxyethylene Sorbitan Fatty Acid Esters, Polyoxyethylene Stearates, Polyvinyl Acetate Phthalate, Polyvinyl Alcohol, Potassium Alginate, Potassium Benzoate, Potassium Bicarbonate, Potassium Chloride, Potassium Citrate, Potassium Hydroxide, Potassium Metabisulfite, Potassium Sorbate, Povidone, Propionic Acid, Propyl Gallate, Propylene Carbonate, Propylene Glycol, Propylene Glycol Alginate, Propylparaben, 2-Pyrrolidone, Raffinose, Saccharin, Saccharin Sodium, Saponite, Sesame Oil, Shellac, Simethicone, Sodium Acetate, Sodium Alginate, Sodium Ascorbate, Sodium Benzoate, Sodium Bicarbonate, Sodium Borate, Sodium Chloride, Sodium Citrate Dihydrate, Sodium Cyclamate, Sodium Hyaluronate, Sodium Hydroxide, Sodium Lactate, Sodium Lauryl Sulfate, Sodium Metabisulfite, Dibasic Sodium Phosphate, Monobasic Sodium Phosphate, Sodium Propionate, Sodium Starch Glycolate, Sodium Stearyl Fumarate, Sodium Sulfite, Sorbic Acid, Sorbitan Esters (Sorbitan Fatty Acid Esters), Sorbitol, Soybean Oil, Starch, Pregelatinized Starch, Sterilizable Maize Starch, Stearic Acid, Stearyl Alcohol, Sucralose, Sucrose, Compressible Sugar, Confectioner's Sugar, Sugar Spheres, Sulfobutylether b-Cyclodextrin, Sulfuric Acid, Sunflower Oil, Hard Fat Suppository Bases, Talc, Tartaric Acid, Tetrafluoroethane (HFC), Thaumatin, Thimerosal, Thymol, Titanium Dioxide, Tragacanth, Trehalose, Triacetin, Tributyl Citrate, Triethanolamine, Triethyl Citrate, Vanillin, Hydrogenated Vegetable Oil, Water, Anionic Emulsifying Wax, Carnauba Wax, Cetyl Esters Wax, Microcrystalline Wax, Nonionic Emulsifying Wax, White Wax, Yellow Wax, Xanthan Gum, Xylitol, Zein, Zinc Acetate, or Zinc Stearate.

[0077] A pharmaceutical composition or vaccine can further comprise a surfactant or emulsifier, or a combination thereof. A surfactant can be polysorbate, polymer glycol, a sorbitan ester, or any combination thereof. In some embodiments, polysorbate can be polysorbate 80. In some embodiments, polymer glycol can be polyethylene glycol. A

Petitioner Merck Ex-1015, 1589

surfactant can be TWEEN. A pharmaceutical composition or vaccine can comprise a specific polyethylene glycol based upon its molecular weight. A pharmaceutical composition or vaccine can comprise a preservative. A pharmaceutical composition or vaccine can comprise a salt. The salt can be an inorganic salt. A pharmaceutical composition or vaccine can further comprise an anti-fungal compound or a salt thereof. An antifungal compound can be thimerosal, phenol, benzethonium chloride, or 2-phenoxyethanol. A pharmaceutical composition or vaccine can further comprise a chelating agent. A chelating agent can be ethylenediaminetetraacetic acid (EDTA). A pharmaceutical composition or vaccine can further comprise a buffering agent. The buffering agent can be succinate buffer agent, tris-acetate- ethylenediaminetetraacetic acid (TAE) buffering agent, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) buffering agent, phosphate buffering agent, sodium phosphate buffering agent, or a potassium phosphate buffering agent. A pharmaceutical composition or vaccine can further comprise sterile water. When the pharmaceutical composition or vaccine can be administered intramuscularly to a human, the pharmaceutical composition or vaccine can elicit an immune response that lasts from about 1 week to about 30 years. A pharmaceutical composition or vaccine retains at least about 60% of its original biological activity when stored in a sealed container for about 24 months at a temperature of about 2°C–8°C when the sealed container is stored in an atmosphere having about 50% relative humidity and 1 atm of atmospheric pressure. A pharmaceutical composition or vaccine can retain at least about 70% of its original biological activity when stored in a sealed container for about 24 months at a temperature of about 2°C–8°C when the sealed container is stored in an atmosphere having about 50% relative humidity and 1 atm of atmospheric pressure. A pharmaceutical composition or vaccine can retain at least about 80% of its original biological activity when stored in a sealed container for about 24 months at a temperature of about 2°C–8°C when the sealed container is stored in an atmosphere having about 50% relative humidity and 1 atm of atmospheric pressure. A pharmaceutical composition or vaccine can retain at least about 90% of its original biological activity when stored in a sealed container for about 24 months at a temperature of about 2°C–8°C when the sealed container is stored in an atmosphere having about 50% relative humidity and 1 atm of atmospheric pressure.

[0078] The polysaccharide-polypeptide conjugates as described herein can be adjuvanted. Suitable adjuvants can include an aluminum hydroxide gel (alum) or aluminum phosphate, but can also be a salt of calcium, magnesium, iron or zinc, or can be an insoluble suspension of acylated tyrosine, or acylated sugars, cationically or anionically derivatized

Petitioner Merck Ex-1015, 1590

polysaccharides, or polyphophazenes. An adjuvant can be 3M-052. When adjuvanted with aluminum salts, the ratio of aluminum salt to polysaccharide can be less than 10:1 (w/w), less than 8:1(w/w), or more than 2:1(w/w) in a pharmaceutical composition dose or formulation, or a vaccine dose or formulation.

[0079] The amount of polypeptide in a pharmaceutical composition dose or vaccine dose can be selected as an amount which can induces an immunoprotective response without significant adverse effects. A dose or formulation can comprise from 0.1-100 μg of polysaccharide and/or for a polysaccharide polypeptide conjugate from 0.1-50 μg of polysaccharide. A polysaccharide-polypeptide conjugate can comprise from 1-10 μg of polysaccharide, 1-5 μg of polysaccharide, or 2-5 μg of polysaccharide. A polysaccharide-polypeptide conjugate can comprise about 0.5 μg of polysaccharide, about 1 μg of polysaccharide, about 1.5 μg of polysaccharide, about 2 μg of polysaccharide, about 2.5 μg of polysaccharide, about 3 μg of polysaccharide, about 3.5 μg of polysaccharide, about 4 μg of polysaccharide, about 5 μg of polysaccharide, about 6 μg of polysaccharide, about 7 μg of polysaccharide, about 8 μg of polysaccharide, about 9 μg of polysaccharide, about 10 μg of polysaccharide, about 11 μg of polysaccharide, about 12 μg of polysaccharide, about 13 μg of polysaccharide, about 14 μg of polysaccharide, about 15 μg of polysaccharide, about 16 μg of polysaccharide, about 17 μg of polysaccharide, about 18 μg of polysaccharide, about 19 μg of polysaccharide, or about 20 μg of polysaccharide. The content of polypeptide in the vaccine can be in the range from 1-100 μg of polypeptide, 5-50 μg of polypeptide, or 5-25 μg of polypeptide.

[0080] The total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in a pharmaceutical composition dose or a vaccine dose in unit dose form, can range from about 0.5 μg to about 5 μg. The total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in a pharmaceutical composition dose or a vaccine dose in unit dose form, can range from 0.5 μg to 5 μg. The total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in a pharmaceutical composition dose or in a vaccine dose in unit dose form, can range from about 1 μg to about 4 μg. The total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in a pharmaceutical composition dose or a vaccine dose in unit dose form, can range from about 1 μg to about 4 μg. The total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus*

Petitioner Merck Ex-1015, 1591

pneumoniae serotype in a pharmaceutical composition dose or in a vaccine dose in unit dose form, can range from about 1 μg to about 8 μg. The total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in a pharmaceutical composition dose or a vaccine dose in unit dose form, can range from about 1 μg to about 8 μg. The total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in a pharmaceutical composition dose or in a vaccine dose in unit dose form, can range from about 1 μg to about 10 μg. The total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in a pharmaceutical composition dose or a vaccine dose in unit dose form, can range from about 1 μg to about 10 μg. The total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in a pharmaceutical composition dose or in a vaccine dose in unit dose form, can range from about 1 μg to about 15 μg. The total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in a pharmaceutical composition dose or a vaccine dose in unit dose form, can range from about 1 μg to about 15 μg. The total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in a pharmaceutical composition dose or in a vaccine dose in unit dose form, can range from about 1 μg to about 20 μg. The total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in a pharmaceutical composition dose or a vaccine dose in unit dose form, can range from about 1 μg to about 20 μg. The total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in a pharmaceutical composition dose or in a vaccine dose in unit dose form, can range from about 4 μg to about 8 μg. The total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in a pharmaceutical composition dose or a vaccine dose in unit dose form, can range from about 4 μg to about 8 μg. The total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in a pharmaceutical composition dose or in a vaccine dose in unit dose form, can range from about 2 μg to about 6 μg. The total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in a pharmaceutical composition dose or a vaccine dose in unit dose form, can range from about 2

Petitioner Merck Ex-1015, 1592

μg to about 6 μg. The total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in a pharmaceutical composition dose or in a vaccine dose in unit dose form, can range from about 3 μg to about 5 μg. The total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in a pharmaceutical composition dose or a vaccine dose in unit dose form, can range from about 3 μg to about 5 μg. The total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in a pharmaceutical composition dose or a vaccine dose in unit dose form, can be about 0.5 μg, about 1 μg, about 2 μg, about 3 μg, about 4 μg, or about 5 μg. The total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in a pharmaceutical composition dose or a vaccine dose in unit dose form, can be 0.5 μg, 1 μg, 2 μg, 3 μg, 4 μg, or 5 μg. In some embodiments, a total amount of unconjugated capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in a pharmaceutical composition dose or vaccine dose in unit dose form, can range from about 0% to about 30% w/w. In some embodiments, a total amount of unconjugated capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in a pharmaceutical composition dose or vaccine dose in unit dose form, can range from 0% to 30% w/w. In some embodiments, a total amount of unconjugated capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in a pharmaceutical composition dose or vaccine dose in unit dose form, can range from about 0% to about 20% w/w. In some embodiments, a total amount of unconjugated capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in a pharmaceutical composition dose or vaccine dose in unit dose form, can range from 0% to 20% w/w. In some embodiments, a total amount of unconjugated capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in a pharmaceutical composition dose or vaccine dose in unit dose form, can range from about 0% to about 10% w/w. In some embodiments, a total amount of unconjugated capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in a pharmaceutical composition dose or vaccine dose in unit dose form, can range from 0% to 10% w/w.

Petitioner Merck Ex-1015, 1593

TABLE 2. Exemplary Total Amount of Polysaccharide in a Pharmaceutical Composition or Vaccine in Unit Dose Form

Polysaccharide Serotype*	Total Amount of Polysaccharide in Polysaccharide-Polypeptide Conjugate**		
1	about 1 μg	about 2 μg	about 4 μg
2	about 1 μg	about 2 μg	about 4 μg
3	about 1 μg	about 2 μg	about 4 μg
4	about 1 μg	about 2 μg	about 4 μg
5	about 1 μg	about 2 μg	about 4 μg
6A	about 1 μg	about 2 μg	about 4 μg
6B	about 1 μg	about 2 μg	about 4 μg
6C	about 1 μg	about 2 μg	about 4 μg
7F	about 1 μg	about 2 μg	about 4 μg
7C	about 1 μg	about 2 μg	about 4 μg
8	about 1 μg	about 2 μg	about 4 μg
9N	about 1 μg	about 2 μg	about 4 μg
9V	about 1 μg	about 2 μg	about 4 μg
10A	about 1 μg	about 2 μg	about 4 μg
11A	about 1 μg	about 2 μg	about 4 μg
12F	about 1 μg	about 2 μg	about 4 μg
14	about 1 μg	about 2 μg	about 4 μg
15A	about 1 μg	about 2 μg	about 4 μg
15B	about 1 μg	about 2 μg	about 4 μg
15C	about 1 μg	about 2 μg	about 4 μg
16F	about 1 μg	about 2 μg	about 4 μg
17F	about 1 μg	about 2 μg	about 4 μg
18C	about 1 μg	about 2 μg	about 4 μg
19F	about 1 μg	about 2 μg	about 4 μg
19A	about 1 μg	about 2 μg	about 4 μg
20A	about 1 μg	about 2 μg	about 4 μg
20B	about 1 μg	about 2 μg	about 4 μg
20 (comprising	about 1 μg	about 2 μg	about 4 μg

Petitioner Merck Ex-1015, 1594

Polysaccharide Serotype*	Total Amount of Polysaccharide in Polysaccharide-Polypeptide Conjugate**		
20A and 20B)			
22F	about 1 μg	about 2 μg	about 4 μg
23F	about 1 μg	about 2 μg	about 4 μg
23A	about 1 μg	about 2 μg	about 4 μg
23B	about 1 μg	about 2 μg	about 4 μg
24F	about 1 μg	about 2 μg	about 4 μg
24B	about 1 μg	about 2 μg	about 4 μg
31	about 1 μg	about 2 μg	about 4 μg
33F	about 1 μg	about 2 μg	about 4 μg
33B	about 1 μg	about 2 μg	about 4 μg
34	about 1 μg	about 2 μg	about 4 μg
35F	about 1 μg	about 2 μg	about 4 μg
35B	about 1 μg	about 2 μg	about 4 μg
38	about 1 μg	about 2 μg	about 4 μg

*Each serotype polysaccharide can be in a pharmaceutical composition or a vaccine in any one of the total amounts listed in the table

**Total amount can refer to the amount of polysaccharide of a serotype in a pharmaceutical composition or a vaccine when the pharmaceutical composition or vaccine is in unit dose form

[0081] A vaccine or pharmaceutical composition can be in unit dose form. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 1, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 1, the immunogenic saccharide- CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an

Petitioner Merck Ex-1015, 1595

immunogenic saccharide, fragment, combination thereof of serotype 2, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 2, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 3, the immunogenic saccharide- CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 3, the immunogenic saccharide- CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 4, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 4, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 5, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an

Petitioner Merck Ex-1015, 1596

immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 5, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 6A, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 6A, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 6B, the immunogenic saccharide- CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 6B, the immunogenic saccharide- CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 7F, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 7F, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from 300kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical

Petitioner Merck Ex-1015, 1597

composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 7C, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 7C, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from 300kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 9V, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 9V, the immunogenic saccharide- CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 14, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 14, the immunogenic saccharide- CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 18C, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or

Petitioner Merck Ex-1015, 1598

combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 18C, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 19A, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 19Athe immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 19F, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 19F, the immunogenic saccharide- CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 23F, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 23F, the immunogenic saccharide- CRM_{197} conjugate can have a molecular weight from 300 kDa to

Petitioner Merck Ex-1015, 1599

10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 6C, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 6C, the immunogenic saccharide- CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 8, the immunogenic saccharide- CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 8, the immunogenic saccharide- CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 9N, the immunogenic saccharide- CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 9N, the immunogenic saccharide- CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 10A, the immunogenic

Petitioner Merck Ex-1015, 1600

saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 10A, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 11A, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 11A, the immunogenic saccharide- CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 12F, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 12F, the immunogenic saccharide- CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 15A, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate

Petitioner Merck Ex-1015, 1601

comprising an immunogenic saccharide, fragment, combination thereof of serotype 15A, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 15B, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 15B, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 15C, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 15C, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 16F, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 16F, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical

Petitioner Merck Ex-1015, 1602

composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 17F, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 17F, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 20A, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 20A, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 20B, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 20B, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 22F, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or

Petitioner Merck Ex-1015, 1603

combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 22F, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 23A, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 23A, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 23B, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 23B, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 24F the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 24F, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from 300 kDa to

Petitioner Merck Ex-1015, 1604

10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 24B, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 24B, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 31, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 31, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 33F, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 33F, the immunogenic saccharide- CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 33B, the immunogenic

Petitioner Merck Ex-1015, 1605

saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 33B, the immunogenic saccharide- CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 35F, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 35F, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 34, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 34, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 35B, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate

Petitioner Merck Ex-1015, 1606

comprising an immunogenic saccharide, fragment, combination thereof of serotype 35B, the immunogenic saccharide-CRM_{197} conjugate can have a molecular weight from 300 kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 38, the immunogenic saccharide- CRM_{197} conjugate can have a molecular weight from about 300 kDa to about 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from about 0.3 to about 3.0. A vaccine or pharmaceutical composition can comprise an immunogenic saccharide-CRM_{197} conjugate comprising an immunogenic saccharide, fragment, combination thereof of serotype 38, the immunogenic saccharide- CRM_{197} conjugate can have a molecular weight from 300kDa to 10,000 kDa, and a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} can be from 0.3 to 3.0. The vaccine or pharmaceutical composition can comprise in any combination of serotypes as described above (*e.g.*, see EXAMPLE 6).

[0082] The vaccine dosage can be in the range from 1-5 μg of polysaccharide per polysaccharide polypeptide conjugate delivered intramuscularly as a single 0.5 mL injection. The vaccine dosage can comprise aluminum phosphate (1 mg/mL) and 0.01% polysorbate 80.

Methods of Use

[0083] The saccharide-polypeptide conjugates as described herein can be formulated for use in a vaccine. The pharmaceutical compositions comprising a saccharide-polypeptide conjugate as described herein can be formulated for use in a vaccine. The pharmaceutical compositions comprising a saccharide-polypeptide conjugate as described herein can be used in a vaccine. The vaccine can be administered to a subject. The vaccine can be used as a prophylactic for disease caused by *S. pneumoniae*, such as meningitis, pneumonia, and severe invasive diseases associated with pneumococcal infection. The subject can be a human. The subject or human can be a subject or human in need thereof.

[0084] The saccharide-polypeptide conjugate can be administered by intramuscular injection. The saccharide-polypeptide conjugate can be administered via intramuscular, intraperitoneal, intradermal or subcutaneous routes, or via mucosal administration to the oral/alimentary, respiratory or genitourinary tracts. The saccharide-polypeptide conjugate can be administered via a suppository. The saccharide-polypeptide conjugate can be administered intranasally.

Petitioner Merck Ex-1015, 1607

The saccharide-polypeptide conjugate can elicit an opsonophagocytic response after administration. The saccharide-polypeptide conjugate can elicit the production of antibodies against the serotype of the saccharide-polypeptide conjugate. This antibody response can be measured by an in vitro opsonophagocytic assay after administration of the saccharide-polypeptide conjugate.

[0085] The pharmaceutical composition or vaccine comprising a saccharide-polypeptide conjugate can be administered by intramuscular injection. The pharmaceutical composition or vaccine comprising a saccharide-polypeptide conjugate can be administered via intramuscular, intraperitoneal, intradermal or subcutaneous routes, or via mucosal administration to the oral/alimentary, respiratory or genitourinary tracts. The pharmaceutical composition or vaccine comprising a saccharide-polypeptide conjugate can be administered intranasally. The pharmaceutical composition or vaccine can be administered intramuscularly and can elicit an immune response that lasts from 1 week to 30 years. The saccharide-polypeptide conjugate can elicit an opsonophagocytic response after administration. The pharmaceutical composition or vaccine comprising a saccharide-polypeptide conjugate can elicit the production of antibodies against the serotype of the saccharide-polypeptide conjugate. This antibody response can be measured by an in vitro opsonophagocytic assay after administration of the pharmaceutical composition or vaccine comprising the saccharide-polypeptide conjugate.

[0086] For example, a pharmaceutical composition or vaccine administered to a subject can comprise a saccharide-polypeptide conjugate comprising a capsular polysaccharide or immunogenic fragment thereof from a serotype of *S. pneumoniae* conjugated to a polypeptide, and wherein the serotype is not at least one of, or is not 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, or 23F; the serotype is at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 21, 22, 23, or 24 of 2, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B); or a combination thereof. A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising at least nine serotypes selected from the group consisting of 2, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least ten serotypes selected from the group consisting of 2, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 34, 35B, 35F, 38 and Serogroup 20

Petitioner Merck Ex-1015, 1608

(comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least eleven serotypes selected from the group consisting of 2, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least twelve serotypes selected from the group consisting of 2, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least thirteen serotypes selected from the group consisting of 2, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least fourteen serotypes selected from the group consisting of 2, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least fifteen serotypes selected from the group consisting of 2, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least sixteen serotypes selected from the group consisting of 2, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least seventeen serotypes selected from the group consisting of 2, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least eighteen serotypes selected from the group consisting of 2, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least nineteen serotypes selected from the group consisting of 2, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least twenty serotypes selected from the group consisting of 2, 6C, 7C, 7F, 8, 9N,

Petitioner Merck Ex-1015, 1609

10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least twenty-one serotypes selected from the group consisting of 2, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least twenty-two serotypes selected from the group consisting of 2, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). For example, a pharmaceutical composition or vaccine administered to a subject can comprise a saccharide-polypeptide conjugate comprising a capsular polysaccharide or immunogenic fragment thereof from a serotype of *S. pneumoniae* conjugated to a polypeptide, and wherein the serotype is not at least one of, or is not 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, or 23F; the serotype is at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or of 2, 6C, 7C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B); or a combination thereof. A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising at least nine serotypes selected from the group consisting of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least ten serotypes selected from the group consisting of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least eleven serotypes selected from the group consisting of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least twelve serotypes selected from the group consisting of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least thirteen serotypes selected from the group consisting of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38, and Serogroup 20 (comprising

Petitioner Merck Ex-1015, 1610

serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least fourteen serotypes selected from the group consisting of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least fifteen serotypes selected from the group consisting of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition administered to a subject can comprise at least sixteen serotypes selected from the group consisting of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least seventeen serotypes selected from the group consisting of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least eighteen serotypes selected from the group consisting of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least nineteen serotypes selected from the group consisting of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least twenty serotypes selected from the group consisting of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least twenty-one serotypes selected from the group consisting of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least twenty-two serotypes selected from the group consisting of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 22F, 23A, 23B, 33F, and

Petitioner Merck Ex-1015, 1611

35B. A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 22F, 23A, 23B, 24F, 33F, and 35B. A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 22F, 23A, 23B, 24F, 33F, and 35B. A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F, and 35B. A pharmaceutical composition administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20B, 22F, 23A, 23B, 33F, and 35B. A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F, 35B and Serogroup 20 (comprising 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 10A, 11A, 15A, 15B, 15C, 22F, 23A, 24B, 33F, 35B, and 38. A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 22F, 23A, 23B, 33F, and 35B. A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 22F, 23A, 23B, 33F, and 35B. A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 22F, 23A, 23B, 24F, 33F, and 35B. A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising 6C, 10A, 11A, 15A, 15B, 15C, 22F, 23A, 24B, 33F, 35B and 38. A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 22F, 23A, 23B, 33F, and 35B. A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 22F, 23A, 23B, 33F, and 35B. A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising at least 13 of the serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 31, 33F,

Petitioner Merck Ex-1015, 1612

33B, 34, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B), or a combination thereof. A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising at least 14 of the serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 31, 33F, 33B, 34, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B), or a combination thereof. A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising at least 15 of the serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 31, 33F, 33B, 34, 35B, and 38, and Serogroup 20 (comprising serotypes 20A and 20B), or a combination thereof. A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising at least 16 of the serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 31, 33F, 33B, 34, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B), or a combination thereof. A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising at least 17 of the serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 31, 33F, 33B, 34, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B), or a combination thereof. A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising at least 18 of the serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 33B, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 31, 33F, 34, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B), or a combination thereof. A pharmaceutical composition or vaccine administered to a subject can comprise can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35F, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B), or a combination thereof. A pharmaceutical composition or vaccine administered to a subject can comprise can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28 additional serotype comprising 1, 3, 4, 6A, 6B, 7F, 8, 9N, 10A, 11A, 12F, 14, 15A, 15B, 15C,

Petitioner Merck Ex-1015, 1613

16F, 19F, 19A, 22F, 23A, 23B, 24F, 24B, 33F, 33B, 34, 35F, 35B, 38 or Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 additional serotype 1, 3, 4, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 19F, 19A, 22F, 23A, 23B, 23F, 24F, 24B, 33F, 33B, 34, 35F, 35B, 38 or Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising at least 13 of the serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 31, 33F, 33B, 34, 35B, 38, and Serogroup 20 (comprising 20A and 20B), or a combination thereof. A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising at least 14 of the serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 31, 33F, 33B, 34, 35B, 38, and Serogroup 20 (comprising 20A and 20B), or a combination thereof. A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising at least 15 of the serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 31, 33F, 33B, 34, 35B, 38, and Serogroup 20 (comprising 20A and 20B), or a combination thereof. A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising at least 16 of the serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 31, 33F, 33B, 34, 35B, 38, and Serogroup 20 (comprising 20A and 20B), or a combination thereof. A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising at least 17 of the serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 31, 33F, 33B, 34, 35B, 38, and Serogroup 20 (comprising 20A and 20B) or a combination thereof. A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising at least 18 of the serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 31, 33F, 33B, 34, 35B, 38, and Serogroup 20 (comprising 20A and 20B), or a combination thereof. A pharmaceutical composition or vaccine administered to a

Petitioner Merck Ex-1015, 1614

subject can comprise can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 additional serotypes comprising 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35F, 35B, 38, and Serogroup 20 (comprising 20A and 20B), or a combination thereof. A pharmaceutical composition or vaccine administered to a subject can comprise can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28 additional serotype comprising 1, 3, 4, 6A, 6B, 7F, 8, 9N, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 19F, 19A, 22F, 23A, 23B, 24F, 24B, 33F, 33B, 34, 35F, 35B, 38, or Serogroup 20 (comprising 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 additional serotype 1, 3, 4, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 19F, 19A, 22F, 23A, 23B, 23F, 24F, 24B, 33F, 33B, 34, 35F, 35B, 38, or Serogroup 20 (comprising 20A and 20B). A pharmaceutical composition or vaccine can comprise administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least one additional serotype selected from 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F, and 35B. A pharmaceutical composition or vaccine can comprise administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 additional serotypes selected from 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F, 34, and 35B. A pharmaceutical composition or vaccine can comprise administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least one additional serotype selected from 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20B, 22F, 23A, 23B, 33F, and 35B. A pharmaceutical composition or vaccine can comprise administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 additional serotypes selected from 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20B, 22F, 23A, 23B, 33F, 34, and 35B. A pharmaceutical composition or vaccine can comprise administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least one additional serotype selected from 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 22F, 23A, 23B,

Petitioner Merck Ex-1015, 1615

33F, 35B, and Serogroup 20 (comprising 20A and 20B). A pharmaceutical composition or vaccine can comprise administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 additional serotypes selected from 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F, 35B, and Serogroup 20 (comprising 20A and 20B). A pharmaceutical composition or vaccine can comprise administered to a subject can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least one additional serotype selected from 3, 4, 7F, 8, 9N, 11A, 12F, 15A, 15B, 15C, 16F, 19A, 22F, 23A, 23B, and 35B. A pharmaceutical composition or vaccine administered to a subject can comprise can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least one additional serotype selected from 1, 3, 4, 6A, 7F, 8, 9N, 10A, 11A, 12F, 14, 19A, 19F, 22F, 23A, 23B, 23F, 24F, and 33F. A pharmaceutical composition or vaccine administered to a subject can comprise can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least one additional serotype selected from 3, 4, 6B, 10A, 15A, 15B, 19A, 19F, 22F, 23F, 24F, and 35B. A pharmaceutical composition or vaccine administered to a subject can comprise can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least one additional serotype selected from 9N, 15A, 15C, 16F, 23A, 23B, and 33B. A pharmaceutical composition or vaccine administered to a subject can comprise can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least one additional serotype selected from 9N, 15A, 15C, 16F, 23A, 23B, and 33F. A pharmaceutical composition or vaccine administered to a subject can comprise can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least one additional serotype selected from 15A, 15C, 16F, 23A, 23B, and 33B. A pharmaceutical composition or vaccine administered to a subject can comprise can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least one additional serotype selected from 15A, 15C, 16F, 23A, 23B, and 33F. A pharmaceutical composition or vaccine administered to a subject can comprise can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least one additional serotype selected from 9N, 15A, 15C, 16F, 17F, 20B, 23A, 23B, 24F, 31, 33B, 34, 35F, and 35B. A pharmaceutical composition or vaccine administered to a subject can comprise can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least one additional serotype selected from 9N, 15A, 15C, 16F, 17F, 20B, 23A, 23B, 24F, 31, 33F, 34, 35F, and 35B. A pharmaceutical composition or vaccine administered to a subject can comprise can

Petitioner Merck Ex-1015, 1616

comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least one additional serotype selected from 15A, 15C, 16F, 20B, 23A, 23B, 24F, 31, 33B, 34, 35F, and 35B. A pharmaceutical composition or vaccine administered to a subject can comprise can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least one additional serotype selected from 15A, 15C, 16F, 20B, 23A, 23B, 24F, 31, 33F, 34, 35F, and 35B. A pharmaceutical composition or vaccine administered to a subject can comprise can comprise a plurality of saccharide-polypeptide conjugates comprising the serotype 6C and at least one additional serotype selected from 6C, 8, 9N, 10A, 11A, 15A, 15B, 15C, 16F, 20A, 22F, 23A, 23B, 33F, and 35B. A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of at least 20 immunogenic saccharide-polypeptide conjugate comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *S. pneumoniae* selected from the group comprising 3, 6C, 7C, 8, 9N, 11A, 12F, 15A, 16F, 19A, 19F, 22F, 23A, 23B, 31, 33F, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of at least 20 immunogenic saccharide-polypeptide conjugate comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *S. pneumoniae* selected from the group comprising 3, 6C, 7F, 7C, 8, 9N, 11A, 12F, 15A, 16F, 19A, 19F, 22F, 23A, 23B, 31, 33F, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of at least 15 immunogenic saccharide-polypeptide conjugate comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *S. pneumoniae* selected from the group comprising 3, 6C, 7F, 7C, 8, 9N, 11A, 12F, 15A, 16F, 19A, 19F, 22F, 23A, 23B, 31, 33F, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of at least 16 immunogenic saccharide-polypeptide conjugate comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *S. pneumoniae* selected from the group comprising 3, 6C, 7F, 7C, 8, 9N, 11A, 12F, 15A, 16F, 19A, 19F, 22F, 23A, 23B, 31, 33F, 35B, 35F, 38, and Serogroup 20

Petitioner Merck Ex-1015, 1617

(comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of at least 15 or 16 immunogenic saccharide-polypeptide conjugate comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *S. pneumoniae* selected from the group comprising 3, 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 19A, 19F, 22F, 23A, 23B, 31, 33F, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of at least 15 or 16 immunogenic saccharide-polypeptide conjugate comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *S. pneumoniae* selected from the group comprising 3, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 19A, 22F, 23A, 23B, 24F, 33F, 35B, and 38. A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of at least 10 immunogenic saccharide-polypeptide conjugate comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *S. pneumoniae* selected from the group comprising 3, 8, 9N, 12F, 15A, 19A, 22F, 23A, 23B, and 24F. A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of at least 11 immunogenic saccharide-polypeptide conjugate comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *S. pneumoniae* selected from the group comprising 3, 8, 9N, 10A, 12F, 15A, 19A, 22F, 23A, 23B, and 24F. A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of at least 24 immunogenic saccharide-polypeptide conjugate comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *S. pneumoniae* selected from the group comprising 3, 4, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 19A, 22F, 23A, 23B, 24F, 31, 33F, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of at least 20 immunogenic saccharide-polypeptide conjugate comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination

Petitioner Merck Ex-1015, 1618

thereof is from a unique *S. pneumoniae* selected from the group comprising 3, 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 19A, 19F, 22F, 23A, 23B, 31, 33F, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise a plurality of at least 20, 21, 22, 23, 24, 25, 26, or 27 immunogenic saccharide-polypeptide conjugate comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *S. pneumoniae* selected from the group comprising 3, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 19F, 22F, 23A, 23B, 24F, 31, 33F, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least 20 serotypes selected from the group consisting of 3, 6C, 7C, 8, 9N, 11A, 12F, 15A, 16F, 19A, 19F, 22F, 23A, 23B, 31, 33F, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least 20 serotypes selected from the group consisting of 3, 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 19A, 19F, 22F, 23A, 23B, 31, 33F, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least 20 serotypes selected from the group consisting of 3, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 19A, 22F, 23A, 23B, 24F, 33F, 35B, and 38. A pharmaceutical composition or vaccine administered to a subject can comprise at least 10 serotypes selected from the group consisting of 3, 8, 9N, 12F, 15A, 19A, 22F, 23A, 23B, and 24F. A pharmaceutical composition or vaccine administered to a subject can comprise at least 11 serotypes selected from the group consisting of 3, 8, 9N, 10A, 12F, 15A, 19A, 22F, 23A, 23B, and 24F. A pharmaceutical composition or vaccine administered to a subject can comprise at least 24 serotypes selected from the group consisting of 3, 4, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 19A, 22F, 23A, 23B, 24F, 31, 33F, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least 20 serotypes selected from the group consisting of 3, 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 19A, 19F, 22F, 23A, 23B, 31, 33F, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). A pharmaceutical composition or vaccine administered to a subject can comprise at least 20, 21, 22, 23, 24, 25, 26, or 27 serotypes selected from the group consisting of 3, 6C, 7C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 19F, 22F, 23A, 23B, 24F, 31, 33F, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B).

Petitioner Merck Ex-1015, 1619

[0087] Each dosage can be formulated in 0.5 mL. The formulation can comprise normal saline. The formulation can have a pH of 6.5. The formulation can be a pH from 6.3 to 6.7 or from 6.2 to 6.8. The formulation can have a pH of 5.8. The formulation can be a pH from 5.5 to 6.1 or from 5.6 to 6.0. The formulation can comprise 0.001% to 0.01% polysorbate 80.

[0088] A first composition and second composition can be administered to a subject. The first composition and the second composition can be distinct. The first composition can be a first pharmaceutical composition or vaccine. The second composition can be a second pharmaceutical composition or vaccine. The first pharmaceutical composition or vaccine can be administered to the subject at least about four weeks, six weeks, two months, six months, eight months, one year, two years, or five years before or at least about four weeks, six weeks, two months, six months, eight months, one year, two years, or five years after an administration to the subject a second pharmaceutical composition or vaccine. The first pharmaceutical composition or vaccine can be administered to a subject who is at least 4 weeks old, 6 weeks old, 12 weeks old, 24 weeks old, 6 months old, 8 months old, 10 months old, 12 months old, 14 months old, 15 months old, 16 months old, 17 months old, 18 months old, 19 months old, 20 months old, 21 months old, 22 months old, 23 months old, 2 years old or older. The first pharmaceutical composition or vaccine can be administered to a subject with an age from 4 weeks to 2 years old. The first pharmaceutical composition or vaccine can be administered to a subject with an age from 18 years old to 100 years old. The first pharmaceutical composition can be administered to a subject with an age of 100 years old or older. In some embodiments, the second pharmaceutical composition or vaccine can comprise a saccharide-polypeptide conjugate comprising a polypeptide that has at least about 70%, 80%, 90%, 95%, 99%, or 100% length homology, about 70%, 80%, 90%, 95%, 99%, or 100% sequence homology, or a combination thereof to a polypeptide of a saccharide-polypeptide conjugate of the first pharmaceutical composition or vaccine. For example, the polypeptide in a saccharide-conjugate of the first pharmaceutical composition or vaccine and the polypeptide in a saccharide-conjugate of the second pharmaceutical composition or vaccine can be CRM_{197}. In other embodiments, the second pharmaceutical composition or vaccine can comprise a saccharide-polypeptide conjugate comprising a polypeptide that has at less than 70% length homology, 70% sequence homology, or a combination thereof to a polypeptide of a saccharide-polypeptide conjugate of the first pharmaceutical composition.

[0089] In some embodiments, the first pharmaceutical composition or vaccine can comprise a saccharide-polypeptide conjugate comprising a capsular polysaccharide or immunogenic fragment thereof from a serotype of *S. pneumoniae* conjugated to a polypeptide, and wherein

Petitioner Merck Ex-1015, 1620

the serotype is not at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13, of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, or 23F; the serotype is at least one of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35F, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B); or a combination thereof. The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 serotypes selected from the group consisting of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). The first pharmaceutical composition or vaccine can comprise at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22 23, or 24 serotypes selected from the group consisting of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). In some embodiments, the first pharmaceutical composition or vaccine can comprise a saccharide-polypeptide conjugate comprising a capsular polysaccharide or immunogenic fragment thereof from a serotype of *S. pneumoniae* conjugated to a polypeptide, and wherein the serotype is not at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13, of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, or 23F; the serotype is at least one of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B,34, 35F, 35B, 38, and Serogroup 20 (comprising 20A and 20B); or a combination thereof. The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 serotypes selected from the group consisting of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38, and Serogroup 20 (comprising 20A and 20B). The first pharmaceutical composition can comprise at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22 23, or 24 serotypes selected from the group consisting of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35B, 35F, 38, and Serogroup 20 (comprising 20A and 20B).The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 22F, 23A, 23B, 33F, and 35B. The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 22F, 23A, 23B, 24F, 33F, and 35B. The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 22F, 23A, 23B, 24F,

Petitioner Merck Ex-1015, 1621

33F, and 35B. The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 10A, 11A, 15A, 15B, 15C, 22F, 23A, 24B, 33F, 35B, and 38. The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F, and 35B. The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 15A, 15B, 15C, 16F, 20B, 22F, 23A, 23B, 33F, and 35B. The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 15A, 15B, 15C, 16F, 20A, 22F, 23A, 23B, 33F, and 35B. The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 33B. The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 33F. The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 15A, 15C, 16F, 23A, 23B, and 33B. The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 15A, 15C, 16F, 23A, 23B, and 33F. The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 9N, 15A, 15C, 16F, 17F, 20B, 23A, 23B, 24F, 31, 33B, 34, 35F, and 35B. . The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 9N, 15A, 15C, 16F, 17F, 20B, 23A, 23B, 24F, 31, 33F, 34, 35F, and 35B. The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 15A, 15C, 16F, 20B, 23A, 23B, 24F, 31, 33B, 34, 35F, and 35B. The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 22F, 23A, 23B, 33F, and 35B. The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 22F, 23A, 23B, 33F, and 35B. The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 22F, 23A, 23B, 24F, 33F, and 35B. The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 10A, 11A, 15A, 15B, 15C, 22F, 23A, 24B, 33F, 35B and 38. The first

Petitioner Merck Ex-1015, 1622

pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 22F, 23A, 23B, 33F, and 35B. The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 22F, 23A, 23B, 33F, and 35B. In other embodiments, the first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising a serotype that is at least one of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 3, 6C, 7C, 8, 9N, 11A, 12F, 15A, 16F, 19F, 19A, 22F, 23A, 23B, 31, 33F, 35F, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B). The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 3, 6C, 7F, 7C, 8, 9N, 11A, 12F, 15A, 16F, 19F, 19A, 22F, 23A, 23B, 31, 33F, 35F, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B). The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 3, 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 19A, 19F, 22F, 23A, 23B, 31, 33F, 35F, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B). The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 3, 8, 9N, 12F, 15A, 19A, 22F, 23A, 23B, and 24F. The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 3, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 19A, 22F, 23A, 23B, 24F, 33F, 35B, and 38. The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 3, 8, 9N, 10A, 12F, 15A, 19A, 22F, 23A, 23B, and 24F. The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 3, 4, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 19A, 22F, 23A, 23B, 24F, 31, 33F, 35F, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B). The first pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 3, 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 19A, 19F, 22F, 23A, 23B, 31, 33F, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B). When administering any of the first pharmaceutical compositions or vaccines described

Petitioner Merck Ex-1015, 1623

above, the first pharmaceutical composition or vaccine can be distinct from the second pharmaceutical composition or vaccine administered to a subject.

[0090] In some embodiments, the second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising a serotype that is at least one of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising a serotype that is at least one of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B), wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising a serotype that is at least one of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F,33B, 34, 35B, 35F, 38, and Serogroup 20 (comprising 20A and 20B), wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a saccharide-polypeptide conjugate comprising a capsular polysaccharide or immunogenic fragment thereof from a serotype of *S. pneumoniae* conjugated to a polypeptide, and wherein the serotype is not at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13, of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, or 23F; and the serotype is at least one of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 35F, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B); wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 serotypes selected from the group consisting of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B), wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 serotypes selected from the group

Petitioner Merck Ex-1015, 1624

consisting of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B), wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a saccharide-polypeptide conjugate comprising a capsular polysaccharide or immunogenic fragment thereof from a serotype of *S. pneumoniae* conjugated to a polypeptide, and wherein the serotype is not at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13, of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, or 23F; and the serotype is at least one of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35F, 35B, 38, and Serogroup 20 (comprising 20A and 20B); wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 serotypes selected from the group consisting of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24B, 24F, 31, 33F, 33B, 34, 35B, 35F, 38, and Serogroup 20 (comprising 20A and 20B), wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 serotypes selected from the group consisting of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35B, 35F, 38, and Serogroup 20 (comprising 20A and 20B), wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 22F, 23A, 23B, 33F, and 35B, wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 22F, 23A, 23B, 24F, 33F, and 35B, wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 22F, 23A, 23B, 24F, 33F, and 35B, wherein the

Petitioner Merck Ex-1015, 1625

serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 10A, 11A, 15A, 15B, 15C, 22F, 23A, 24B, 33F, 35B, and 38, wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F, and 35B, wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 15A, 15B, 15C, 16F, 20B, 22F, 23A, 23B, 33F, and 35B, wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 15A, 15B, 15C, 16F, 20A, 22F, 23A, 23B, 33F, and 35B, wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 33B, wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 33F, wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 15A, 15C, 16F, 23A, 23B, and 33B, wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 15A, 15C, 16F, 23A, 23B, and 33F, wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates

Petitioner Merck Ex-1015, 1626

comprising the serotypes 6C, 9N, 15A, 15C, 16F, 17F, 20B, 23A, 23B, 24F, 31, 33B, 34, 35F, and 35B, wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 9N, 15A, 15C, 16F, 17F, 20B, 23A, 23B, 24F, 31, 33F, 34, 35F, and 35B, wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 15A, 15C, 16F, 20B, 23A, 23B, 24F, 31, 33B, 34, 35F, and 35B, wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 15A, 15C, 16F, 20B, 23A, 23B, 24F, 31, 33F, 34, 35F, and 35B, wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 22F, 23A, 23B, 33F, and 35B, wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 22F, 23A, 23B, 33F, and 35B, wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 22F, 23A, 23B, 24F, 33F, and 35B, wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 10A, 11A, 15A, 15B, 15C, 22F, 23A, 24B, 33F, 35B, and 38, wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 22F, 23A, 23B, 33F, and 35B, wherein the serotype of the first pharmaceutical composition or

Petitioner Merck Ex-1015, 1627

vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 22F, 23A, 23B, 33F, and 35B, wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 3, 6C, 7C, 8, 9N, 11A, 12F, 15A, 16F, 19F, 19A, 22F, 23A, 23B, 31, 33F, 35F, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B), wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct.. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 3, 6C, 7F, 7C, 8, 9N, 11A, 12F, 15A, 16F, 19F, 19A, 22F, 23A, 23B, 31, 33F, 35F, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B), wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 3, 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 19A, 19F, 22F, 23A, 23B, 31, 33F, 35F, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B), wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 3, 8, 9N, 12F, 15A, 19A, 22F, 23A, 23B, and 24F, wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 3, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 19A, 22F, 23A, 23B, 24F, 33F, 35B, and 38, wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 3, 8, 9N, 10A, 12F, 15A, 19A, 22F, 23A, 23B, and 24F, wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 3, 4, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F,

Petitioner Merck Ex-1015, 1628

19A, 22F, 23A, 23B, 24F, 31, 33F, 35F, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B), wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct. The second pharmaceutical composition or vaccine can comprise a plurality of saccharide-polypeptide conjugates comprising the serotypes 3, 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 19A, 19F, 22F, 23A, 23B, 31, 33F, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B), wherein the serotype of the first pharmaceutical composition or vaccine and the serotype of the second pharmaceutical composition or vaccine are distinct.

[0091] In other embodiments, the first pharmaceutical composition or vaccine and the second pharmaceutical composition or vaccine can be administered at least about 4 weeks apart, at least 6 about weeks apart, at least 2 about months apart, at a least about 3 months apart, at least about 4 months apart, at least about 5 months apart, at least 6 months apart, at least about 7 months apart, at least about 8 months apart, at least about 9 months apart, at least about 10 months apart, at least 11 about months apart, at least about 1 year apart, at least about 1.5 years apart, at least about 2 years apart, at least about 5 years apart, at least about 10 years apart, at least about 15 year, at least about 20 years apart, or at least about 30 years apart.

[0092] In some embodiments, a serotype of the first pharmaceutical composition or vaccine can be from a different bacteria than the serotype of the second pharmaceutical composition or vaccine. For example, the serotype of the first composition or vaccine can be from *Streptococcus pneumoniae*, and the serotype of the second composition or vaccine can be from *Neisseria meningitidis*, *Salmonella enterica*, or *Haemophilus influenzae*. The serotype of the first pharmaceutical composition or vaccine can be from *Neisseria meningitidis*, *Salmonella enterica*, or *Haemophilus influenzae*, and the serotype of the second pharmaceutical composition or vaccine can be from *Streptococcus pneumoniae*.

[0093] In some embodiments, a serotype of the first pharmaceutical composition or vaccine can be from the same bacteria as a serotype for the second pharmaceutical composition or vaccine. For example, the first pharmaceutical composition or vaccine can comprise at least one of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*, and the second pharmaceutical composition or vaccine can comprise at least one of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35B, 35F 38 and Serogroup 20 (comprising serotypes 20A and 20B) from *Streptococcus pneumoniae*. The first pharmaceutical composition or vaccine can comprise at least one of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F,

Petitioner Merck Ex-1015, 1629

24B, 31, 33F,33B, 34, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B), from *Streptococcus pneumoniae*, and the second pharmaceutical composition or vaccine can comprise at least one of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*. The first pharmaceutical composition or vaccine can comprise at least one of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*, and the second pharmaceutical composition or vaccine can comprise at least one of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B) from *Streptococcus pneumoniae*. The first pharmaceutical composition or vaccine can comprise at least one of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B) from *Streptococcus pneumoniae*, and the second pharmaceutical composition or vaccine can comprise at least one of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*. The first pharmaceutical composition or vaccine can comprise at least one of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*, and the second pharmaceutical composition or vaccine comprises at least one of 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F, and 35B from *Streptococcus pneumoniae*. The first pharmaceutical composition or vaccine can comprise at least one of 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F, and 35B from *Streptococcus pneumoniae*, and the second pharmaceutical composition or vaccine can comprise at least one of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*. The first pharmaceutical composition or vaccine can comprise at least one of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*, and the second pharmaceutical composition or vaccine comprises at least one of 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F, 35B and Serogroup 20 (comprising serotypes 20A and 20B) from *Streptococcus pneumoniae*. The first pharmaceutical composition or vaccine can comprise at least one of 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F, 35B, and Serogroup 20 (comprising serotypes 20A and 20B) from *Streptococcus pneumoniae*, and the second pharmaceutical composition or vaccine can comprise at least one of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*. The first pharmaceutical composition or vaccine can comprise at least one of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*, and the second pharmaceutical composition or vaccine can comprise at least one of 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F,

Petitioner Merck Ex-1015, 1630

35B, and Serogroup 20 (comprising serotypes 20A and 20B) from *Streptococcus pneumoniae*. The first pharmaceutical composition or vaccine can comprise at least one of 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F, 35B and Serogroup 20 (comprising serotypes 20A and 20B) from *Streptococcus pneumoniae*, and the second pharmaceutical composition or vaccine can comprise at least one of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*. The first pharmaceutical composition or vaccine can comprise the serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*, and the second pharmaceutical composition or vaccine can comprise the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F, and 35B from *Streptococcus pneumoniae*. The first pharmaceutical composition or vaccine can comprise the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F, and 35B from *Streptococcus pneumoniae*, and the second pharmaceutical composition or vaccine can comprise the serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*. The first pharmaceutical composition or vaccine can comprise the serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*, and the second pharmaceutical composition or vaccine can comprise the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20B, 22F, 23A, 23B, 33F, and 35B from *Streptococcus pneumoniae*. The first pharmaceutical composition or vaccine can comprise the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20B, 22F, 23A, 23B, 33F, and 35B from *Streptococcus pneumoniae*, and the second pharmaceutical composition or vaccine can comprise the serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*. The first pharmaceutical composition or vaccine can comprise the serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*, and the second pharmaceutical composition or vaccine can comprise the serotypes 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 33B from *Streptococcus pneumoniae*. The first pharmaceutical composition or vaccine can comprise the serotypes 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 33B from *Streptococcus pneumoniae*, and the second pharmaceutical composition or vaccine can comprise the serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*. The first pharmaceutical composition or vaccine can comprise the serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*, and the second pharmaceutical composition or vaccine can comprise the serotypes 6C, 15A, 15C, 16F, 23A, 23B, and 33B from *Streptococcus pneumoniae*. The first pharmaceutical composition or vaccine can comprise the serotypes 6C, 15A, 15C, 16F, 23A, 23B, and 33B

Petitioner Merck Ex-1015, 1631

from *Streptococcus pneumoniae*, and the second pharmaceutical composition or vaccine can comprise the serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*. The first pharmaceutical composition or vaccine can comprise the serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*, and the second pharmaceutical composition or vaccine can comprise the serotypes 6C, 9N, 15A, 15C, 16F, 17F, 20B, 23A, 23B, 24F, 31, 33B, 34, 35F, and 35B from *Streptococcus pneumoniae*. The first pharmaceutical composition or vaccine can comprise the serotypes 6C, 9N, 15A, 15C, 16F, 17F, 20B, 23A, 23B, 24F, 31, 33B, 34, 35F, and 35B from *Streptococcus pneumoniae*, and the second pharmaceutical composition or vaccine can comprise the serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*. The first pharmaceutical composition or vaccine can comprise the serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*, and the second pharmaceutical composition or vaccine can comprise the serotypes 6C, 15A, 15C, 16F, 20B, 23A, 23B, 24F, 31, 33B, 34, 35F, and 35B from *Streptococcus pneumoniae*. The first pharmaceutical composition or vaccine can comprise the serotypes 6C, 15A, 15C, 16F, 20B, 23A, 23B, 24F, 31, 33B, 34, 35F, and 35B from *Streptococcus pneumoniae*, and the second pharmaceutical composition or vaccine can comprise the serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*. The first pharmaceutical composition or vaccine can comprise the serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*, and the second pharmaceutical composition or vaccine can comprise the serotypes 6C, 8, 9N, 10A, 11A, 15A, 15B, 15C, 16F, 20A, 22F, 23A, 23B, 33F, and 35B from *Streptococcus pneumoniae*. The first pharmaceutical composition or vaccine can comprise the serotypes 6C, 8, 9N, 10A, 11A, 15A, 15B, 15C, 16F, 20A, 22F, 23A, 23B, 33F, and 35B from *Streptococcus pneumoniae*, and the second pharmaceutical composition or vaccine can comprise the serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*. The first pharmaceutical composition or vaccine can comprise the serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*, and the second pharmaceutical composition or vaccine can comprise the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F, 35B, and Serogroup 20 (comprising serotypes 20A and 20B) from *Streptococcus pneumoniae*. The first pharmaceutical composition or vaccine can comprise the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F, 35B, and Serogroup 20 (comprising serotypes 20A and 20B) from *Streptococcus pneumoniae*, and the second

Petitioner Merck Ex-1015, 1632

pharmaceutical composition or vaccine can comprise the serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*.

[0094] Different serotypes of *S. pneumoniae* can be more pervasive or endemic in different geographical areas. For example, a certain group of serotypes can commonly cause pneumococcal disease in the United States and Canada. This group of serotypes can be different for Europe, the Middle East, North Africa, Japan and Korea. For example, administration of a pharmaceutical composition or vaccine to a subject comprising a plurality of saccharide-polypeptide conjugates comprising the serotypes 3, 4, 6A, 6B, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 19F, 19A, 20A, 22F, 23A, 23B, 33F, 35F, 35B, and 38 can improve protection against *S. pneumoniae* disease for the subject in the United States and/or Canada. Administration of a pharmaceutical composition or vaccine to a subject comprising a plurality of saccharide-polypeptide conjugates comprising the serotypes 3, 4, 6A, 6B, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 19F, 19A, 22F, 23A, 23B, 33F, 35F, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B) can improve protection against *S. pneumoniae* disease for the subject in the United States and/or Canada. Administration of a pharmaceutical composition or vaccine to a subject comprising a plurality of saccharide-polypeptide conjugates comprising the serotypes 3, 6C, 7C, 8, 9N, 11A, 12F, 15A, 16F, 19F, 19A, 22F, 23A, 23B, 31, 33F, 35F, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B) can improve protection against *S. pneumoniae* disease for the subject in the United States. Administration of a pharmaceutical composition or vaccine to a subject comprising a plurality of saccharide-polypeptide conjugates comprising the serotypes 3, 6C, 7F, 7C, 8, 9N, 11A, 12F, 15A, 16F, 19F, 19A, 22F, 23A, 23B, 31, 33F, 35F, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B) can improve protection against *S. pneumoniae* disease for the subject in the United States. Administration of a pharmaceutical composition or vaccine to a subject comprising a plurality of saccharide-polypeptide conjugates comprising the serotypes 3, 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 19A, 19F, 22F, 23A, 23B, 31, 33F, 35F, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B) can improve protection against *S. pneumoniae* disease for the subject in the United States. Administration of a pharmaceutical composition or vaccine to a subject comprising a plurality of saccharide-polypeptide conjugates comprising the serotypes 3, 8, 9N, 12F, 15A, 19A, 22F, 23A, 23B, and 24F can improve protection against *S. pneumoniae* disease for the subject in the United States. Administration of a pharmaceutical composition or vaccine to a subject comprising a plurality of saccharide-polypeptide conjugates comprising the serotypes 3, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 19A, 22F,

Petitioner Merck Ex-1015, 1633

23A, 23B, 24F, 33F, 35B, and 38 can improve protection against *S. pneumoniae* disease for the subject in the United Kingdom. Administration of a pharmaceutical composition or vaccine to a subject comprising a plurality of saccharide-polypeptide conjugates comprising the serotypes 3, 8, 9N, 10A, 12F, 15A, 19A, 22F, 23A, 23B, and 24F can improve protection against *S. pneumoniae* disease for the subject in the United Kingdom or in Europe. Administration of a pharmaceutical composition or vaccine to a subject comprising a plurality of saccharide-polypeptide conjugates comprising the serotypes 3, 4, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 19A, 22F, 23A, 23B, 24F, 31, 33F, 35F, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B) can improve protection against *S. pneumoniae* disease for the subject in Germany. Administration of a pharmaceutical composition or vaccine to a subject comprising a plurality of saccharide-polypeptide conjugates comprising the serotypes 3, 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 19A, 19F, 22F, 23A, 23B, 31, 33F, 35B, 35F, 38 and Serogroup 20 (comprising serotypes 20A and 20B) can improve protection against *S. pneumoniae* disease for the subject in Germany. Administration of a pharmaceutical composition or vaccine to a subject comprising a plurality of saccharide-polypeptide conjugates comprising the serotypes 1, 3, 4, 6A, 6B, 6C, 7F, 8, 9N, 10A, 11A, 12F, 14, 15A, 15B, 16F, 18C, 19F, 19A, 22F, 23F, 23A, 23B, 24F, 33F, 35F, 35B, and 38 can improve protection against *S. pneumoniae* disease for the subject in the Europe, the Middle East, and/or North Africa. Administration of a pharmaceutical composition or vaccine to a subject comprising a plurality of saccharide-polypeptide conjugates comprising the serotypes 3, 4, 6A, 6B, 6C, 7F, 10A, 11A, 14, 15A, 15B, 15C, 19F, 19A, 22F, 23F, 23A, 24F, 35F, 35B, and 38 can improve protection against *S. pneumoniae* disease for the subject in the Japan and/or Korea. Additionally, invasive clinical disease can be caused by serotype 20B (as opposed to serotype 20A). The subject can be a human who resides in the specific geographical location as indicated above, or can be a human who is visiting the specific geographical location as indicated above.

[0095] A method of administration can comprise administering a first saccharide-polypeptide conjugate composition to a subject; administering a second saccharide-polypeptide conjugate composition to the subject at least four weeks after administering the first saccharide-polypeptide conjugate composition; wherein the first saccharide-polypeptide conjugate composition comprises a first polypeptide that has at least about 70%, 80%, 90%, 95%, 99%, or 100% length homology, about 70%, 80%, 90%, 95%, 99%, or 100% sequence homology, or a combination thereof to a second polypeptide of the second saccharide-polypeptide conjugate composition; and wherein the first saccharide-polypeptide conjugate composition

Petitioner Merck Ex-1015, 1634

comprises a first serotype; wherein the second saccharide-polypeptide conjugate composition comprises a second serotype, and wherein the first serotype and the second serotype are different. In some embodiments, the first serotype is from the same bacteria as the second serotype. For example, the polypeptide in a saccharide-conjugate of the first pharmaceutical composition and the polypeptide in a saccharide-conjugate of the second pharmaceutical composition can be CRM_{197}. In other embodiments, the second pharmaceutical composition comprises a saccharide-polypeptide conjugate comprising a polypeptide that has at less than about 70% length homology, about 70% sequence homology, or a combination thereof to a polypeptide of a saccharide-polypeptide conjugate of the first pharmaceutical composition. The first saccharide-polypeptide conjugate composition can be a vaccine comprising a plurality of unique immunogenic saccharide-polypeptide conjugates that can comprise individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof can be from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 23A and 23B in a vaccine. The first saccharide-polypeptide conjugate composition can be a vaccine comprising at least 2 immunogenic saccharide-polypeptide conjugates that can each comprise individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof can be from a unique *Streptococcus pneumoniae* serotype group, wherein one serotype can be 23A and at least one additional serotype can be selected from the group consisting of 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 20B, 22F, 23B, 24F, 24B, 31, 33F, 33B, 34, 35B, 35F, and 38. The first saccharide-polypeptide conjugate composition can be a vaccine comprising at least 2 immunogenic saccharide-polypeptide conjugates that can each comprise individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof can be from a unique *Streptococcus pneumoniae* serotype group, wherein one serotype can be 23B and at least one additional serotype can be selected from the group consisting of 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 20B, 22F, 23A, 24F, 24B, 31, 33F, 33B, 34, 35B, 35F, and 38. The second saccharide-polypeptide conjugate composition can be a vaccine comprising a plurality of unique immunogenic saccharide-polypeptide conjugates that can comprise individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or

Petitioner Merck Ex-1015, 1635

combination thereof can be from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 23A and 23B. The second saccharide-polypeptide conjugate composition be a vaccine comprising at least 2 immunogenic saccharide-polypeptide conjugates that can each comprise individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof can be from a unique *Streptococcus pneumoniae* serotype group, wherein one serotype can be 23A and at least one additional serotype can be selected from the group consisting of 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 20B, 22F, 23B, 24F, 24B, 31, 33F, 33B, 34, 35B, 35F, and 38, in a vaccine. The second saccharide-polypeptide conjugate composition can be a vaccine comprising at least 2 immunogenic saccharide-polypeptide conjugates that can each comprise individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof can be from a unique *Streptococcus pneumoniae* serotype group, wherein one serotype can be 23B and at least one additional serotype can be selected from the group consisting of 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 20B, 22F, 23A, 24F, 24B, 31, 33F, 33B, 34, 35B, 35F, and 38. The first saccharide-polypeptide conjugate composition and the second saccharide-polypeptide conjugate composition can be distinct.

[0096] In other embodiments, the conducting of any of the methods described herein may not result in more than about: 50%, 40%, 30%, 20%, 10%, 5%, 4%, 3%, 2%, or 1% suppression of an immunity conveyed by a first vaccine containing an immunogenic saccharide-polypeptide conjugate, as measured by antibody response to the saccharide of the immunogenic saccharide-polypeptide conjugate, wherein the antibody response is measured by measuring antibody titers.

Saccharide-polypeptide Conjugate Kits

[0097] The saccharide-polypeptide conjugates, pharmaceutical compositions, and vaccines described herein can be contained in a kit. The kit can further comprise instructions for use. The saccharide-polypeptide conjugates and/or pharmaceutical compositions and/or vaccines can be stored in a container. The container can be a syringe. The container can be a vial. The vial can be a 2 mL borosilicate glass vial. The vial can be 3 mL Vials USP Type I glass, non-siliconized. The top can be an aluminum crimp top. The container can be a vial with a rubber septum or a septum made of flexible, reclose-able material. The container can be a vial with a

Petitioner Merck Ex-1015, 1636

stopper. The stopper can be a non-siliconized stopper. The vial can have a fill volume of 0.6 mL. The extractable volume can be 0.5 mL.

EXAMPLES

[0098] The following examples are included to further describe some aspects of the present disclosure, and should not be used to limit the scope of the embodiments described herein.

EXAMPLE 1

Method of Establishing a Cell Bank

[0099] This example shows the establishment of a cell bank for a *S. pneumoniae* strain for use in producing polysaccharides for a polysaccharide-CRM_{197} conjugate vaccine. Any strain that produces the polysaccharides of **TABLE 1** or of **FIGS. 10A-10F** (e.g., polysaccharides from serotypes 1, 2, 3, 4, 5, 6A, 6B, 7C, 7F, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 35F, 35B, or 38 and Serogroup 20 (comprising serotypes 20A and 20B)) are established as a cell bank by this method. A *S. pneumoniae* strain is provided by either the Center for Disease Control and Prevention (CDC), United States or the Culture Collection, University of Gothenburg (CCUG). The cell bank process is depicted in **FIG. 2**. A vial of a strain of *S. pneumoniae* is seeded and then is grown overnight on an agar plate. A single colony is picked from this plate and streaked onto a new agar plate for overnight growth. This process is repeated three times to purify the strain before a flask is seeded and is incubated. After allowing the seeded flask sufficient time for growth, the flask contents are harvested by centrifugation. The centrifugation product is resuspended in a medium of about 20% glycerol and then is dispensed into cryogenic vials. The cell bank is contained in the cryogenic vials, which are stored at -70°C until use.

[0100] *S. pneumoniae* strains that produce serotype 6C polysaccharide was acquired by the University of Alabama, Birmingham (UAB) for establishing a 6C cell bank. The cell bank process is depicted in **FIG. 2**. For 6C polysaccharide serotype, a vial of the strain of *S. pneumoniae* is seeded and then is grown overnight on an agar plate. A single colony is picked from this plate and streaked onto a new agar plate for overnight growth. This process is repeated three times to purify the strain before a flask is seeded and is incubated. After allowing the seeded flask sufficient time for growth, the flask contents are harvested by centrifugation. The centrifugation product is resuspended in a medium of about 20% glycerol

Petitioner Merck Ex-1015, 1637

and then is dispensed into cryogenic vials. The cell bank for each strain are contained in the cryogenic vials, which are stored at -70°C until use.

[0101] *S. pneumoniae* strains that produce serotype 8 polysaccharide, serotype 10A polysaccharide, serotype 11A polysaccharide, serotype 12F polysaccharide, serotype 22F polysaccharide, or serotype 33F polysaccharide were acquired by either the Center for Disease Control and Prevention (CDC), United States or the Culture Collection, University of Gothenburg (CCUG) for establishing a cell bank. The cell bank process is depicted in **FIG. 2**. For each polysaccharide serotype, a vial of the strain of *S. pneumoniae* was seeded and then was grown overnight on an agar plate. A single colony was picked from this plate and streaked onto a new agar plate for overnight growth. This process was repeated three times to purify the strain before a flask was seeded and was incubated. After allowing the seeded flask sufficient time for growth, the flask contents were harvested by centrifugation. The centrifugation product was resuspended in a medium of about 20% glycerol and then was dispensed into cryogenic vials. The cell bank for each strain were contained in the cryogenic vials, which were stored at -70°C until use.

EXAMPLE 2

Method of Isolating and Purifying Polysaccharides

[0102] This examples shows how polysaccharides are isolated and purified from cell banks for use in a polysaccharide-CRM_{197} conjugate vaccine. Any of the polysaccharides of **TABLE 1** or of **FIGS. 10A-10F** (e.g., polysaccharides from serotypes 1, 2, 3, 4, 5, 6A, 6B, 7C, 7F, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33B, 33F, 34, 35F, 35B, or 38 and Serogroup 20 (comprising serotypes 20A and 20B)) are isolated and purified by this method. This process for the isolation and purification of polysaccharides is shown in **FIG. 4**. A vial of a cell bank produced as described in **EXAMPLE 1** is used to inoculate a flask containing an appropriate culture medium and incubated overnight. This culture is used to seed a new culture for fermentation in a fermenter. The culture is allowed to grow under the appropriate conditions for that strain. After fermentation, the cells are inactivated and then are treated with deoxycholate to break open the cells and release the capsular polysaccharide. Subsequently, debris is removed by centrifugation, which is followed by a depth filter step through a 0.45 μm filter and the cell free broth is collected. The product is then purified and the polysaccharide size is determined. Quality control tests are performed on the product, such as a purity assay and confirmation of strain inactivation (no growth after plating).

Petitioner Merck Ex-1015, 1638

[0103] A cell bank of an *S. pneumoniae* strain that produces serotype 8, serotype 10A, serotype 11A, serotype 12F, serotype 22F, or serotype 33F was used to inoculate a flask containing the appropriate culture medium and incubated overnight. This culture was used to seed a new culture for fermentation in a fermenter. The culture was allowed to grow under the appropriate conditions for the specific strain. After fermentation, the cells were inactivated and then were treated with deoxycholate to break open the cells and release the capsular polysaccharide. Subsequently, debris was removed by centrifugation, which was followed by a depth filter step through a 0.45 μm filter and the cell free broth was collected. The product was then purified and the polysaccharide size was determined. Quality control tests were performed on the product, such as a purity assay and confirmation of strain inactivation (no growth after plating).

EXAMPLE 3

Method of CRM_{197} production

[0104] This example shows the production of CRM_{197} (SEQ ID NO: 1) for use in saccharide polypeptide vaccines, which is depicted in **FIG. 3.** A vial from a working cell bank of CRM_{197} was seeded into a flask containing the appropriate culture medium and incubated overnight. The fermentation culture was centrifuged and the contents were harvested, were clarified, and then were filtered through a 0.2 μm filter. The filtrate was concentrated about ten-fold, and then was diafiltered to exchange the buffer and remove contaminants. The protein was further purified by microfiltration using an appropriate pore size membrane. Then the filtrate was further purified by anion exchange chromatography, followed by ammonium sulfate precipitation, and filtration (0.45 μm). A final purification using hydrophobic chromatography was conducted, and the highly purified CRM_{197} protein was concentrated and diafiltered, and then filtered through a 0.2 μm filter. The product was stored at -70°C until use in conjugation with a polysaccharide, such as any polysaccharide listed in **TABLE 1** or of **FIGS. 10A-10F** (e.g., polysaccharides from serotypes 1, 2, 3, 4, 5, 6A, 6B, 7C, 7F, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35F, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B)). Quality control tests were performed on the product to assess concentration (BCA for Lowry NLT 15 mg/mL), purity (SDS-PAGE gel with a target of ≥ 95% pure), confirming CRM_{197} identification (using a monoclonal antibody), assessing size (SDS-Page with a target of ~58 kDa), assessing endotoxin level (LAL kit with target of <1 IU/μg of protein), assessing lack of toxicity (Vero Cytotoxicity or DT enzyme test; non-lethal

Petitioner Merck Ex-1015, 1639

in Guinea Pigs), assessing pH (meter, target of 6.5 ± 0.2), and assessing appearance (visually, target for clear liquid).

EXAMPLE 4

Method of conjugation

[0105] This example shows the conjugation of a capsular polysaccharide to a polypeptide via CDAP conjugation chemistry. The polysaccharide are isolated as described in **EXAMPLE 2** and are thawed. The polypeptide is chosen from any of the following: diphtheria and tetanus toxoids, and variants thereof (*e.g.*, DT, CRM_{197},TT), cholera toxoid, pertussis toxoid, inactivated or mutant pneumococcal pneumolysin, pneumococcal surface protein A, pneumococcal adhesion protein A, pneumococcal lipoprotein PsaA, C5a peptidase group A or group B streptococcus, non-typable *H. influenzae* P4 protein, non-typable *H. influenzae* P6 protein, *M catarrhalis* uspA, keyhole limpet haemocyanin (KLH), OMPC from *N. meningitidis*, the purified protein derivative of tuberculin(PPD), protein D from *H. influenzae*, or any fragment thereof. The polysaccharide is activated via CDAP chemistry in a CDAP solution. The polypeptide is added to the activated polysaccharides, and then the conjugation reaction is quenched. The reaction mixture is filtered, is diafiltrated, and is concentrated. The polysaccharide polypeptide conjugates are then separated using gel filtration chromatography. These conjugates are then concentrated for the final polysaccharide polypeptide conjugate.

EXAMPLE 5

Method of Polysaccharide-CRM_{197} Conjugation

[0106] This example shows the conjugation of a capsular polysaccharide to CRM_{197} via CDAP conjugation chemistry. The isolated polysaccharide is any polysaccharide as described in **TABLE 1** or of **FIGS. 10A-10F** (e.g., polysaccharides from serotypes 1, 2, 3, 4, 5, 6A, 6B, 7C, 7F, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35F, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B)), or in **EXAMPLE 2**, and CRM_{197} is as described in **EXAMPLE 3**. The conjugation process is depicted in **FIG. 5**. The polysaccharide and CRM_{197} are thawed. The polysaccharide is mixed with CDAP solution, which is then incubated at the appropriate temperature for polysaccharide activation. A calculated amount of CRM_{197} is added to the activated polysaccharides. The reaction is then quenched using glycine or any other suitable quenching reagent. The conjugation reaction mixture is filtered, is diafiltered, and is

Petitioner Merck Ex-1015, 1640

concentrated for the polysaccharide-CRM_{197} conjugates. The polysaccharide-CRM_{197} conjugates are then purified by gel filtration chromatography. The fractions containing the polysaccharide-CRM_{197} conjugates are pooled, are concentrated, and then are filtered through a 0.2 μm filter. The product is stored at 2-8°C.

[0107] The isolated polysaccharide from serotype 8, serotype 10A, serotype 11A, serotype 12F, serotype 22F, or serotype 33F as described in **TABLE 1** and **EXAMPLE 2**, and CRM_{197} as described in **EXAMPLE 3** were thawed. The polysaccharide from serotype 8, serotype 10A, serotype 11A, serotype 12F, serotype 22F, or serotype 33F were mixed with CDAP solution, which was then incubated at the appropriate temperature for polysaccharide activation. A calculated amount of CRM_{197} was added to the activated polysaccharides. The reaction was then quenched using glycine or any other suitable quenching reagent. The conjugation reaction mixture was filtered, was diafiltered, and was concentrated for the polysaccharide-CRM_{197} conjugates. The polysaccharide-CRM_{197} conjugates were then purified by gel filtration chromatography. The fractions containing the polysaccharide-CRM_{197} conjugates were pooled, were concentrated, and then were filtered through a 0.2 μm filter. The product is stored at 2-8°C.

EXAMPLE 6

Combinations of Polysaccharide-CRM_{197} Conjugates in a Vaccine Composition

[0108] This example shows combinations of polysaccharides that are used in a polysaccharide-CRM_{197} conjugate vaccine. Each polysaccharide serotype is individually conjugated to a CRM_{197} to produce the polysaccharide CRM_{197} conjugate. The polysaccharide-CRM_{197} conjugates for each serotype are combined into vaccine composition. See the below **TABLE 3** for exemplary polysaccharide-CRM_{197} conjugate serotype combinations.

TABLE 3. Combinations of Polysaccharides in Polysaccharide-CRM_{197} Conjugate Vaccines

List of Polysaccharide Serotype Combinations
1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F
6C, 8, 9N, 10A, 12F, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F, and 35B
6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 22F, 23A, 23B, 33F, and 35B
6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 22F, 23A, 23B, 24F, 33F, and 35B
6C, 8, 9N, 10A, 11A, 12F, 15A, 22F, 23A, 23B, 24F, 33F, and 35B

Petitioner Merck Ex-1015, 1641

List of Polysaccharide Serotype Combinations
6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 22F, 23A, 23B, 33F, and 35B
6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 22F, 23A, 23B, 33F, and 35B
6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F, and 35B
6C, 8, 9N, 10A, 11A, 12F, 15A, 22F, 23A, 23B, 24F, 33F, and 35B
6C, 10A, 11A, 15A, 15B, 15C, 22F, 23A, 24B, 33F, 35B and 38
6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 22F, 23A, 23B, 33F, and 35B
1, 3, 4, 6A, 6B, 6C, 7F, 8, 9N, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 19F, 19A, 20A, 22F, 23A, 23B, 24F, 33F, 35F, 35B, and 38
3, 4, 6C, 7F, 8, 9N, 11A, 12F, 15A, 15B, 15C, 16F, 19A, 22F, 23A, 23B, and 35B
1, 3, 4, 6A, 6C, 7F, 8, 9N, 10A, 11A, 12F, 14, 19A, 19F, 22F, 23A, 23B, 23F, 24F, and 33F
3, 4, 6B, 6C, 10A, 15A, 15B, 19A, 19F, 22F, 23F, 24F, and 35B
6C, 9N, 15A, 15C, 16F, 20A, 23A, 23B, 24F, 31, 34, 35F, and 38
6C, 15A, 15C, 16F, 23A, 23B, 24F, 31, 34, 35F, and 38
6C, 15A, 15C, 16F, 23A, 23B, and 35B
6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B
6C, 9N, 15A, 15C, 16F, 23A, 23B, 33F, and 35B
6C, 9N, 15A, 15C, 16F, 17F, 20A, 23A, 23B, 33F, 34, 35F, 35B, 24F, and 31
6C, 9N, 15A, 15C, 16F, 17F, 20B, 23A, 23B, 33F, 34, 35F, 35B, 24F, and 31
6C, 9N, 15A, 15C, 16F, 23A, 23B, 33F, 35F, and 35B
1, 3, 4, 6A, 6B, 6C, 7F, 8, 9N, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 19F, 19A, 20A, 22F, 23A, 23B, 24F, 33F, 35F, 35B, and 38
1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 19F, 19A, 20A, 22F, 23F, 23A, 23B, 24F, 31, 33F, 35F, 35B, and 38
1, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 20A, 22F, 23F, 23A, 23B, 24F, 31, 33F, 35F, 35B, and 38
6C, 15A, 15C, 16F, 23A, 23B, 31, 33F, 34, 35B, and 38
1, 4, 6A, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19F, 19A, 20A, 22F, 23A, 23B, 31, 33F, 34, 35B, 35F, 38
1, 3, 4, 6A, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, 34, 35B, 35F, and 38
1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 20B, and 23F

Petitioner Merck Ex-1015, 1642

List of Polysaccharide Serotype Combinations
6C, 8, 9N, 10A, 12F, 15A, 15B, 15C, 16F, 20B, 22F, 23A, 23B, 33F, and 35B
6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 20B, 22F, 23A, 23B, 33F, and 35B
6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 20B, 22F, 23A, 23B, 24F, 33F, and 35B
6C, 8, 9N, 10A, 11A, 12F, 15A, 20B, 22F, 23A, 23B, 24F, 33F, and 35B
6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 20B, 22F, 23A, 23B, 33F, and 35B
6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 20B, 22F, 23A, 23B, 33F, and 35B
6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20B, 22F, 23A, 23B, 33F, and 35B
6C, 8, 9N, 10A, 11A, 12F, 15A, 20B, 22F, 23A, 23B, 24F, 33F, and 35B
6C, 10A, 11A, 15A, 15B, 15C, 20B, 22F, 23A, 24B, 33F, 35B and 38
6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 20B, 22F, 23A, 23B, 33F, and 35B
1, 3, 4, 6A, 6B, 6C, 7F, 8, 9N, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 24F, 33F, 35F, 35B, and 38
3, 4, 6C, 7F, 8, 9N, 11A, 12F, 15A, 15B, 15C, 16F, 19A, 20B, 22F, 23A, 23B, and 35B
1, 3, 4, 6A, 6C, 7F, 8, 9N, 10A, 11A, 12F, 14, 19A, 19F, 20B, 22F, 23A, 23B, 23F, 24F, and 33F
3, 4, 6B, 6C, 10A, 15A, 15B, 19A, 19F, 20B, 22F, 23F, 24F, and 35B
6C, 9N, 15A, 15C, 16F, 20A, 20B, 23A, 23B, 24F, 31, 34, 35F, and 38
6C, 15A, 15C, 16F, 20B, 23A, 23B, 24F, 31, 34, 35F, and 38
6C, 15A, 15C, 16F, 20B, 23A, 23B, and 35B
6C, 9N, 15A, 15C, 16F, 20B, 23A, 23B, and 35B
6C, 9N, 15A, 15C, 16F, 20B, 23A, 23B, 33F, and 35B
6C, 9N, 15A, 15C, 16F, 17F, 20A, 20B, 23A, 23B, 33F, 34, 35F, 35B, 24F, and 31
6C, 9N, 15A, 15C, 16F, 20B, 23A, 23B, 33F, 35F, and 35B
1, 3, 4, 6A, 6B, 6C, 7F, 8, 9N, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 24F, 33F, 35F, 35B, and 38
1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 19F, 19A, 20A, 20B, 22F, 23F, 23A, 23B, 24F, 31, 33F, 35F, 35B, and 38
1, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 20A, 20B, 22F, 23F, 23A, 23B, 24F, 31, 33F, 35F, 35B, and 38
6C, 15A, 15C, 16F, 20B, 23A, 23B, 31, 35B, 34, 35F, and 38

Petitioner Merck Ex-1015, 1643

List of Polysaccharide Serotype Combinations
1, 4, 6A, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 31, 33F, 34, 35B, 35F, 38
1, 3, 4, 6A, 6B, 6C, 7F, 8, 9N, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 19F, 19A, 20B, 22F, 23A, 23B, 24F, 33F, 35F, 35B, and 38
6C, 9N, 15A, 15C, 16F, 20B, 23A, 23B, 24F, 31, 34, 35F, and 38
1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 19F, 19A, 20B, 22F, 23F, 23A, 23B, 24F, 31, 33F, 35F, 35B, and 38
1, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 20B, 22F, 23F, 23A, 23B, 24F, 31, 33F, 35F, 35B, and 38
1, 4, 6A, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19F, 19A, 20B, 22F, 23A, 23B, 31, 33F, 34, 35B, 35F, 38
1, 3, 4, 6A, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F, 34, 35B, 35F, and 38
6C, 15A, 15C, 16F, 20B, 23A, 23B, 24F, 31, 33F, 34, 35F, and 35B
6C, 8, 9N, 10A, 11A, 15A, 15B, 15C, 16F, 20A, 22F, 23A, 23B, 33F, and 35B
6C, 15A, 15C, 16F, 20B, 23A, 23B, 24F, 31, 33F, 34, 35F, and 35B
6C, 9N, 15A, 15C, 16F, 23A, 23B, and 33F
6C, 15A, 15C, 16F, 23A, 23B, and 33F
6C, 9N, 15A, 15C, 16F, 17F, 20B, 23A, 23B, 24F, 31, 33F, 34, 35F, and 35B
3, 6C, 7C, 8, 9N, 11A, 12F, 15A, 16F, 19A, 19F, 20 (comprising 20A and 20B), 22F, 23A, 23B, 31, 33F, 35B, 35F, and 38
3, 6C, 7C, 7F, 8, 9N, 11A, 12F, 15A, 16F, 19A, 19F, 20 (comprising 20A and 20B), 22F, 23A, 23B, 31, 33F, 35B, 35F, and 38
3, 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 19A, 19F, (comprising 20A and 20B), 22F, 23A, 23B, 31, 33F, 35B, 35F, 38
3, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 19A, 22F, 23A, 23B, 24F, 33F, 35B, and 38
3, 8, 9N, 12F, 15A, 19A, 22F, 23A, 23B, and 24F
3, 8, 9N, 10A, 12F, 15A, 19A, 22F, 23A, 23B, and 24F
3, 4, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 19A, (comprising 20A and 20B), 22F, 23A, 23B, 24F, 31, 33F, 35B, 35F, and 38
3, 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 19A, 19F, (comprising 20A and 20B),

Petitioner Merck Ex-1015, 1644

List of Polysaccharide Serotype Combinations
22F, 23A, 23B, 31, 33F, 35B, 35F, and 38

EXAMPLE 7

Formulation of Polysaccharide-CRM_{197} Conjugate Vaccine

[0109] This example shows a formulation for a polysaccharide-CRM_{197} conjugate vaccine. Any combination of polysaccharide-CRM_{197} conjugates from **EXAMPLE 5** or the combinations listed in **EXAMPLE 6** are used in the vaccine composition. In addition to the polysaccharide-CRM_{197} conjugates, the vaccine is composed of normal saline and 0.01% Polysorbate 80, with a pH of 6.5 ± 0.2. This formulation of the polysaccharide CRM_{197} vaccine composition is stored in 2 mL glass vials with an aluminum crimp top and stopper at 2-8°C. The vial is filled to a volume of 0.60 mL to allow for an extractable volume of 0.50 mL.

EXAMPLE 8

Process for Formulating a Polysaccharide-CRM_{197} Conjugate Vaccine

[0110] This example shows the formulating process for a polysaccharide CRM_{197} conjugate vaccine. The polysaccharide CRM_{197} conjugates are prepared as described in the above Examples. The formulation process is depicted in **FIG. 6**. 0.9% w/v sterile saline is added to a formulation container. Each type of conjugate is separately sterilized and the appropriate volume of each monovalent bulk polysaccharide-CRM_{197} conjugate is added (volume is based on the polysaccharide concentration) to the formulation container one at a time. The pH is adjusted to 6.5 ± 0.2 using 1 N HCl or 1 N NaOH. Optionally, an adjuvant is added to the polysaccharide-CRM_{197} conjugate mixture, such as aluminum phosphate to 1 mg/mL final concentration. A calculated volume of sterile saline is added to reach the appropriate final concentration, and then the mixture is blended for approximately two hours. The formulate in the bulk container is then attached to the filling machine, which fills, stoppers, and seals the vials of the final vaccine product. These vial then are inspected, labeled, and packed for distribution. During this process, the pH, appearance of the vaccine, and the vaccine sterility is monitored. At the filling, stoppering, and sealing step, the appearance, pH, identity of polysaccharides, identity of CRM_{197}, sterility, saccharide content, total protein content, endotoxin content, pyrogen content, general safety, osmolality, and extractable volume are assessed. 1-5 microgram of polysaccharide per each serotype CRM_{197} conjugate is contained in a 0.5 mL of vaccine in a vial.

Petitioner Merck Ex-1015, 1645

EXAMPLE 9

Rabbit Toxicology Safety Study

[0111] This example shows the rabbit toxicology studies that are used to assess vaccine safety. The polysaccharide polypeptide conjugate is produced according to the above **EXAMPLES 1**, **2**, **3**, and **5**, and comprises the *S. pneumoniae* polysaccharides from the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F, and 35B, which are conjugated to CRM_{197}. Alternatively, the polysaccharide polypeptide conjugate is produced according to the above Examples 1, 2, 3, and 5, and comprises the *S. pneumoniae* polysaccharides from the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20B, 22F, 23A, 23B, 33F, and 35B, which are conjugated to CRM_{197}. These polysaccharide-CRM_{197} conjugates are used in a vaccine formulated according to **EXAMPLES 6** and **7**. This polysaccharide CRM_{197} conjugate vaccine is administered intramuscularly on days 1, 22, 43, 64, and 85 to rabbits, 5 months of age, (10/gender) at a dose of 0.5 ml/injection into the right thigh muscle. 0.5 ml 0.9% sodium chloride is injected in the Control groups (10/gender). 0.125 mg aluminum phosphate as an adjuvant is injected in the AlP04 group (10/gender). A 4 week dose free recovery period is undertaken in five (5) animals/gender/group after the last injection. Treatment-related mortality and any other toxicologically relevant changes in relative food consumption, ophthalmoscopic parameters, heart rate, respiratory rate, gross anatomy or organ weight is assessed to support lack of systemic toxicity. Injection site are analyzed for reactions and any chronic inflammation. Specific serum antibodies to each of the polysaccharides in the polysaccharide CRM_{197} conjugate vaccine is found in the test group.

[0112] The polysaccharide polypeptide conjugate is produced according to the above Examples 1, 2, 3, and 5, and comprises the *S. pneumoniae* polysaccharides from the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F, and 35B, which are conjugated to CRM_{197}. Alternatively, the polysaccharide polypeptide conjugate is produced according to the above Examples 1, 2, 3, and 5, and comprises the *S. pneumoniae* polysaccharides from the serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20B, 22F, 23A, 23B, 33F, and 35B, which are conjugated to CRM_{197}. These polysaccharide CRM_{197} conjugates are used in a vaccine formulated according to **EXAMPLES 6** and **7**. This polysaccharide CRM_{197} conjugate vaccine is administered intramuscularly with and without an aluminum phosphate adjuvant as a single 0.5 mL injection into the left thigh muscle of 3 male rabbits/group, 5 months of age. 0.5 ml 0.9% sodium chloride is administered to the control group (3 males). Treatment related mortality, changes in body weight, relative food consumption, or treatment related macroscopic or microscopic lesions is assessed.

Petitioner Merck Ex-1015, 1646

EXAMPLE 10

Composition and Method of Administration of a Vaccine

[0113] This example shows a vaccine composition and a method of administration of that vaccine composition. An aqueous vaccine composition is composed of an immunogenic polysaccharide polypeptide conjugate comprising capsular polysaccharides from any serotype from **TABLE 1** conjugated to any one of diphtheria and tetanus toxoids, and variants thereof (*e.g.*, DT, CRM_{197},TT), cholera toxoid, pertussis toxoid, inactivated or mutant pneumococcal pneumolysin, pneumococcal surface protein A, pneumococcal adhesion protein A, pneumococcal lipoprotein PsaA, C5a peptidase group A or group B streptococcus, non-typable *H. influenzae* P4 protein, non-typable *H. influenzae* P6 protein, *M catarrhalis* uspA, keyhole limpet haemocyanin (KLH), OMPC from *N. meningitidis*, the purified protein derivative of tuberculin(PPD), protein D from *H. influenzae,* or any fragment thereof; or any combination of polysaccharide polypeptide conjugates as described in Example 6. The aqueous vaccine is formulated to contain from 1-4 microgram of each serotype of polysaccharide per polysaccharide polypeptide conjugate, aluminum phosphate (1 mg/mL), and 0.01% polysorbate 80 in a single 0.5 mL injection delivered intramuscularly to a subject. This vaccine is administered to subject, wherein the subject is a child of 4 weeks to 2 years old. This vaccine is administered to subject, wherein the subject is a child of 2 to 18 years old. This vaccine is administered to a subject, wherein the subject is an adult of at least 50 years of age.

EXAMPLE 11

Vaccination for Protection Against Endemic *S. pneumoniae* Serotypes in the United States and Canada

[0114] This example shows a vaccination of a subject that provides protection against *S. pneumoniae* for a subject residing in or visiting the United States and/or Canada. The aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate comprising capsular polysaccharides from the *S. pneumoniae* serotypes 3, 4, 6A, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 19F, 19A, 22F, 23A, 23B, 33F, 35F, 35B, 38 and Serogroup 20 (comprising serotypes 20A and 20B), such as serotypes 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 22F, 23A, 23B, 33F, and 35B. The aqueous vaccine is formulated to contain from 1-5 microgram of each serotype and aluminum phosphate as an adjuvant. A single 0.5 mL dose of the aqueous vaccine is given by intramuscular injection to the subject.

Petitioner Merck Ex-1015, 1647

After administration, immunity of the subject against *S. pneumoniae* disease endemic in the United States and Canada is improved.

EXAMPLE 12

Vaccination for Protection against Endemic *S. pneumoniae* Serotypes in Europe, the Middle East, and North Africa

[0115] This example shows a vaccine composition that provides protection against *S. pneumoniae* for subjects residing in or visiting Europe, the Middle East, and/or North Africa. The aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate comprising capsular polysaccharides from the *S. pneumoniae* serotypes 1, 3, 4, 6A, 6B, 6C, 7F, 8, 9N, 10A, 11A, 12F, 14, 15A, 15B, 16F, 18C, 19F, 19A, 22F, 23F, 23A, 23B, 24F, 33F, 35F, 35B, and 38, such as serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 22F, 23A, 23B, 24F, 33F, and 35F. The aqueous vaccine is formulated to contain from 1-5 microgram of each serotype and aluminum phosphate as an adjuvant. A single 0.5 mL dose of the aqueous vaccine is given by intramuscular injection to the subject. After administration, immunity of the subject against *S. pneumoniae* disease endemic in Europe, the Middle East, and North Africa is improved.

EXAMPLE 13

Vaccination for Protection Against Endemic *S. pneumoniae* Serotypes in Japan and Korea

[0116] This example shows a vaccine composition that provides protection against *S. pneumoniae* for subjects residing in or visiting Japan and/or Korea. The aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate comprising capsular polysaccharides from the *S. pneumoniae* serotypes 3, 4, 6A, 6B, 6C, 7F, 10A, 11A, 14, 15A, 15B, 19F, 19A, 22F, 23F, 23A, 24F, 35F, 35B, and 38, such as serotypes 6C, 10A, 11A, 15A, 15B, 15C, 22F, 23A, 24B, 33F, 35B, and 38. The aqueous vaccine is formulated to contain from 1-5 microgram of each serotype and aluminum phosphate as an adjuvant. A single 0.5 mL dose of the aqueous vaccine is given by intramuscular injection to the subject. After administration, immunity of the subject against *S. pneumoniae* disease endemic in Japan and Korea is improved.

EXAMPLE 14

Method of Making a 6C-CRM_{197} Conjugate Pharmaceutical Composition

Petitioner Merck Ex-1015, 1648

[0117] This example shows a method of making a saccharide-polypeptide conjugate pharmaceutical composition. A 6C serotype capsular polysaccharide is isolated from *S. pneumoniae*. The CRM_{197} is produced and purified. The 6C polysaccharide is mixed with CDAP solution, which is then incubated at the appropriate temperature for 6C polysaccharide activation. A calculated amount of CRM_{197} is added to the activated 6C polysaccharides. The reaction is then quenched using glycine or any other suitable quenching reagent. The conjugation reaction mixture is filtered, is diafiltered, and is concentrated for the 6C-CRM_{197} conjugates. The 6C-CRM_{197} conjugates are then purified by gel filtration chromatography. The fractions containing the 6C-CRM_{197} conjugates are pooled, are concentrated, and then are filtered through a 0.2 μm filter. The 6C-CRM_{197} conjugate is formulated for use in a vaccine and is contacted with an excipient.

EXAMPLE 15

Method of Making a 20B-CRM_{197} Conjugate Pharmaceutical Composition

[0118] This example shows a method of making a saccharide-polypeptide conjugate pharmaceutical composition. A 20B serotype capsular polysaccharide is isolated from *S. pneumoniae*. The CRM_{197} is produced and purified. The 20B polysaccharide is mixed with CDAP solution, which is then incubated at the appropriate temperature for 20B polysaccharide activation. A calculated amount of CRM_{197} is added to the activated 20B polysaccharides. The reaction is then quenched using glycine or any other suitable quenching reagent. The conjugation reaction mixture is filtered, is diafiltered, and is concentrated for the 20B-CRM_{197} conjugates. The 20B-CRM_{197} conjugates are then purified by gel filtration chromatography. The fractions containing the 20B-CRM_{197} conjugates are pooled, are concentrated, and then are filtered through a 0.2 μm filter. The 20B-CRM_{197} conjugate is formulated for use in a vaccine and is contacted with an excipient.

EXAMPLE 16

Composition of a Kit with a Saccharide-Polypeptide Conjugate

[0119] This example shows the composition of a kit with a saccharide-polypeptide conjugate. A saccharide-polypeptide conjugate in a vial or a pre-filled syringe is placed in a container. The container is further associated with instructions of use.

Petitioner Merck Ex-1015, 1649

EXAMPLE 17

Vaccination Against *S. pneumoniae*

[0120] This example shows a vaccine composition and administration of the vaccine composition to a human subject. An aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate containing capsular polysaccharides from the *S. pneumoniae* serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 22F, 23A, 23B, 33F, and 35B. The aqueous vaccine is formulated to contain from 1-5 microgram of each serotype and aluminum phosphate as an adjuvant.

[0121] A single 0.5 mL dose of the aqueous vaccine is given by intramuscular injection to a human subject. Twenty-eight days later blood is drawn from the human subject and tested for antibodies against each serotype of polysaccharide of the immunogenic saccharide-polypeptide conjugate in the vaccine by in vitro opsonophagocytic assays. After administration of the vaccine, the human subject is found to have antibodies against each serotype of polysaccharide of the immunogenic saccharide-polypeptide conjugate in the vaccine, and therefore, human subject's immunity against these *S. pneumonaie* serotypes is improved.

EXAMPLE 18

Vaccination Against *S. pneumoniae*

[0122] This example shows a vaccine composition and administration of the vaccine composition to a human subject. An aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate containing capsular polysaccharides from the *S. pneumoniae* serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 20B, 22F, 23A, 23B, 33F, and 35B. The aqueous vaccine is formulated to contain from 1-5 microgram of each serotype and aluminum phosphate as an adjuvant.

[0123] A single 0.5 mL dose of the aqueous vaccine is given by intramuscular injection to a human subject. Twenty-eight days later blood is drawn from the human subject and tested for antibodies against each serotype of polysaccharide of the immunogenic saccharide-polypeptide conjugate in the vaccine by in vitro opsonophagocytic assays. After administration of the vaccine, the human subject is found to have antibodies against each serotype of polysaccharide of the immunogenic saccharide-polypeptide conjugate in the vaccine, and therefore, human subject's immunity against these *S. pneumonaie* serotypes is improved.

Petitioner Merck Ex-1015, 1650

EXAMPLE 19

Vaccination Against *S. pneumoniae*

[0124] This example shows a vaccine composition and administration of the vaccine composition to a human subject. An aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate containing capsular polysaccharides from the *S. pneumoniae* serotypes of any of the combinations listed in **TABLE 3**. The aqueous vaccine is formulated to contain from 1-5 microgram of each serotype and aluminum phosphate as an adjuvant.

[0125] A single 0.5 mL dose of the aqueous vaccine is given by intramuscular injection to a human subject. Twenty-eight days later blood is drawn from the human subject and tested for antibodies against each serotype of polysaccharide of the immunogenic saccharide-polypeptide conjugate in the vaccine by in vitro opsonophagocytic assays. After administration of the vaccine, the human subject is found to have antibodies against each serotype of polysaccharide of the immunogenic saccharide-polypeptide conjugate in the vaccine, and therefore, human subject's immunity against these *S. pneumonaie* serotypes is improved.

EXAMPLE 20

Method of Vaccination

[0126] This example shows vaccine compositions and a dosing schedule for the vaccine compositions for a human subject. A first aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate containing capsular polysaccharides from the *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. A second aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate containing capsular polysaccharides from the *S. pneumoniae* serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 22F, 23A, 23B, 33F, and 35B. Each aqueous vaccine is formulated to contain from 1-5 microgram of each serotype and aluminum phosphate as an adjuvant.

[0127] A single 0.5 mL dose of the first aqueous vaccine is given by intramuscular injection to a human subject. Four weeks later a single 0.5 mL dose of the second aqueous vaccine is given by intramuscular injection to the human subject. Alternatively to four weeks later, one year later a single 0.5 mL of the second aqueous vaccine is given by intramuscular injection to the human subject.

Petitioner Merck Ex-1015, 1651

EXAMPLE 21

Method of Vaccination

[0128] This example shows vaccine compositions and a dosing schedule for the vaccine compositions for a human subject. A first aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate containing capsular polysaccharides from the *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. A second aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate containing capsular polysaccharides from the *S. pneumoniae* serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 20B, 22F, 23A, 23B, 33F, and 35B. Each aqueous vaccine is formulated to contain from 1-5 microgram of each serotype and aluminum phosphate as an adjuvant.

[0129] A single 0.5 mL dose of the first aqueous vaccine is given by intramuscular injection to a human subject. Four weeks later a single 0.5 mL dose of the second aqueous vaccine is given by intramuscular injection to the human subject. Alternatively to four weeks later, one year later a single 0.5 mL of the second aqueous vaccine is given by intramuscular injection to the human subject.

EXAMPLE 22

Method of Vaccination for an Adult Aged 50 Years Old or Older

[0130] This example shows vaccine compositions and a dosing schedule for the vaccine compositions for an adult age 50 years old or older. A first aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate containing capsular polysaccharides from the *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. A second aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate containing capsular polysaccharides from the *S. pneumoniae* serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 22F, 23A, 23B, 33F, and 35B. Alternatively, a second aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate containing capsular polysaccharides from the *S. pneumoniae* serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 20B, 22F, 23A, 23B, 33F, and 35B. Each aqueous vaccine is formulated to contain from 1-5 microgram of each serotype and aluminum phosphate as an adjuvant.

[0131] A single 0.5 mL dose of the first aqueous vaccine is given by intramuscular injection to an adult age 50 years old or older. Four weeks later a single 0.5 mL dose of the second aqueous vaccine is given by intramuscular injection to the adult aged 50 years old or older.

Petitioner Merck Ex-1015, 1652

Alternatively to four weeks later, one year later a single 0.5 mL of the second aqueous vaccine is given by intramuscular injection to the adult aged 50 years old or older.

EXAMPLE 23

Method of Vaccination for a Child Aged 2 to 18 Years Old

[0132] This example shows vaccine compositions and a dosing schedule for the vaccine compositions for a child aged 2 to 18 years old. A first aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate containing capsular polysaccharides from the *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. A second aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate containing capsular polysaccharides from the *S. pneumoniae* serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 22F, 23A, 23B, 33F, and 35B. Alternatively, a second aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate containing capsular polysaccharides from the *S. pneumoniae* serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 20B, 22F, 23A, 23B, 33F, and 35B. Each aqueous vaccine is formulated to contain from 1-5 microgram of each serotype and aluminum phosphate as an adjuvant.

[0133] A single 0.5 mL dose of the first aqueous vaccine is given by intramuscular injection to a child aged 2 to 18 years old. Four weeks later a single 0.5 mL dose of the second aqueous vaccine is given by intramuscular injection to the child aged 2 to 18 years old. Alternatively to four weeks later, one year later a single 0.5 mL of the second aqueous vaccine is given by intramuscular injection to the child aged 2 to 18 years old.

EXAMPLE 24

Method of Vaccination for a Child Aged 4 Weeks to 2 Years Old

[0134] This example shows vaccine compositions and a dosing schedule for the vaccine compositions for a child aged 4 weeks to 2 years old. A first aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate containing capsular polysaccharides from the *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. A second aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate containing capsular polysaccharides from the *S. pneumoniae* serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 22F, 23A, 23B, 33F, and 35B. Alternatively, a second aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate containing capsular polysaccharides from the *S.*

Petitioner Merck Ex-1015, 1653

pneumoniae serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 20B, 22F, 23A, 23B, 33F, and 35B. Each aqueous vaccine is formulated to contain from 1-5 microgram of each serotype and aluminum phosphate as an adjuvant.

[0135] A single 0.5 mL dose of the first aqueous vaccine is given by intramuscular injection to a child aged 4 weeks to 2 years old. Four weeks later a single 0.5 mL dose of the second aqueous vaccine is given by intramuscular injection to the child who is 2-18 years old. Alternatively to four weeks later, one year later a single 0.5 of the second aqueous vaccine is given by intramuscular injection to the child aged 4 weeks to 2 years old.

EXAMPLE 25

Method of Vaccination for *S. pneumoniae* and *N. meningitidis*

[0136] This example shows vaccine compositions and a dosing schedule that provides protection against *S. pneumoniae* and *N. meningitidis*. A first aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate containing capsular polysaccharides from the *S. pneumoniae* 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 22F, 23A, 23B, 33F, and 35B conjugated to CRM_{197}. A second aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate containing *N. meningitidis* group C capsular saccharide conjugated to CRM_{197}. Each vaccine is formulated for intramuscular injection.

[0137] A single 0.5 mL dose of the first aqueous vaccine is given by intramuscular injection to a subject. One month later a single dose of the second aqueous vaccine is given by intramuscular injection to a subject. Alternatively, the first aqueous vaccine is given by intramuscular injection one month after the second aqueous vaccine is given by intramuscular injection.

EXAMPLE 26

Method of Vaccination for *S. pneumoniae* and *S. enterica*

[0138] This example shows vaccine compositions and a dosing schedule that provides protection against *S. pneumoniae* and *S. enterica*. A first aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate containing capsular polysaccharides from the *S. pneumoniae* 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 22F, 23A, 23B, 33F, and 35B conjugated to CRM_{197}. A second aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate containing *S. enterica*

Petitioner Merck Ex-1015, 1654

subspecies enterica serovar Typhi Vi-capsular saccharide conjugated to CRM_{197}. Each aqueous vaccine is formulated for intramuscular injection.

[0139] A single 0.5 mL dose of the first aqueous vaccine is given by intramuscular injection to a subject. One month later a single dose of the second aqueous vaccine is given by intramuscular injection to a subject. Alternatively, the first aqueous vaccine is given by intramuscular injection one month after the second aqueous vaccine by intramuscular injection.

EXAMPLE 27

Method of Vaccination for *S. pneumoniae*, *N. meningitidis*, and *H. influenzae*

[0140] This example shows vaccine compositions and a dosing schedule that provides protection against *S. pneumoniae*, *N. meningitidis*, and *H. influenzae*. A first aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate containing capsular polysaccharides from the *S. pneumoniae* 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 22F, 23A, 23B, 33F, and 35B conjugated to a tetanus toxoid carrier protein. A second aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate containing *N. meningitidis* group C and group Y saccharide and *H. influenzae* type b saccharide individually conjugated a tetanus toxoid carrier protein. Each aqueous vaccine is formulated for intramuscular injection.

[0141] A single 0.5 mL dose of the first aqueous vaccine is given by intramuscular injection to a subject. One month later a single dose of the second aqueous vaccine is given by intramuscular injection to a subject. Alternatively, the first aqueous vaccine is given by intramuscular injection one month after the second aqueous vaccine by intramuscular injection.

EXAMPLE 28

Serotype 23A Vaccination Against *S. pneumoniae*

[0142] This example shows a vaccine composition and administration of the vaccine composition to a human subject. An aqueous vaccine composition is comprised of immunogenic saccharide-polypeptide conjugates comprising a capsular polysaccharide from the *S. pneumoniae* serotypes 23A. The aqueous vaccine is formulated to contain from 1-5 microgram of each serotype and aluminum phosphate as an adjuvant.

[0143] A single 0.5 mL dose of the aqueous vaccine is given by intramuscular injection to a human subject. Twenty-eight days later blood is drawn from the human subject and tested for

Petitioner Merck Ex-1015, 1655

antibodies against each serotype of polysaccharide of the immunogenic saccharide-polypeptide conjugate in the vaccine by in vitro opsonophagocytic assays. After administration of the vaccine, the human subject is found to have antibodies against each serotype of polysaccharide of the immunogenic saccharide-polypeptide conjugate in the vaccine, and therefore, human subject's immunity against these *S. pneumonaie* serotypes is improved.

EXAMPLE 29

Serotype 23B Vaccination Against *S. pneumoniae*

[0144] This example shows a vaccine composition and administration of the vaccine composition to a human subject. An aqueous vaccine composition is comprised of immunogenic saccharide-polypeptide conjugates comprising a capsular polysaccharide from the *S. pneumoniae* serotypes 23B. The aqueous vaccine is formulated to contain from 1-5 microgram of each serotype and aluminum phosphate as an adjuvant.

[0145] A single 0.5 mL dose of the aqueous vaccine is given by intramuscular injection to a human subject. Twenty-eight days later blood is drawn from the human subject and tested for antibodies against each serotype of polysaccharide of the immunogenic saccharide-polypeptide conjugate in the vaccine by in vitro opsonophagocytic assays. After administration of the vaccine, the human subject is found to have antibodies against each serotype of polysaccharide of the immunogenic saccharide-polypeptide conjugate in the vaccine, and therefore, human subject's immunity against these *S. pneumonaie* serotypes is improved.

EXAMPLE 30

Vaccination for Protection Against Endemic *S. pneumoniae* Serotypes in the United States

[0146] This example shows a vaccination of a subject that provides protection against *S. pneumoniae* for a subject residing in or visiting the United States. The aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate comprising capsular polysaccharides from the *S. pneumoniae* serotypes 3, 6C, 7C, 8, 9N, 11A, 12F, 15A, 16F, 19A, 19F, 22F, 23A, 23B, 31, 33F, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). The immunogenic saccharide-polypeptide conjugates are made using the methods as described herein. The aqueous vaccine is formulated to contain from 1-5 microgram of each serotype and aluminum phosphate as an adjuvant. A single 0.5 mL dose

Petitioner Merck Ex-1015, 1656

of the aqueous vaccine is given by intramuscular injection to the subject. After administration, immunity of the subject against *S. pneumoniae* disease endemic in the United States is improved.

EXAMPLE 31

Vaccination for Protection Against Endemic *S. pneumoniae* Serotypes in the United States

[0147] This example shows a vaccination of a subject that provides protection against *S. pneumoniae* for a subject residing in or visiting the United States. The aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate comprising capsular polysaccharides from the *S. pneumoniae* serotypes 3, 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 19A, 19F, 22F, 23A, 23B, 31, 33F, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). The immunogenic saccharide-polypeptide conjugates are made using the methods as described herein. The aqueous vaccine is formulated to contain from 1-5 microgram of each serotype and aluminum phosphate as an adjuvant. A single 0.5 mL dose of the aqueous vaccine is given by intramuscular injection to the subject. After administration, immunity of the subject against *S. pneumoniae* disease endemic in the United States is improved.

EXAMPLE 32

Vaccination for Protection Against Endemic *S. pneumoniae* Serotypes in the United Kingdom

[0148] This example shows a vaccination of a subject that provides protection against *S. pneumoniae* for a subject residing in or visiting the United Kingdom. The aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate comprising capsular polysaccharides from the *S. pneumoniae* serotypes 3, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 19A, 22F, 23A, 23B, 24F, 33F, 35B, and 38. The immunogenic saccharide-polypeptide conjugates are made using the methods as described herein. The aqueous vaccine is formulated to contain from 1-5 microgram of each serotype and aluminum phosphate as an adjuvant. A single 0.5 mL dose of the aqueous vaccine is given by intramuscular injection to the subject. After administration, immunity of the subject against *S. pneumoniae* disease endemic in the United Kingdom is improved.

Petitioner Merck Ex-1015, 1657

EXAMPLE 33

Vaccination for Protection Against Endemic *S. pneumoniae* Serotypes in Germany

[0149] This example shows a vaccination of a subject that provides protection against *S. pneumoniae* for a subject residing in or visiting Germany. The aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate comprising capsular polysaccharides from the *S. pneumoniae* serotypes 3, 4, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 19A, 22F, 23A, 23B, 24F, 31, 33F, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). The immunogenic saccharide-polypeptide conjugates are made using the methods as described herein. The aqueous vaccine is formulated to contain from 1-5 microgram of each serotype and aluminum phosphate as an adjuvant. A single 0.5 mL dose of the aqueous vaccine is given by intramuscular injection to the subject. After administration, immunity of the subject against *S. pneumoniae* disease endemic in Germany is improved.

EXAMPLE 34

Vaccination for Protection Against Endemic *S. pneumoniae* Serotypes in Germany

[0150] This example shows a vaccination of a subject that provides protection against *S. pneumoniae* for a subject residing in or visiting Germany. The aqueous vaccine composition is composed of an immunogenic saccharide-polypeptide conjugate comprising capsular polysaccharides from the *S. pneumoniae* serotypes 3, 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 19A, 22F, 23A, 23B, 31, 33F, 35B, 35F, 38, and Serogroup 20 (comprising serotypes 20A and 20B). The immunogenic saccharide-polypeptide conjugates are made using the methods as described herein. The aqueous vaccine is formulated to contain from 1-5 microgram of each serotype and aluminum phosphate as an adjuvant. A single 0.5 mL dose of the aqueous vaccine is given by intramuscular injection to the subject. After administration, immunity of the subject against *S. pneumoniae* disease endemic in Germany is improved.

[0151] While preferred embodiments of the present invention have been shown and described herein, it will be apparent to those skilled in the art that such embodiments are provided by way of example only. It is not intended that the invention be limited by the specific examples provided within the specification. While the invention has been described with reference to the aforementioned specification, the descriptions and illustrations of the embodiments herein are not meant to be construed in a limiting sense. Numerous variations,

Petitioner Merck Ex-1015, 1658

changes, and substitutions will now occur to those skilled in the art without departing from the invention. Furthermore, it shall be understood that all aspects of the invention are not limited to the specific depictions, configurations or relative proportions set forth herein which depend upon a variety of conditions and variables. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is therefore contemplated that the invention shall also cover any such alternatives, modifications, variations or equivalents. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

Petitioner Merck Ex-1015, 1659

CLAIMS

WHAT IS CLAIMED IS:

1. A pharmaceutical composition in unit dose form comprising a plurality of at least eight unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 2, 6C, 7F, 7C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 20B, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35B, 35F, and 38, and wherein a total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in the pharmaceutical composition in unit dose form, ranges from about 0.5 μg to about 5 μg.
2. The pharmaceutical composition of claim 1, comprising a plurality of at least 9 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 20B, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 35B, 35F, and 38.
3. The pharmaceutical composition of claim 1, comprising a plurality of at least 10 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 20B, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 35B, 35F, and 38.
4. The pharmaceutical composition of claim 1, comprising a plurality of at least 13 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 22F, 23A, 23B, 33F, and 35B.
5. The pharmaceutical composition of claim 1, comprising a plurality of at least 14 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular

Petitioner Merck Ex-1015, 1660

polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 22F, 23A, 23B, 24F, 33F and 35B.

6. The pharmaceutical composition of claim 1, comprising a plurality of at least 13 unique immunogenic saccharide-polypeptide each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 6C, 8, 9N, 10A, 11A, 12F, 15A, 22F, 23A, 23B, 24F, 33F, and 35B.
7. The pharmaceutical composition of claim 1, comprising a plurality of at least 12 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 6C, 10A, 11A, 15A, 15B, 15C, 22F, 23A, 24B, 33F, 35B, and 38.
8. The pharmaceutical composition of claim 1, comprising a plurality of at least 13 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 22F, 23A, 23B, 33F, and 35B.
9. The pharmaceutical composition of claim 1, comprising a plurality of at least 13 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 22F, 23A, 23B, 33F, and 35B.
10. The pharmaceutical composition of claim 1, comprising a plurality of at least 13 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 6C, 8, 9N, 10A, 11A, 12F, 15A, 22F, 23A, 23B, 24F, 33F, and 35B.

Petitioner Merck Ex-1015, 1661

11. The pharmaceutical composition of claim 1, comprising a plurality of at least 12 unique immunogenic saccharide-polypeptide conjugates each comprising a unique serotype selected from the group consisting of 6C, 10A, 11A, 15A, 15B, 15C, 22F, 23A, 24B, 33F, 35B and 38.
12. The pharmaceutical composition of claim 1, comprising a plurality of at least 11 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 22F, 23A, 23B, 33F, and 35B.
13. The pharmaceutical composition of claim 1, comprising a plurality of at least 11 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 6C, 8, 9N, 11A, 12F, 15A, 15B, 16F, 22F, 23A, 23B, 33F, and 35B.
14. The pharmaceutical composition of claim 1, comprising a plurality of at least 15 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F, and 35B.
15. The pharmaceutical composition of claim 1, comprising a plurality of at least 16 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20B, 22F, 23A, 23B, 33F, and 35B.
16. The pharmaceutical composition of claim 1, comprising a plurality of at least 8 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B.

Petitioner Merck Ex-1015, 1662

17. The pharmaceutical composition of claim 1, comprising a plurality of at least 7 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 6C, 15A, 15C, 16F, 23A, 23B, and 35B.
18. The pharmaceutical composition of claim 1, comprising a plurality of at least 15 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 6C, 9N, 15A, 15C, 16F, 17F, 20B, 23A, 23B, 24F, 31, 33F, 34, 35F, and 35B.
19. The pharmaceutical composition of claim 1, comprising a plurality of at least 13 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 6C, 15A, 15C, 16F, 20B, 23A, 23B, 24F, 31, 33F, 34, 35F, and 35B.
20. The pharmaceutical composition of claim 1, comprising a plurality of at least 15 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 6C, 8, 9N, 10A, 11A, 15A, 15B, 15C, 16F, 20A, 22F, 23A, 23B, 33F, and 35B.
21. The pharmaceutical composition of claim 1, comprising a plurality of at least 15 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 6C, 9N, 15A, 15C, 16F, 17F, 20A, 23A, 23B, 24F, 31, 34, 35F, 35B, and 38.
22. The pharmaceutical composition of claim 1, comprising a plurality of at least 15 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a

Petitioner Merck Ex-1015, 1663

unique *Streptococcus pneumoniae* serotype selected from a group consisting of 6C, 9N, 15A, 15C, 16F, 17F, 20A, 23A, 23B, 24F, 31, 34, 35F, 35B, and 38.

23. The pharmaceutical composition of claim 1, comprising a plurality of at least 15, 16, or 20 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique Streptococcus pneumoniae serotype selected from a group consisting of 3, 6C, 7C, 8, 9N, 11A, 12F, 15A, 16F, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 31, 33F, 35B, 35F, and 38.
24. The pharmaceutical composition of claim 1, comprising a plurality of at least 15, 16, or 20 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique Streptococcus pneumoniae serotype selected from a group consisting of 3, 6C, 8, 9N, 11A, 12F, 15A, 15C, 16F, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 31, 33F, 35B, 35F, and 38.
25. The pharmaceutical composition of claim 1, comprising a plurality of at least 15, 16, or 20 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique Streptococcus pneumoniae serotype selected from a group consisting of 3, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 19A, 22F, 23A, 23B, 24F, 33F, 35B, and 38.
26. The pharmaceutical composition of claim 1, comprising a plurality of at least 15, 16, or 20 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique Streptococcus pneumoniae serotype selected from a group consisting of 3, 4, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 19A, 20A, 20B, 22F, 23A, 23B, 24F, 31, 33F, 35B, 35F, and 38.
27. The pharmaceutical composition of claim 1, comprising a plurality of at least 15, 16, or 20 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination

Petitioner Merck Ex-1015, 1664

thereof is from a unique Streptococcus pneumoniae serotype selected from a group consisting of 6C, 9N, 15A, 15C, 16F, 17F, 20A, 23A, 23B, 24F, 31, 34, 35F, 35B, and 38.

28. The pharmaceutical composition of any one of claims 1-27, wherein the unique *Streptococcus pneumoniae* serotype is not any of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.

29. A pharmaceutical composition in unit dose form comprising a plurality of at least 29 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 1, 2, 3, 4, 5, 6A, 6B, 7F, 7C, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 20B, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 35F, 34, 35B, and 38, and wherein a total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in the pharmaceutical composition in unit dose form, ranges from about 0.5 μg to about 5 μg.

30. The pharmaceutical composition of claim 29, comprising a plurality of at least 15 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 1, 3, 4, 6A, 6B, 6C, 7F, 8, 9N, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 24F, 24B, 33F, 35F, 35B, and 38.

31. The pharmaceutical composition of claim 29, comprising a plurality of at least 25 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 3, 4, 6A, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 24B, 33F, 35F, 35F, 35B and 38.

32. The pharmaceutical composition of claim 29, comprising a plurality of at least 27 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide,

Petitioner Merck Ex-1015, 1665

wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 1, 3, 4, 6A, 6B, 6C, 7F, 8, 9N, 10A, 11A, 12F, 14, 15A, 15B, 16F, 18C, 19F, 19A, 20A, 20B, 22F, 23F, 23A, 23B, 24F, 33F, 35F, and 35B.

33. The pharmaceutical composition of claim 29, comprising a plurality of at least 19 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 3, 4, 6A, 6B, 6C, 7F, 10A, 11A, 14, 15A, 15B, 19F, 19A, 20A, 20B, 22F, 23F, 23A, 24F, 35B and 38.

34. A pharmaceutical composition in unit dose form comprising at least 2 immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype group, wherein one serotype is 6C and at least one additional serotype is selected from the group consisting of 1, 2, 3, 4, 5, 6A, 6B, 7F, 7C, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 20B, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35B, 35F, and 38, and wherein a total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in the pharmaceutical composition in unit dose form, ranges from about 0.5 μg to about 5 μg.

35. The pharmaceutical composition of claim 34, wherein the at least one additional serotype is selected from the group consisting of 1, 3, 4, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 33F, 35F, 35B, and 38.

36. The pharmaceutical composition of claim 34, wherein the at least one additional serotype is selected from the group consisting of 8, 9N, 10A, 11A, 12F, 15A, 15B, 22F, 23A, 23B, 33F, and 35B.

37. The pharmaceutical composition of claim 34, wherein the at least one additional serotype is selected from the group consisting of 8, 9N, 11A, 12F, 15A, 15B, 16F, 22F, 23A, 23B, 24F, 33F, and 35B.

Petitioner Merck Ex-1015, 1666

38. The pharmaceutical composition of claim 34, wherein the at least one additional serotype is selected from the group consisting of 8, 9N, 10A, 11A, 12F, 15A, 22F, 23A, 23B, 24F, 33F, and 35B.
39. The pharmaceutical composition of claim 34, wherein the at least one additional serotype is selected from the group consisting of 10A, 11A, 15A, 15B, 15C, 22F, 23A, 24B, 33F, 35B, and 38.
40. The pharmaceutical composition of claim 34, wherein the at least one additional serotype is selected from the group consisting of 8, 9N, 10A, 11A, 15A, 15B, 15C, 22F, 23A, 23B, 33F, and 35B.
41. The pharmaceutical composition of claim 34, wherein the at least one additional serotype is selected from the group consisting of 8, 9N, 10A, 11A, 15A, 15B, 15C, 20B, 22F, 23A, 23B, 33F, and 35B.
42. The pharmaceutical composition of claim 34, wherein the at least one additional serotype is selected from the group consisting of 9N, 15A, 15C, 16F, 23A, 23B, and 35B.
43. The pharmaceutical composition of claim 34, wherein the at least one additional serotype is selected from the group consisting of 15A, 15C, 16F, 23A, 23B, and 35B.
44. The pharmaceutical composition of claim 34, wherein the at least one additional serotype is selected from the group consisting of 9N, 15A, 15C, 16F, 17F, 20B, 23A, 23B, 24F, 31, 33F, 34, 35F, and 35B.
45. The pharmaceutical composition of claim 34, wherein the at least one additional serotype is selected from the group consisting of 15A, 15C, 16F, 20B, 23A, 23B, 24F, 31, 33F, 34, 35F, and 35B.
46. The pharmaceutical composition of claim 34, wherein the at least one additional serotype is selected from the group consisting of 8, 9N, 10A, 11A, 15A, 15B, 15C, 16F, 20A, 22F, 23A, 23B, 33F, and 35B.
47. The pharmaceutical composition of claim 4, wherein the at least one additional serotype consists of 8, 9N, 10A, 11A, 12F, 15A, 15B, 22F, 23A, 23B, 33F, and 35B.
48. The pharmaceutical composition of claim 34, wherein the at least one additional serotype consists of 8, 9N, 11A, 12F, 15A, 15B, 16F, 22F, 23A, 23B, 33F, and 35B.
49. The pharmaceutical composition of claim 34, wherein the at least one additional serotype consists of 8, 9N, 10A, 11A, 12F, 15A, 22F, 23A, 23B, 24F, 33F, and 35B.
50. The pharmaceutical composition of claim 34, wherein the at least one additional serotype consists of 10A, 11A, 15A, 15B, 15C, 22F, 23A, 24B, 33F, 35B and 38.

Petitioner Merck Ex-1015, 1667

51. The pharmaceutical composition of claim 4, wherein the at least one additional serotype consists of 8, 9N, 10A, 11A, 12F, 15A, 15B, 22F, 23A, 23B, 33F, and 35B.
52. The pharmaceutical composition of claim 34, wherein the at least one additional serotype consists of 3, 4, 7F, 8, 9N, 11A, 12F, 15A, 15B, 15C, 16F, 19A, 22F, 23A, 23B, and 35B.
53. The pharmaceutical composition of claim 34, wherein the at least one additional serotype consists of 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F, and 35B.
54. The pharmaceutical composition of claim 34, wherein the at least one additional serotype consists of 1, 3, 4, 6A, 7F, 8, 9N, 10A, 11A, 12F, 14, 19A, 19F, 22F, 23A, 23B, 23F, 24F, and 33F.
55. The pharmaceutical composition of claim 34, wherein the at least one additional serotype consists of 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 22F, 20B, 23A, 23B, 33F, and 35B.
56. The pharmaceutical composition of claim 34, wherein the at least one additional serotype consists of 3, 4, 6B, 10A, 15A, 15B, 19A, 19F, 22F, 23F, 24F, and 35B.
57. The pharmaceutical composition of claim 34, wherein the at least one additional serotype consists of 15A, 15C, 16F, 23A, 23B, and 35B.
58. The pharmaceutical composition of claim 34, wherein the at least one additional serotype consists of 9N, 15A, 15C, 16F, 23A, 23B, 35B.
59. The pharmaceutical composition of claim 34, wherein the at least one additional serotype consists of 9N, 15A, 15C, 16F, 23A, 23B, 33F, and 35B.
60. The pharmaceutical composition of claim 34, wherein the at least one additional serotype consists of 9N, 15A, 15C, 16F, 17F, 20A, 23A, 23B, 33F, 34, 35F, 35B, 24F, and 31.
61. The pharmaceutical composition of claim 34, wherein the at least one additional serotype consists of 9N, 15A, 15C, 16F, 23A, 23B, 33F, 35F, and 35B.
62. The pharmaceutical composition of claim 34, wherein the at least one additional serotype consists of 9N, 15A, 15C, 16F, 23A, 23B, and 35B.
63. The pharmaceutical composition of claim 34, wherein the at least one additional serotype consists of the group consisting of 15A, 15C, 16F, 23A, 23B, and 35B.
64. The pharmaceutical composition of claim 34, wherein the at least one additional serotype consists of 9N, 15A, 15C, 16F, 17F, 20B, 23A, 23B, 24F, 31, 33F, 34, 35F, and 35B.
65. The pharmaceutical composition of claim 34, wherein the at least one additional serotype consists of 15A, 15C, 16F, 20B, 23A, 23B, 24F, 31, 33F, 34, 35F, and 35B.
66. The pharmaceutical composition of claim 34, wherein the at least one additional serotype consists of 8, 9N, 10A, 11A, 15A, 15B, 15C, 16F, 20A, 22F, 23A, 23B, 33F, and 35B.

Petitioner Merck Ex-1015, 1668

67. The pharmaceutical composition of claim 34, wherein the at least one additional serotype consists of 3, 7C, 8, 9N, 10A, 11A, 12F, 15A, 16F, 19A, 19F, 20, 22F, 23A, 23B, 31, 33F, 35B, 35F, and 38.
68. The pharmaceutical composition of claim 34, wherein the at least one additional serotype consists of 3, 8, 9N, 11A, 12F, 15A, 15B, 16F, 19A, 19F, 20, 22F, 23A, 23B, 31, 33F, 35B, 35F, and 38.
69. The pharmaceutical composition of claim 34, wherein the at least one additional serotype consists of 3, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 19A, 22F, 23A, 23B, 24F, 33F, 35B, and 38.
70. The pharmaceutical composition of claim 34, wherein the at least one additional serotype consists of 3, 4, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F, 35B, 35F, and 38.
71. The pharmaceutical composition of claim 34, wherein the at least one additional serotype consists of 3, 8, 9N, 11A, 12F, 15A, 15B, 16F, 19A, 19F, 20, 22F, 23A, 23B, 31, 33F, 35B, 35F, and 38.
72. A pharmaceutical composition in unit dose form comprising at least 2 immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype group, wherein one serotype is 20B and at least one additional serotype is selected from the group consisting of 1, 2, 3, 4, 5, 6A, 6B, 6C, 7C, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35B, and 38, and wherein a total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in the pharmaceutical composition in unit dose form, ranges from about 0.5 μg to about 5 μg.
73. The pharmaceutical composition of claim 72, wherein the at least one additional serotype consists of 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F, 34, and 35B.
74. The pharmaceutical composition of claim 72, wherein the at least one additional serotype is selected from the group consisting of 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F, and 35B.

Petitioner Merck Ex-1015, 1669

75. The pharmaceutical composition of claim 72, wherein the at least one additional serotype is selected from the group consisting of 6C, 15A, 15C, 16F, 23A, 23B, 24F, 31, 33F, 34, 35F, and 35B.
76. The pharmaceutical composition of claim 72, wherein the at least one additional serotype is selected from the group consisting of 6C, 15A, 15C, 16F, 23A, 23B, 24F, 31, 33F, 35F, and 35B.
77. A pharmaceutical composition comprising an immunogenic saccharide-polypeptide conjugate comprising, individually, at least two unique capsular polysaccharides, fragments thereof, or combinations thereof conjugated to a polypeptide, wherein the at least two unique capsular polysaccharides, fragments thereof, or combinations thereof are from a *Streptococcus pneumoniae* serotype selected from a group consisting of 1, 2, 3, 4, 5, 6A, 6B, 7C, 7F, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 20B, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35F, 35B, and 38.
78. The pharmaceutical composition of claim 77, wherein the at least two unique capsular polysaccharides, fragments thereof, or combinations thereof are from a *Streptococcus pneumoniae* serotype selected from a group consisting of 6C, 8, 9N, 10A, 11A, 15A, 15B, 15C, 20B, 22F, 23A, 23B, 33F, and 35B.
79. The pharmaceutical composition of claim 77, wherein the at least two unique capsular polysaccharides, fragments thereof, or combinations thereof are from a *Streptococcus pneumoniae* serotype selected from a group consisting of 6C, 8, 9N, 10A, 11A, 15A, 15B, 15C, 22F, 23A, 23B, 33F, and 35B.
80. The pharmaceutical composition of claim 77, further comprising at least one unique immunogenic saccharide-polypeptide conjugate each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 1, 2, 3, 4, 5, 6A, 6B, 7F, 7C, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 20B, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 35F, 35B, and 38.
81. The pharmaceutical composition of any one of claims 1-80, wherein the total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in the pharmaceutical composition in unit dose form, ranges from 0.5 μg to 5 μg.
82. The pharmaceutical composition of any one of claims 1-81, wherein the total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each

Petitioner Merck Ex-1015, 1670

Streptococcus pneumoniae serotype in the pharmaceutical composition in unit dose form, ranges from about 1 μg to about 4 μg.

83. The pharmaceutical composition of any one of claims 1-82, wherein the total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in the pharmaceutical composition in unit dose form, ranges from 1 μg to 4 μg.
84. The pharmaceutical composition of any one of claims 1-83, wherein the total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in the pharmaceutical composition in unit dose form, is selected from the group consisting of about 1 μg, about 2 μg, and about 4 μg.
85. The pharmaceutical composition of any one of claims 1-84, wherein the total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in the pharmaceutical composition in unit dose form, is selected from the group consisting of 1 μg, 2 μg, and 4 μg.
86. The pharmaceutical composition of any one of claims 1-85, wherein a total amount of unconjugated capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in the pharmaceutical composition in unit dose form, ranges from about 0% to about 30% w/w.
87. The pharmaceutical composition of any one of claims 1-86, wherein a total amount of unconjugated capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in the pharmaceutical composition in unit dose form, ranges from about 0% to about 20% w/w.
88. The pharmaceutical composition of any one of claims 1-87, wherein a total amount of unconjugated capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in the pharmaceutical composition in unit dose form, ranges from about 0% to about 10% w/w.
89. The pharmaceutical composition of any one of claims 29, 30, 32, 34-66, and 77-88, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 1, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

Petitioner Merck Ex-1015, 1671

90. The pharmaceutical composition of any one of claims 1-3, 28, 29, 34-66, and 72-89, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 2, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.
91. The pharmaceutical composition of any one of claims 29-90, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 3, the immunogenic saccharide- CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.
92. The pharmaceutical composition of any one of claims 26, 29-66, 70, and 72-91, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 4, the immunogenic saccharide- CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.
93. The pharmaceutical composition of any one of claims 29, 34-66 and 72-92, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide- CRM_{197} conjugate comprises serotype 5, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.
94. The pharmaceutical composition of any one of claims 29-66 and 72-93, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 6A, the immunogenic saccharide- CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

Petitioner Merck Ex-1015, 1672

95. The pharmaceutical composition of any one of claims 29, 30, 32-66 and 72-94, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide- CRM_{197} conjugate comprises serotype 6B, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.
96. The pharmaceutical composition of any one of claims 25, 26, 29-66, 69, 70, and 72-95, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 7F, the immunogenic saccharide- CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.
97. The pharmaceutical composition of any one of claims 23, 29, 34, 67, and 80-95, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 7C, the immunogenic saccharide- CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.
98. The pharmaceutical composition of any one of claims 29, 34-66, and 72-96, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide- CRM_{197} conjugate comprises serotype 9V, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.
99. The pharmaceutical composition of any one of claims 29, 30, 32-66, and 72-98, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide- CRM_{197} conjugate comprises serotype 14, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the

Petitioner Merck Ex-1015, 1673

capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

100. The pharmaceutical composition of any one of claims 29, 30, 34-66, and 72-99, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide- CRM_{197} conjugate comprises serotype 18C, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

101. The pharmaceutical composition of any one of claims 29-100, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 19A, the immunogenic saccharide- CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

102. The pharmaceutical composition of any one of claims 23, 24, 27, 29-66, 67, 68, and 71-101, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 19F, the immunogenic saccharide- CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

103. The pharmaceutical composition of any one of claims 29, 32-66, and 72-102, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide- CRM_{197} conjugate comprises serotype 23F, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

104. The pharmaceutical composition of any one of claims 1-103, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 6C, the immunogenic saccharide- CRM_{197} conjugate has a molecular

Petitioner Merck Ex-1015, 1674

weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

105. The pharmaceutical composition of any one of claims 1-6, 8-10, 12-15, 20, 23-28-32, and 34-104, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 8, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

106. The pharmaceutical composition of any one of claims 1-6, 8-10, 12-15, 20, 23-32, and 34-105, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 9N, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

107. The pharmaceutical composition of any one of claims 1-4, 6-8, 10-12, 14, 15, 20, 25, 26, 28-66, 69, 70, and 72-106, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 10A, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

108. The pharmaceutical composition of any one of claims 1-15, 20, and 23-107, wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 11A, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

109. The pharmaceutical composition of any one of claims 1-6, 8-10, 12, 14, 15, 23-32, and 34-108, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 12F, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio

Petitioner Merck Ex-1015, 1675

(w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

110. The pharmaceutical composition of any one of claims 1-109, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 15A, the immunogenic saccharide- CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

111. The pharmaceutical composition of any one of claims 1-5, 7-9, 11-15, 20, 2428-66, and 68-110, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 15B, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

112. The pharmaceutical composition of any one of claims 1-3, 7, 11, 14-22, 25, 26, 28-31, 34-66, 69, 70 and 72-111, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 15C, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

113. The pharmaceutical composition of any one of claims 1-3, 5, 9, 13-32, and 34-112, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 16F, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

114. The pharmaceutical composition of any one of claims 1-3, 18, 21, 22, 28, 29, 34-66, and 72-102, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 17F, the immunogenic saccharide-CRM_{197}

Petitioner Merck Ex-1015, 1676

conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

115. The pharmaceutical composition of any one of claims 1-3, 20-24, 26-68, and 70-114, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 20A, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

116. The pharmaceutical composition of any one of claims 1-3, 15, 18-19, and 23. 24, 26-68, and 70-115, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 20B, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

117. The pharmaceutical composition of any one of claims 1-15, 17, 20, and 23-116, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 22F, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

118. The pharmaceutical composition of any one of claims 1-117, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 23A, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

119. The pharmaceutical composition of any one of claims 1-32, and 34-118, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate

Petitioner Merck Ex-1015, 1677

comprises serotype 23B, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

120. The pharmaceutical composition of any one of claims 1-3, 5, 6, 10, 18, 19, 21, 22, 25, 26, 28-30, 32-66, 69, 70, and 72-119, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 24F, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

121. The pharmaceutical composition of any one of claims 1-3, 7, 28-31, 34-66, and 72-120, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 24B, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

122. The pharmaceutical composition of any one of claims 1-3, 18, 19, 21, 22-24, 26-29, 34-68, and 70-121, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 31, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

123. The pharmaceutical composition of any one of claims 1-15, 20, 23-32, and 34-122, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 33F, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

124. The pharmaceutical composition of any one of claims 1, 16-19, 23-29, 34-66, and 72-123, wherein the immunogenic saccharide-polypeptide conjugate comprises an

Petitioner Merck Ex-1015, 1678

immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 33B, the immunogenic saccharide- CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

125. The pharmaceutical composition of any one of claims 1, 2, 18, 19, 21-24, 26-32, 34-68, and 70-124, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide- CRM_{197} conjugate comprises serotype 35F, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

126. The pharmaceutical composition of any one of claims 1, 18, 19, 21, 22, 28, 29, 34-66, and 72-125, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 34, the immunogenic saccharide- CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

127. The pharmaceutical composition of any one of claims 1-15 and 18-126, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide- CRM_{197} conjugate comprises serotype 35B, the immunogenic saccharide- CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

128. The pharmaceutical composition of any one of claims 1-3, 7, 11, 21-31, and 33-127, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide- CRM_{197} conjugate comprises serotype 38, the immunogenic saccharide- CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

Petitioner Merck Ex-1015, 1679

129. The pharmaceutical composition of any one of claims 1-128, wherein at least one of the unique immunogenic saccharide-polypeptide conjugate comprises the capsular polysaccharide.

130. The pharmaceutical composition of any one of claims 1-129, wherein at least one of the unique immunogenic saccharide-polypeptide conjugate comprises the fragment of the capsular polysaccharide.

131. The pharmaceutical composition of claim 130, wherein the fragment of the capsular polysaccharide comprises a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, or a hexasaccharide.

132. The pharmaceutical composition of any one of claims 1-131, wherein at least one polypeptide of the plurality is an oligopeptide.

133. The pharmaceutical composition of any one of claims 1-132, wherein at least one polypeptide of the plurality comprises CRM_{197}, tetanus toxoid, a diphtheria toxoid, cholera toxoid, pertussis toxoid, inactivated or mutant pneumococcal pneumolysin, pneumococcal surface protein A, pneumococcal adhesion protein A, pneumococcal lipoprotein PsaA, C5a peptidase group A or group B streptococcus, a non-typable *H. influenzae* P4 protein, a non-typable *H. influenzae* P6 protein, *M. catarrhalis* uspA, keyhole limpet haemocyanin (KLH), OMPC from N. meningitidis, a purified protein derivative of tuberculin(PPD), protein D from *H. influenzae*, PspA, any fragment thereof, or any combination thereof.

134. The pharmaceutical composition of any one of claims 1-133, wherein the polypeptide comprises a mixture of polypeptides.

135. The pharmaceutical composition of any one of claims 1-134, wherein a toxin activity of at least one of the polypeptides of the plurality is at least partly mitigated.

136. The pharmaceutical composition of any one of claims 1-135, further comprising an adjuvant.

137. The pharmaceutical composition in unit dose form of claim 136, wherein the adjuvant is an aluminum-cation comprising adjuvant.

138. The pharmaceutical composition of claim 136, wherein the adjuvant is aluminum phosphate, aluminum sulfate, or aluminum hydroxide.

139. The pharmaceutical composition of any one of claims 1-138, wherein the pharmaceutical composition is in the form of an intramuscularly injectable composition, intradermally injectable composition, subcutaneously injectable composition, or an intranasally administrable composition.

Petitioner Merck Ex-1015, 1680

140. The pharmaceutical composition of any one of claims 1-139, further comprising a chelating agent.

141. The pharmaceutical composition of claim 140, wherein the chelating agent comprises ethylenediaminetetraacetic acid (EDTA).

142. The pharmaceutical composition of any one of claims 1-141, which is in a form of a suspension.

143. The pharmaceutical composition of any one of claims 1-142, which is in the form of a homogenous mixture or a heterogeneous mixture.

144. The pharmaceutical composition of claim 143, wherein the pharmaceutical composition is in a form of a homogenous mixture.

145. The pharmaceutical composition of any one of claims 1-144, which is contained in a pre-filled syringe.

146. The pharmaceutical composition of any one of claims 1-145, further comprising a surfactant , an emulsifier, or a combination thereof.

147. The pharmaceutical composition of claim 146, comprising the surfactant, wherein the surfactant is a polysorbate, a polymer glycol, a sorbitan ester, or any combination thereof.

148. The pharmaceutical composition of claim 147, comprising the polysorbate, wherein the polysorbate is polysorbate 80.

149. The pharmaceutical composition of claim 148, comprising the polymer glycol, wherein the polymer glycol is polyethylene glycol.

150. The pharmaceutical composition of any one of claims 1-149, further comprising a buffering agent.

151. The pharmaceutical composition of claim 150, wherein the buffering agent is a succinate buffer agent, a tris-acetate- ethylenediaminetetraacetic acid (TAE) buffering agent, a 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) buffering agent, a phosphate buffering agent, a sodium phosphate buffering agent, a potassium phosphate buffering agent, or any combination thereof.

152. The pharmaceutical composition of any one of claims 1-151, further comprising sterile water.

153. The pharmaceutical composition of any one of claims 1-152, wherein when the pharmaceutical composition is administered to a plurality of humans, the administration elicits at least one of the following side effects in less than about 10% of the plurality of humans: fatigue, headache, muscle pain, joint pain, decreased appetite, chills, or rash.

Petitioner Merck Ex-1015, 1681

154. The pharmaceutical composition of any one of claims 1-153, wherein when the pharmaceutical composition is administered intramuscularly to a human, the pharmaceutical composition elicits an immune response that lasts from about 1 week to about 30 years.

155. The pharmaceutical composition of any one of claims 1-154, wherein the unique immunogenic saccharide-polypeptide conjugate elicits an opsonophagocytic response.

156. The pharmaceutical composition of any one of claims 1-155, wherein the pharmaceutical composition retains at least about 80% of its original biological activity when stored in a sealed container for about 24 months at a temperature of about 2°C–8°C and the sealed container is stored in an atmosphere having about 50% relative humidity and 1 atm of atmospheric pressure.

157. The pharmaceutical composition of any one of claims 1-156, wherein the pharmaceutical composition is in unit dose form.

158. The pharmaceutical composition of any one of claims 1-157, further comprising a preservative.

159. The pharmaceutical composition of any one of claims 1-158, further comprising an anti-fungal compound or a salt thereof.

160. The pharmaceutical composition of any one of claims 1-159, further comprising a salt.

161. The pharmaceutical composition of any one of claims 1-160, wherein the salt is an inorganic salt.

162. The pharmaceutical composition of any one of claims 1-161, wherein the immunogenic saccharide-polypeptide conjugate is isolated and purified.

163. The pharmaceutical composition of any one of claims 1-162, which is a vaccine.

164. The pharmaceutical composition of any one of claims 1-163, wherein the immunogenic saccharide-polypeptide conjugate(s) are individually, respectively, or collectively present in an amount of about: 0.001, 0.01, 0.1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 95, or 100%, by weight, based on the weight of the composition.

165. The pharmaceutical composition of any one of claims 1-164, wherein the immunogenic saccharide-polypeptide conjugate is produced using bacteria.

166. The pharmaceutical composition of any one of claims 1-165, wherein the immunogenic saccharide-polypeptide conjugate is produced using *E. coli*.

Petitioner Merck Ex-1015, 1682

167. The pharmaceutical composition of any one of claims 1-166, wherein the immunogenic saccharide-polypeptide comprises the capsular polysaccharide at least partially embedded in the polypeptide.

168. The pharmaceutical composition of any one of claims 1-167, wherein the immunogenic saccharide-polypeptide comprises the capsular polysaccharide chemically cross-linked to the polypeptide.

169. The pharmaceutical composition of any one of claims 1-168, wherein the immunogenic saccharide-polypeptide comprises the capsular polysaccharide at least partially chemically cross-linked to the polypeptide.

170. A vaccine in unit dose form comprising at least one immunogenic saccharide-polypeptide conjugate comprising a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a *Streptococcus pneumoniae* serotype selected from a group consisting of 23A, and 23B, or a combination thereof.

171. The vaccine of claim 170, comprising at least 2 immunogenic saccharide-polypeptide conjugates each comprising a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a *Streptococcus pneumoniae* serotype group, wherein one serotype is 23A and at least one additional serotype is selected from the group consisting of 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 7C, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 20B, 22F, 23B, 24F, 24B, 31, 33F, 33B, 34, 35B, 35F, and 38, or a combination thereof.

172. The vaccine of claim 170, comprising at least 2 immunogenic saccharide-polypeptide conjugates each comprising a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a *Streptococcus pneumoniae* serotype group, wherein one serotype is 23B and at least one additional serotype is selected from the group consisting of 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 7C, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 20B, 22F, 23A, 24F, 24B, 31, 33F, 33B, 34, 35B, 35F, and 38.

173. The vaccine of any one of claims 170-172, wherein the total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in the vaccine in unit dose form, ranges from 0.5 μg to 5 μg.

Petitioner Merck Ex-1015, 1683

174. The vaccine of any one of claims 170-173, wherein the total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in the pharmaceutical composition in unit dose form, ranges from about 1 μg to about 4 μg.

175. The vaccine of any one of claims 170-174, wherein the total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in the vaccine in unit dose form, ranges from 1 μg to 4 μg.

176. The vaccine of any one of claims 170-175, wherein the total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in the vaccine in unit dose form, is selected from the group consisting of about 1 μg, about 2 μg, and about 4 μg.

177. The vaccine of any one of claims 170-176, wherein the total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in vaccine in unit dose form, is selected from the group consisting of 1 μg, 2 μg, and 4 μg.

178. The vaccine of any one of claims 170-177, wherein a total amount of unconjugated capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in the vaccine in unit dose form, ranges from about 0% to about 30% w/w.

179. The vaccine of any one of claims 170-178, wherein a total amount of unconjugated capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in the vaccine in unit dose form, ranges from about 0% to about 20% w/w.

180. The vaccine of any one of claims 170-179, wherein a total amount of unconjugated capsular polysaccharide, fragment thereof, or combination thereof, individually for each *Streptococcus pneumoniae* serotype in the vaccine in unit dose form, ranges from about 0% to about 10% w/w.

181. The vaccine of any one of claims 170-180, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 23A, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

Petitioner Merck Ex-1015, 1684

182. The vaccine of any one of claims 170-181, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 23B, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

183. The vaccine of any one of claims 171-182, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 1, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

184. The vaccine of any one of claims 171-183, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 2, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

185. The vaccine of any one of claims 171-184, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 3, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

186. The vaccine of any one of claims 171-185, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 4, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

187. The vaccine of any one of claims 171-186, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide- CRM_{197} conjugate comprises serotype 5, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and

Petitioner Merck Ex-1015, 1685

10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

188. The vaccine of any one of claims 171-187, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 6A, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

189. The vaccine of any one of claims 171-188, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 6B, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

190. The vaccine of any one of claims 171-189, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 7F, the immunogenic saccharide- CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

191. The vaccine of any one of claims 171-190, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 7C, the immunogenic saccharide- CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

192. The vaccine of any one of claims 171-191, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide- CRM_{197} conjugate comprises serotype 9V, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

193. The vaccine of any one of claims 171-192, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and

Petitioner Merck Ex-1015, 1686

wherein the immunogenic saccharide- CRM_{197} conjugate comprises serotype 14, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

194. The vaccine of any one of claims 171-193, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide- CRM_{197} conjugate comprises serotype 18C, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

195. The vaccine of any one of claims 171-194, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 19A, the immunogenic saccharide- CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

196. The vaccine of any one of claims 171-195, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 19F, the immunogenic saccharide- CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

197. The vaccine of any one of claims 171-196, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide- CRM_{197} conjugate comprises serotype 23F, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

198. The vaccine of any one of claims 171-197, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 6C, the immunogenic saccharide- CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

Petitioner Merck Ex-1015, 1687

199. The vaccine of any one of claims 171-198, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide- CRM_{197} conjugate comprises serotype 8, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

200. The vaccine of any one of claims 171-199, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide- CRM_{197} conjugate comprises serotype 9N, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

201. The vaccine of any one of claims 171-200, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 10A, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

202. The vaccine of any one of claims 171-201, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 11A, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

203. The vaccine of any one of claims 171-202, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 12F, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

204. The vaccine of any one of claims 171-203, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 15A, the immunogenic saccharide- CRM_{197} conjugate has a molecular weight of from 300 kDa and

Petitioner Merck Ex-1015, 1688

10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

205. The vaccine of any one of claims 171-204, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 15B, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

206. The vaccine of any one of claims 171-205, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 15C, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

207. The vaccine of any one of claims 171-206, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 16F, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

208. The vaccine of any one of claims 171-207, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 17F, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

209. The vaccine of any one of claims 171-208, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 20A, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

210. The vaccine of any one of claims 171-209, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and

Petitioner Merck Ex-1015, 1689

wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 20B, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

211. The vaccine of any one of claims 171-210, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 22F, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

212. The vaccine of any one of claims 171-211, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 24F, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

213. The vaccine of any one of claims 171-212, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 24B, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

214. The vaccine of any one of claims 171-213, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 31, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

215. The vaccine of any one of claims 171-214, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide-CRM_{197} conjugate comprises serotype 33F, the immunogenic saccharide-CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

Petitioner Merck Ex-1015, 1690

216. The vaccine of any one of claims 171-215, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide- CRM_{197} conjugate comprises serotype 33B, the immunogenic saccharide- CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

217. The vaccine of any one of claims 171-216, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide- CRM_{197} conjugate comprises serotype 35F, the immunogenic saccharide- CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

218. The vaccine of any one of claims 171-217, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide- CRM_{197} conjugate comprises serotype 34, the immunogenic saccharide- CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

219. The vaccine of any one of claims 171-218, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide- CRM_{197} conjugate comprises serotype 35B, the immunogenic saccharide- CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

220. The vaccine of any one of claims 171-219, wherein the immunogenic saccharide-polypeptide conjugate comprises an immunogenic saccharide-CRM_{197} conjugate, and wherein the immunogenic saccharide- CRM_{197} conjugate comprises serotype 38, the immunogenic saccharide- CRM_{197} conjugate has a molecular weight of from 300 kDa and 10,000 kDa, and wherein a ratio (w/w) of the capsular polysaccharide, fragment thereof, or combination thereof to the CRM_{197} is from 0.3 to 3.0.

221. The vaccine of any one of claims 170-220, wherein at least one of the immunogenic saccharide-polypeptide conjugate comprises the capsular polysaccharide.

222. The vaccine of any one of claims 170-221, wherein at least one of the immunogenic saccharide-polypeptide conjugates comprises the fragment of the capsular polysaccharide.

Petitioner Merck Ex-1015, 1691

223. The vaccine of claim 222, wherein the fragment of the capsular polysaccharide comprises a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, or a hexasaccharide.

224. The vaccine of any one of claims 170-223, wherein at least one polypeptide is an oligopeptide.

225. The vaccine of any one of claims 170-224, wherein at least one polypeptide comprises CRM_{197}, tetanus toxoid, a diphtheria toxoid, cholera toxoid, pertussis toxoid, inactivated or mutant pneumococcal pneumolysin, pneumococcal surface protein A, pneumococcal adhesion protein A, pneumococcal lipoprotein PsaA, C5a peptidase group A or group B streptococcus, a non-typable H. influenzae P4 protein, a non-typable H. influenzae P6 protein, M. catarrhalis uspA, keyhole limpet haemocyanin (KLH), OMPC from N. meningitidis, a purified protein derivative of tuberculin(PPD), protein D from H. influenzae, PspA, any fragment thereof, or any combination thereof.

226. The vaccine of any one of claims 170-225, wherein the polypeptide comprises a mixture of polypeptides.

227. The vaccine of any one of claims 1-226, wherein a toxin activity of at least one of the polypeptides is at least partly mitigated.

228. The vaccine of any one of claims 1-227, further comprising an adjuvant.

229. The vaccine in unit dose form of claim 228, wherein the adjuvant is an aluminum-cation comprising adjuvant.

230. The vaccine of claim 228, wherein the adjuvant is aluminum phosphate, aluminum sulfate, or aluminum hydroxide.

231. The vaccine or pharmaceutical composition of any one of claims 1-230, wherein the vaccine is in the form of an intramuscularly injectable composition, intradermally injectable composition, subcutaneously injectable composition, or an intranasally administrable composition.

232. The vaccine or pharmaceutical composition of any one of claims 1-231, further comprising a chelating agent.

233. The vaccine or pharmaceutical composition of claim 232, wherein the chelating agent comprises ethylenediaminetetraacetic acid (EDTA).

234. The vaccine or pharmaceutical composition of any one of claims 1-233, which is in a form of a suspension.

235. The vaccine or pharmaceutical composition of any one of claims 1-234, which is in the form of a homogenous mixture or a heterogeneous mixture.

Petitioner Merck Ex-1015, 1692

236. The vaccine or pharmaceutical composition of claim 235, wherein the vaccine is in a form of a homogenous mixture.

237. The vaccine or pharmaceutical composition of any one of claims 1-236, which is contained in a pre-filled syringe.

238. The vaccine or pharmaceutical composition of any one of claims 1-237, further comprising a surfactant, an emulsifier, or a combination thereof.

239. The vaccine or pharmaceutical composition of claim 238, comprising the surfactant, wherein the surfactant is a polysorbate, a polymer glycol, a sorbitan ester, or any combination thereof.

240. The vaccine or pharmaceutical composition of claim 239, comprising the polysorbate, wherein the polysorbate is polysorbate 80.

241. The vaccine or pharmaceutical composition of claim 240, comprising the polymer glycol, wherein the polymer glycol is polyethylene glycol.

242. The vaccine or pharmaceutical composition of any one of claims 1-241, further comprising a buffering agent.

243. The vaccine or pharmaceutical composition of claim 242, wherein the buffering agent is a succinate buffer agent, a tris-acetate- ethylenediaminetetraacetic acid (TAE) buffering agent, a 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) buffering agent, a phosphate buffering agent, a sodium phosphate buffering agent, a potassium phosphate buffering agent, or any combination thereof.

244. The vaccine or pharmaceutical composition of any one of claims 1-243, further comprising sterile water.

245. The vaccine or pharmaceutical composition of any one of claims 1-244, wherein when the vaccine is administered to a plurality of humans, the administration elicits at least one of the following side effects in less than about 10% of the plurality of humans: fatigue, headache, muscle pain, joint pain, decreased appetite, chills, or rash.

246. The vaccine or pharmaceutical composition of any one of claims 1-245, wherein when the vaccine is administered intramuscularly to a human, the pharmaceutical composition elicits an immune response that lasts from about 1 week to about 30 years.

247. The vaccine or pharmaceutical composition of any one of claims 1-246, wherein the unique immunogenic saccharide-polypeptide conjugate elicits an opsonophagocytic response.

248. The vaccine or pharmaceutical composition of any one of claims 1-247, wherein the vaccine retains at least about 80% of its original biological activity when stored in a

Petitioner Merck Ex-1015, 1693

sealed container for about 24 months at a temperature of about 2°C–8°C and the sealed container is stored in an atmosphere having about 50% relative humidity and 1 atm of atmospheric pressure.

249. The vaccine or pharmaceutical composition of any one of claims 1-248, wherein the vaccine is in unit dose form.

250. The vaccine or pharmaceutical composition of any one of claims 1-249, further comprising a preservative.

251. The vaccine or pharmaceutical composition of any one of claims 1-250, further comprising an anti-fungal compound or a salt thereof.

252. The vaccine or pharmaceutical composition of any one of claims 1-251, further comprising a salt.

253. The vaccine or pharmaceutical composition of any one of claims 1-252, wherein the salt is an inorganic salt.

254. The vaccine or pharmaceutical composition of any one of claims 1-253, wherein the immunogenic saccharide-polypeptide conjugate is isolated and purified.

255. The vaccine or pharmaceutical composition of any one of claims 1-254, which is a vaccine.

256. The vaccine or pharmaceutical composition of any one of claims 1-255, wherein the immunogenic saccharide-polypeptide conjugate(s) are individually, respectively, or collectively present in an amount of about: 0.001, 0.01, 0.1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 95, or 100%, by weight, based on the weight of the composition.

257. The vaccine or pharmaceutical composition of any one of claims 1-256, wherein the immunogenic saccharide-polypeptide conjugate is produced using bacteria.

258. The vaccine or pharmaceutical composition of any one of claims 1-257, wherein the immunogenic saccharide-polypeptide conjugate is produced using E. coli.

259. The vaccine or pharmaceutical composition of any one of claims 1-258, wherein the immunogenic saccharide-polypeptide comprises the capsular polysaccharide at least partially embedded in the polypeptide.

260. The vaccine or pharmaceutical composition of any one of claims 1-259, wherein the immunogenic saccharide-polypeptide comprises the capsular polysaccharide chemically cross-linked to the polypeptide.

Petitioner Merck Ex-1015, 1694

261. The vaccine or pharmaceutical composition of any one of claims 1-260, wherein the immunogenic saccharide-polypeptide comprises the capsular polysaccharide at least partially chemically cross-linked to the polypeptide

262. A method comprising administering to a subject a first composition, wherein the first composition is the pharmaceutical composition of any one of claims 1-169 or the vaccine of any one of 170-262.

263. The method of claim 262, wherein the administering to the subject the first composition occurs at least about four weeks before or at least about four weeks after an administration of a second composition comprising an immunogenic saccharide-polypeptide conjugate comprising a second polypeptide to the subject, wherein the second polypeptide has at least about 70% length homology, at least about 70% sequence homology, or a combination thereof, to the polypeptide of the first composition.

264. The method of claim 263, wherein the second composition comprises an immunogenic saccharide-polypeptide conjugate comprising a capsular polysaccharide or fragment of the capsular polysaccharide from a serotype of *Streptococcus pneumoniae* conjugated to the second polypeptide.

265. The method of any one of claims 263-264, wherein the second composition comprises the pharmaceutical composition of any one of claims 1-169 or the vaccine of any one of claims 170-262, wherein the serotype of the first composition and the serotype of the second composition are distinct.

266. The method of any one of claims 263-265, wherein the second composition comprises a plurality of at least 13 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.

267. The method of any one of claims 263-266, wherein the second composition comprises at least 1 unique immunogenic saccharide-polypeptide conjugate comprising each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F.

Petitioner Merck Ex-1015, 1695

268. The method of any one claims 263-267, wherein the second composition comprising at least 1 unique immunogenic saccharide-polypeptide conjugate comprising each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype selected from a group consisting of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 20B, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 35F, 35B, and 38, wherein the serotype of the first composition and the serotype of the second composition are distinct.

269. The method of claim 268, wherein the immunogenic saccharide polypeptide conjugate of the second composition comprises a capsular polysaccharide.

270. The method of claim 269, wherein the immunogenic saccharide polypeptide conjugate of the second composition comprises a fragment of the capsular polysaccharide.

271. The method of claim 270, wherein the fragment of the capsular polysaccharide of the second composition comprises a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, or a hexasaccharide.

272. The method of any one of claims 263-271, wherein the second polypeptide is an oligopeptide.

273. The method of any one of claims 263-272, wherein the second polypeptide comprises CRM_{197}, tetanus toxoid, a diphtheria toxoid, cholera toxoid, pertussis toxoid, inactivated or mutant pneumococcal pneumolysin, pneumococcal surface protein A, pneumococcal adhesion protein A, pneumococcal lipoprotein PsaA, C5a peptidase group A or group B streptococcus, a non-typable *H. influenzae* P4 protein, a non-typable *H. influenzae* P6 protein, *M. catarrhalis* uspA, keyhole limpet haemocyanin (KLH), OMPC from N. meningitidis, a purified protein derivative of tuberculin(PPD), protein D from *H. influenzae*, PspA, any fragment thereof, or any combination thereof.

274. The method of any one of claims 263-273, wherein a toxin activity of the second polypeptide is at least partly mitigated.

275. The method of any one of claims 263-274, wherein the second composition further comprises an adjuvant.

276. The method of claim 275, wherein the adjuvant is an aluminum-cation comprising adjuvant.

277. The method of claim 276, wherein the adjuvant is aluminum phosphate, aluminum sulfate, or aluminum hydroxide.

Petitioner Merck Ex-1015, 1696

278. The method any one of claims 263-277, wherein the second composition is in the form of an intramuscularly injectable composition, intradermally injectable composition, subcutaneously injectable composition, or an intranasally administrable composition.

279. The method of any one of claims 263-278, wherein the second composition is in unit dose form.

280. The method of any one of claims 263-279, wherein the second composition further comprises a chelating agent.

281. The method of claim 280, wherein the chelating agent is ethylenediaminetetraacetic acid (EDTA).

282. The method any one of claims 263-281, wherein the second composition is in a form of a suspension.

283. The method any one of claims 263-282, wherein the second composition is in a form of a homogenous mixture or a heterogeneous mixture.

284. The method any one of claims 263-283, wherein the second composition is in the form of a homogenous mixture.

285. The method any one of claims 263-284, wherein the second composition is contained in a pre-filled syringe.

286. The method any one of claims 263-285, wherein the second composition further comprises a surfactant, an emulsifier, or a combination thereof.

287. The method claim 286, wherein the second composition further comprises the surfactant, wherein the surfactant is polysorbate, polymer glycol, a sorbitan ester, or any combination thereof.

288. The method of claim 287, wherein the second composition comprises the polysorbate, wherein the polysorbate is polysorbate 80.

289. The method of claim 288, wherein the second composition comprises the polymer glycol wherein the polymer glycol is polyethylene glycol.

290. The method any one of claims 263-289, wherein the second composition further comprises a buffering agent.

291. The method of claim 290, wherein the buffering agent is a succinate buffer agent, a tris-acetate- ethylenediaminetetraacetic acid (TAE) buffering agent, a 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) buffering agent, a phosphate buffering agent, a sodium phosphate buffering agent, a potassium phosphate buffering agent, or any combination thereof.

Petitioner Merck Ex-1015, 1697

292. The method any one of claims 263-291, wherein the second composition further comprises sterile water.

293. The method any one of claims 263-292, wherein when the second composition is administered to a plurality of humans, the administration elicits at least one of the following side effects in less than about 10% of the plurality of humans: fatigue, headache, muscle pain, joint pain, decreased appetite, chills, or rash.

294. The method any one of claims 263-293, wherein when the second composition is administered intramuscularly to a human, the pharmaceutical composition elicits an immune response that lasts from about 1 week to about 30 years.

295. The method any one of claims 263-294, wherein when the unique immunogenic saccharide-polypeptide conjugate of the second composition elicits an opsonophagocytic response.

296. The method of any one of claims 263-295, wherein when the second composition is administered intramuscularly, the second composition elicits an immune response that lasts from about 1 week to about 30 years.

297. The method of any one of claims 263-296, wherein second composition retains at least about 80% of its original biological activity when stored in a sealed container for about 24 months at a temperature of about 2°C–8°C and the sealed container is stored in an atmosphere having about 50% relative humidity and 1 atm of atmospheric pressure.

298. The method of any one of claims 263-297, wherein the second composition further comprises a preservative.

299. The method of any one of claims 263-298, wherein the second composition further comprises an anti-fungal compound or a salt thereof.

300. The method of any one of claims 263-299, wherein the second composition further comprises a salt.

301. The method of claim 300, wherein the salt is an inorganic salt.

302. The method of any one of claims 263-301, wherein the immunogenic saccharide-polypeptide conjugate of the second composition is isolated and purified.

303. The method of any one of claims 263-302, wherein the second composition is a vaccine.

304. The method of any one of claims 263-303, which is a method of vaccinating a subject.

305. The method of claim 304, wherein the subject is a human.

306. The method of any one of claims 304-305, wherein the subject or human is a subject or human in need thereof.

Petitioner Merck Ex-1015, 1698

307. The method of any one of claims 263-306, wherein the immunogenic saccharide-polypeptide conjugates of the second composition are individually, respectively, or collectively present in an amount of about: 0.001, 0.01, 0.1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 95, or 100%, by weight, based on the weight of the composition.

308. The method of any one of claims 263-307, which when conducted, does not result in more than about: 50%, 40%, 30%, 20%, 10%, 5%, 4%, 3%, 2%, or 1% suppression of an immunity conveyed by a first vaccine containing an immunogenic saccharide-polypeptide conjugate, as measured by antibody response to the saccharide of the immunogenic saccharide-polypeptide conjugate of the second composition, wherein the antibody response is measured by measuring antibody titers.

309. The method of any one of claims 263-308, wherein the immunogenic saccharide-polypeptide conjugate of the second composition is produced using bacteria.

310. The method of any one of claims 263-309, wherein the immunogenic saccharide-polypeptide conjugate of the second composition is produced using *E. coli*.

311. The method of any one of claims 263-310, wherein the immunogenic saccharide-polypeptide of the second composition comprises the capsular polysaccharide at least partially embedded in the polypeptide.

312. The method of any one of claims 263-311, wherein the immunogenic saccharide-polypeptide of the second composition comprises the capsular polysaccharide chemically cross-linked to the polypeptide.

313. The method of any one of claims 263-312, wherein the immunogenic saccharide-polypeptide of the second composition comprises the capsular polysaccharide at least partially chemically cross-linked to the polypeptide.

314. A method comprising:

administering a second immunogenic saccharide-polypeptide conjugate composition to a subject at least four weeks after a first immunogenic saccharide-polypeptide conjugate composition was administered;

wherein the second immunogenic saccharide-polypeptide conjugate composition comprises a first polypeptide that has at least about 70% length homology, at least about 70% sequence homology, or a combination thereof, to a second polypeptide of the second immunogenic saccharide-polypeptide conjugate composition;

Petitioner Merck Ex-1015, 1699

and wherein the first immunogenic saccharide-polypeptide conjugate composition comprises a first serotype;

wherein the second immunogenic saccharide-polypeptide conjugate composition comprises a second serotype, and wherein the first serotype and the second serotype are different;

wherein the first immunogenic saccharide-polypeptide conjugate composition or the second immunogenic saccharide-polypeptide conjugate composition is the vaccine of any one of claims 170-261.

315. The method of claim 314, wherein the first immunogenic saccharide-polypeptide conjugate composition is the pharmaceutical composition of any one of claims 1-158 wherein the first immunogenic saccharide-polypeptide conjugate composition and the second immunogenic saccharide-polypeptide conjugate composition are distinct.

316. The method of any one of claims 314-315, wherein the second immunogenic saccharide-polypeptide conjugate composition is the pharmaceutical composition of any one of claims 1-169 wherein the first immunogenic saccharide-polypeptide conjugate composition and the second immunogenic saccharide-polypeptide conjugate composition are distinct.

317. The method of any one of claims 314-316, wherein the first immunogenic saccharide-polypeptide conjugate composition comprises a capsular polysaccharide.

318. The method of any one of claims 314-317, wherein the first immunogenic saccharide-polypeptide conjugate composition comprises a fragment of the capsular polysaccharide.

319. The method of any one of claims 314-318, wherein the fragment of the capsular polysaccharide comprises a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, or a hexasaccharide.

320. The method of any one of claims 314-319, wherein the first polypeptide is an oligopeptide.

321. The method of any one of claims 314-320, wherein the second polypeptide is an oligopeptide.

322. The method of any one of claims 314-321, wherein the first polypeptide comprises CRM_{197}, tetanus toxoid, a diphtheria toxoid, cholera toxoid, pertussis toxoid, inactivated or mutant pneumococcal pneumolysin, pneumococcal surface protein A, pneumococcal adhesion protein A, pneumococcal lipoprotein PsaA, C5a peptidase group A or group B streptococcus, a non-typable *H. influenzae* P4 protein, a non-typable *H. influenzae* P6 protein, *M. catarrhalis* uspA, keyhole limpet haemocyanin (KLH), OMPC from N.

Petitioner Merck Ex-1015, 1700

meningitidis, a purified protein derivative of tuberculin(PPD), protein D from *H. influenzae*, any fragment thereof, or any combination thereof.

323. The method of any one of claims 314-322, wherein a toxin activity of the first polypeptide is at least partly mitigated.

324. The method of any one of claims 314-323, wherein the second polypeptide comprises CRM_{197}, tetanus toxoid, a diphtheria toxoid, cholera toxoid, pertussis toxoid, inactivated or mutant pneumococcal pneumolysin, pneumococcal surface protein A, pneumococcal adhesion protein A, pneumococcal lipoprotein PsaA, C5a peptidase group A or group B streptococcus, a non-typable *H. influenzae* P4 protein, a non-typable *H. influenzae* P6 protein, *M. catarrhalis* uspA, keyhole limpet haemocyanin (KLH), OMPC from N. meningitidis, a purified protein derivative of tuberculin(PPD), protein D from *H. influenzae*, PspA, any fragment thereof, or any combination thereof.

325. The method of any one of claims 314-324, wherein a toxin activity of the second polypeptide is at least partly mitigated.

326. The method of any one of claims 314-325, wherein the first serotype is from a same bacteria as the second serotype.

327. The method of any one of claims 314-326, wherein the first serotype is from a different bacteria than the second serotype.

328. The method of any one of claims 314-327, wherein the first serotype is from *Streptococcus pneumoniae*.

329. The method of any one of claims 314-328, wherein the first serotype is from *Neisseria meningitidis*, *Salmonella enterica*, or *Haemophilus influenzae*.

330. The method of any one of claims 314-329, wherein the second serotype is from *Streptococcus pneumoniae*.

331. The method of any one of claims 314-330, wherein the second bacteria is from *Neisseria meningitidis*, *Salmonella enterica*, or *Haemophilus influenzae*.

332. The method of any one of claims 314-331, wherein the first serotype comprises at least one of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, or 23F from *Streptococcus pneumoniae*, and the second serotype comprises at least eight of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 22F, 23A, 23B, 24F, 24B, 31, 33F, 35F, 35B, or 38 from *Streptococcus pneumoniae*.

333. The method of any one of claims 314-331, wherein the first serotype comprises at least one of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, or 23F from *Streptococcus pneumoniae*, and the second serotype comprises at least eight of 2, 6C, 8, 9N, 10A, 11A,

Petitioner Merck Ex-1015, 1701

12F, 15A, 15B, 15C, 16F, 17F, 20A, 20B, 22F, 23A, 23B, 24F, 24B, 31, 33F, 35F, 35B, or 38 from *Streptococcus pneumoniae*.

334. The method of any one of claims 314-331, wherein the first serotype comprises at least eight of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 20B, 22F, 23A, 23B, 24F, 24B, 31, 33F, 35F, 35B, and 38 from *Streptococcus pneumoniae*, and the second serotype comprises at least one of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*.

335. The method of any one of claims 314-331, wherein the first serotype comprises at least eight of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 22F, 23A, 23B, 24F, 24B, 31, 33F, 35F, 35B, and 38 from *Streptococcus pneumoniae*, and the second serotype comprises at least one of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*.

336. The method of any one of claims 314-331, wherein the first serotype comprises 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*, and the second serotype comprises 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B from *Streptococcus pneumoniae*.

337. The method of any one of claims 314-331, wherein the first serotype comprises 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*, and the second serotype comprises 6C, 15A, 16F, 23A, 23B, and 35B from *Streptococcus pneumoniae*.

338. The method of any one of claims 314-331, wherein the first serotype comprises 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*, and the second serotype comprises 6C, 9N, 15A, 15C, 16F, 17F, 20B, 23A, 23B, 24F, 31, 33F, 34, 35F, and 35B from *Streptococcus pneumoniae*.

339. The method of any one of claims 314-331, wherein the first serotype comprises 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*, and the second serotype comprises 6C, 15A, 15C, 16F, 20B, 23A, 23B, 24F, 31, 33F, 34, 35F, and 35B from *Streptococcus pneumoniae*.

340. The method of any one of claims 314-331, wherein the first serotype comprises 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*, and the second serotype comprises 6C, 8, 9N, 10A, 11A, 15A, 15B, 15C, 16F, 20A, 22F, 23A, 23B, 33F, and 35B from *Streptococcus pneumoniae*.

341. The method of any one of claims 314-331, wherein the first serotype comprises 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B from *Streptococcus pneumoniae*, and the second

Petitioner Merck Ex-1015, 1702

serotype comprises 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*.

342. The method of any one of claims 314-331, wherein the first serotype comprises 6C, 15A, 16F, 23A, 23B, and 35B from *Streptococcus pneumoniae*, and the second serotype comprises 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*.

343. The method of any one of claims 314-331, wherein the first serotype comprises 6C, 9N, 15A, 15C, 16F, 17F, 20B, 23A, 23B, 24F, 31, 33F, 34, 35F, and 35B from *Streptococcus pneumoniae*, and the second serotype comprises 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*.

344. The method of any one of claims 314-331, wherein the first serotype comprises 6C, 15A, 15C, 16F, 20B, 23A, 23B, 24F, 31, 33F, 34, 35F, and 35B from *Streptococcus pneumoniae*, and the second serotype comprises 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*.

345. The method of any one of claims 314-331, wherein the first serotype comprises 6C, 8, 9N, 10A, 11A, 15A, 15B, 15C, 16F, 20A, 22F, 23A, 23B, 33F, and 35B from *Streptococcus pneumoniae*, and the second serotype comprises 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*.

346. The method of any one of claims 314-331, wherein the first serotype comprises at least one of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, or 23F from *Streptococcus pneumoniae*, and the second serotype comprises at least eight of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 35F, 35B, 38, and Serogroup 20 (comprising serotypes 20A and 20B) from *Streptococcus pneumoniae*.

347. The method of any one of claims 314-331, wherein the first serotype comprises at least one of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, or 23F from *Streptococcus pneumoniae*, and the second serotype comprises at least eight of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 35F, 35B, 38, and Serogroup 20 (comprising serotypes 20A and 20B) from *Streptococcus pneumoniae*.

348. The method of any one of claims 314-331, wherein the first serotype comprises at least eight of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 35F, 35B, 38, and Serogroup 20 (comprising serotypes 20A and 20B) from *Streptococcus pneumoniae*, and the second serotype comprises at least one of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*.

Petitioner Merck Ex-1015, 1703

349. The method of any one of claims 314-331, wherein the first serotype comprises at least eight of 2, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 22F, 23A, 23B, 24F, 24B, 31, 33F, 35F, 35B, 38, and Serogroup 20 (comprising serotypes 20A and 20B) from *Streptococcus pneumoniae*, and the second serotype comprises at least one of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F from *Streptococcus pneumoniae*.

350. The method of any one of claims 314-349, wherein the first immunogenic saccharide-polypeptide conjugate composition further comprises an adjuvant.

351. The method of claim 350, wherein the adjuvant is an aluminum-cation comprising adjuvant.

352. The method of claim 351, wherein the adjuvant is aluminum phosphate, aluminum sulfate, or aluminum hydroxide.

353. The method of any one of claims 314-352, wherein the first immunogenic saccharide-polypeptide conjugate composition is in the form of an intramuscularly injectable composition, intradermally injectable composition, subcutaneously injectable composition, or an intranasally administrable composition.

354. The method of any one of claims 314-353, wherein the first immunogenic saccharide-polypeptide conjugate composition further comprises a chelating agent.

355. The method of claim 354, wherein the chelating agent is ethylenediaminetetraacetic acid (EDTA).

356. The method of any one of claims 314-355, wherein the first immunogenic saccharide-polypeptide conjugate composition is in a form of a suspension.

357. The method of any one of claims 302-356, wherein the first immunogenic saccharide-polypeptide conjugate composition is in a form of a homogenous mixture or a heterogeneous mixture.

358. The method of any one of claims 314-357, wherein the first immunogenic saccharide-polypeptide conjugate composition is in a form of a homogenous mixture.

359. The method of any one of claims 314-358, wherein the first immunogenic saccharide-polypeptide conjugate composition is contained in a pre-filled syringe.

360. The method of any one of claims 314-359, wherein the first immunogenic saccharide-polypeptide conjugate composition further comprises a surfactant or emulsifier, or a combination thereof.

361. The method of claim 360, wherein the first immunogenic saccharide-polypeptide composition comprises the surfactant wherein the surfactant is a polysorbate, a polymer glycol, a sorbitan ester, or any combination thereof.

Petitioner Merck Ex-1015, 1704

362. The method of claim 361, wherein the first immunogenic saccharide-polypeptide composition comprises the polysorbate wherein the polysorbate is polysorbate 80.

363. The method claim 361, wherein the first immunogenic saccharide-polypeptide composition comprises the polymer glycol wherein the polymer glycol is polyethylene glycol.

364. The method of any one of claims 314-363, wherein the first immunogenic saccharide-polypeptide conjugate composition further comprises a buffering agent.

365. The method of claim 364, wherein the buffering agent is a succinate buffer agent, a tris-acetate- ethylenediaminetetraacetic acid (TAE) buffering agent, a 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) buffering agent, a phosphate buffering agent, a sodium phosphate buffering agent, a potassium phosphate buffering agent, or any combination thereof.

366. The method of any one of claims 314-365, wherein the first immunogenic saccharide-polypeptide conjugate composition further comprises sterile water.

367. The method of any one of claims 314-366, wherein when the first immunogenic saccharide-polypeptide conjugate composition is administered to a plurality of humans, the administration elicits at least one of the following side effects in less than about 10% of the plurality of humans: fatigue, headache, muscle pain, joint pain, decreased appetite, chills, or rash.

368. The method of any one of claims 314-367, wherein when first immunogenic saccharide-polypeptide conjugate composition is administered intramuscularly to a human, the first immunogenic saccharide-polypeptide conjugate composition elicits an immune response that lasts from about 1 week to about 30 years.

369. The method any one of claims 314-368, wherein when first immunogenic saccharide-polypeptide conjugate composition elicits an opsonophagocytic response.

370. The method of any one of claims 314-369, wherein the first immunogenic saccharide-polypeptide conjugate composition retains at least about 80% of its original biological activity when stored in a sealed container for about 24 months at a temperature of about 2°C–8°C and the sealed container is stored in an atmosphere having about 50% relative humidity and 1 atm of atmospheric pressure.

371. The method of any one of claims 314-370, wherein the second immunogenic saccharide-polypeptide conjugate composition further comprises an adjuvant.

372. The method of claim 371, wherein the adjuvant is an aluminum-cation comprising adjuvant.

Petitioner Merck Ex-1015, 1705

373. The method of claim 372, wherein the adjuvant is aluminum phosphate, aluminum sulfate, or aluminum hydroxide.

374. The method of any one of claims 314-373, wherein the second immunogenic saccharide-polypeptide conjugate composition is in a form of an intramuscularly injectable composition, intradermally injectable composition, subcutaneously injectable composition, or an intranasally administrable composition.

375. The method of any one of claims 314-374, wherein the second immunogenic saccharide-polypeptide conjugate composition further comprises a chelating agent.

376. The method of claim 375, wherein the chelating agent is ethylenediaminetetraacetic acid (EDTA).

377. The method of any one of claims 314-376, wherein the second immunogenic saccharide-polypeptide conjugate composition is in a form of a suspension.

378. The method of any one of claims 314-377, wherein the second immunogenic saccharide-polypeptide conjugate composition is in a form of a homogenous mixture or a heterogeneous mixture.

379. The method of claim 378, wherein the second immunogenic saccharide-polypeptide conjugate composition is in a form of a homogenous mixture.

380. The method of any one of claims 314-379, wherein the second immunogenic saccharide-polypeptide conjugate composition is contained in a pre-filled syringe.

381. The method of any one of claims 314-380, wherein the second immunogenic saccharide-polypeptide conjugate composition further comprises a surfactant, an emulsifier, or a combination thereof.

382. The method of claim 381, wherein the second immunogenic saccharide-polypeptide conjugate composition comprises the surfactant wherein the surfactant is polysorbate, polymer glycol, a sorbitan ester, or any combination thereof.

383. The method of claim 382, wherein the second immunogenic saccharide-polypeptide conjugate composition comprises the polysorbate wherein the polysorbate is polysorbate 80.

384. The method of claim 383, wherein the second immunogenic saccharide-polypeptide conjugate composition comprises the polymer glycol wherein the polymer glycol is polyethylene glycol.

385. The method of any one of claims 314-384, wherein the second immunogenic saccharide-polypeptide conjugate composition further comprises a buffering agent.

Petitioner Merck Ex-1015, 1706

386. The method of claim 385, wherein the buffering agent is a succinate buffer agent, a tris-acetate- ethylenediaminetetraacetic acid (TAE) buffering agent, a 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) buffering agent, a phosphate buffering agent, a sodium phosphate buffering agent, a potassium phosphate buffering agent, or any combination thereof.

387. The method of any one of claims 314-386, wherein the second immunogenic saccharide-polypeptide conjugate composition further comprises sterile water.

388. The method of any one of claims 314-387, wherein when the second immunogenic saccharide-polypeptide conjugate composition is administered to a plurality of humans, the administration elicits at least one of the following side effects in less than about 10% of the plurality of humans: fatigue, headache, muscle pain, joint pain, decreased appetite, chills, or rash.

389. The method of any one of claims 314-388, wherein when the second immunogenic saccharide-polypeptide conjugate composition is administered intramuscularly to a human, the second immunogenic saccharide-polypeptide conjugate composition elicits an immune response that lasts from about 1 week to about 30 years.

390. The method of any one of claims 314-389, wherein when the second immunogenic saccharide-polypeptide conjugate composition elicits an opsonophagocytic response.

391. The method of any one of claims 314-390, wherein the second immunogenic saccharide-polypeptide conjugate composition retains at least about 80% of its original biological activity when stored in a sealed container for about 24 months at a temperature of about 2°C–8°C and the sealed container is stored in an atmosphere having about 50% relative humidity and 1 atm of atmospheric pressure.

392. The method of any one of claims 314-391, wherein the first immunogenic saccharide-polypeptide conjugate composition and/or the second immunogenic saccharide polypeptide composition is in unit dose form.

393. The method of any one of claims 314-392, wherein the first immunogenic saccharide-polypeptide conjugate composition and/or the second immunogenic saccharide polypeptide composition further comprises a preservative.

394. The method of any one of claims 314-393, wherein the first immunogenic saccharide-polypeptide conjugate composition and/or the second immunogenic saccharide polypeptide composition further comprises an anti-fungal compound or a salt thereof.

Petitioner Merck Ex-1015, 1707

395. The method of any one of claims 314-394, wherein the first immunogenic saccharide-polypeptide conjugate composition and/or the second immunogenic saccharide polypeptide composition further comprise a salt.

396. The method of claim 395, wherein the salt is an inorganic salt.

397. The method of any one of claims 314-396, wherein the first immunogenic saccharide-polypeptide conjugate composition and/or the second immunogenic saccharide polypeptide composition is isolated and purified.

398. The method of any one of claims 314-397, wherein the first immunogenic saccharide-polypeptide conjugate composition and/or the second immunogenic saccharide polypeptide composition which is a vaccine.

399. The method of any one of claims 314-398, which is a method of vaccinating a subject.

400. The method of any claim 399, wherein the subject is a human.

401. The method of any one of claims 399-400, wherein the subject or human is a subject or human in need thereof.

402. The method of any one of claims 314-401, wherein the first immunogenic saccharide-polypeptide conjugate composition and/or the second immunogenic saccharide polypeptide composition comprise immunogenic saccharide-polypeptide conjugate(s) individually, respectively, or collectively present in an amount of about: 0.001, 0.01, 0.1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 95, or 100%, by weight, based on the weight of the composition.

403. The method of any one of claims 314-402, wherein administration of the second immunogenic saccharide-polypeptide conjugate composition does not result in more than about: 50%, 40%, 30%, 20%, 10%, 5%, 4%, 3%, 2%, or 1% suppression of an immunity as measured by antibody response to the saccharide of the immunogenic saccharide-polypeptide conjugate, wherein the antibody response is measured by measuring antibody titers.

404. The method of any one of claims 314-403, wherein the first immunogenic saccharide-polypeptide conjugate composition and/or the second immunogenic saccharide polypeptide composition is produced using a bacteria.

405. The method of any one of claims 314-404, wherein the first immunogenic saccharide-polypeptide conjugate composition and/or the second immunogenic saccharide polypeptide composition is produced using *E. coli*.

406. The method of any one of claims 314-405, wherein the first immunogenic saccharide-polypeptide conjugate composition and/or the second immunogenic saccharide

Petitioner Merck Ex-1015, 1708

polypeptide composition comprises the capsular polysaccharide at least partially embedded in the polypeptide.

407. The method of any one of claims 314-406, wherein the first immunogenic saccharide-polypeptide conjugate composition and/or the second immunogenic saccharide polypeptide composition comprises the capsular polysaccharide chemically cross-linked to the polypeptide.

408. The method of any one of claims 314-407, wherein the first immunogenic saccharide-polypeptide conjugate composition and/or the second immunogenic saccharide polypeptide composition comprises the capsular polysaccharide at least partially chemically cross-linked to the polypeptide.

409. A method of making a composition comprising:

contacting the immunogenic saccharide-polypeptide conjugate of any one of claims 1-261 with an excipient, an adjuvant, or any combination thereof.

410. The method of claim 409, wherein the composition is injectable or intranasally administrable.

411. The method claim 410, comprising contacting with the adjuvant, wherein the adjuvant is aluminum phosphate, aluminum sulfate, or aluminum hydroxide.

412. The method of any one of claims 409-411, wherein the composition is in the form of an intramuscularly injectable composition.

413. The method of any one of claims 409-412, further comprising contacting the composition with a chelating agent.

414. The method of claim 413, further comprising contacting the composition with a chelating agent, wherein the chelating agent is ethylenediaminetetraacetic acid (EDTA).

415. The method of any one of claims 409-414, wherein the composition is in a form of a suspension.

416. The method of any one of claims 409-415, wherein the composition is in a form of a homogenous mixture or a heterogeneous mixture.

417. The method of claim 416, wherein the composition is in a form of a homogenous mixture.

418. The method of any one of claims 409-417, wherein the composition is contained in a pre-filled syringe.

419. The method of any one of claims 409-418, further comprising contacting the composition with a surfactant, an emulsifier, or a combination thereof.

Petitioner Merck Ex-1015, 1709

420. The method of claim 419, comprising contacting the composition with the surfactant, wherein the surfactant is a polysorbate, a polymer glycol, a sorbitan ester, or any combination thereof.

421. The method of claim 420, comprising contacting the composition with the polysorbate, wherein the polysorbate is polysorbate 80.

422. The method of claim 421, comprising contacting the composition with the polymer glycol, wherein the polymer glycol is polyethylene glycol.

423. The method of any one of claims 409-422, further comprising contacting the composition with a buffering agent.

424. The method of claim 423, wherein the buffering agent is a succinate buffer agent, a tris-acetate- ethylenediaminetetraacetic acid (TAE) buffering agent, a 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) buffering agent, a phosphate buffering agent, a sodium phosphate buffering agent, a potassium phosphate buffering agent, or any combination thereof.

425. The method of any one of claims 409-424, further comprising contacting the composition with sterile water.

426. The method of any one of claims 409-425, wherein when the composition is administered to a plurality of humans, the administration elicits at least one of the following side effects in less than about 10% of the plurality of humans: fatigue, headache, muscle pain, joint pain, decreased appetite, chills, or rash.

427. The method of any one of claims 409-426, wherein when the composition is administered intramuscularly to a human, the composition elicits an immune response that lasts from about 1 week to about 30 years.

428. The method of any one of claims 409-427, wherein the immunogenic saccharide-polypeptide conjugate elicits an opsonophagocytic response.

429. The method of any one of claims 409-428, wherein the composition retains at least about 80% of its original biological activity when stored in a sealed container for about 24 months at a temperature of about 2°C–8°C and the sealed container is stored in an atmosphere having about 50% relative humidity and 1 atm of atmospheric pressure.

430. The method of any one of claims 409-429, wherein the composition further comprises a preservative.

431. The method of any one of claims 409-430, wherein the composition further comprises an anti-fungal compound or a salt thereof.

Petitioner Merck Ex-1015, 1710

432. The method of any one of claims 409-431, wherein the composition further comprises a salt.

433. The method claim 432, wherein the salt is an inorganic salt.

434. The method of any one of claims 409-433, wherein the immunogenic saccharide-polypeptide conjugate of the composition is isolated and purified.

435. The method of any one of claims 409-434, wherein the composition is used as a vaccine.

436. The method of any one of claims 409-435, wherein the composition is used for vaccinating a subject.

437. The method of claim 436, wherein the subject is a human.

438. The method of any one of claims 185-437, wherein the subject or human is a subject or human in need thereof.

439. The method of any one of claims 409-438, wherein the immunogenic saccharide-polypeptide conjugate(s) of the composition are individually, respectively, or collectively present in an amount of about: 0.001, 0.01, 0.1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 95, or 100%, by weight, based on the weight of the composition.

440. The method of any one of claims 409-439, wherein the immunogenic saccharide-polypeptide conjugate of the composition is produced using bacteria.

441. The method of any one of claims 409-440, wherein the immunogenic saccharide-polypeptide conjugate of the composition is produced using E. coli.

442. The method of any one of claims 409-441, wherein the immunogenic saccharide-polypeptide conjugate of the composition comprises the capsular polysaccharide at least partially embedded in the polypeptide.

443. The method of any one of claims 409-442, wherein the immunogenic saccharide-polypeptide conjugate of the composition comprises the capsular polysaccharide chemically cross-linked to the polypeptide.

444. The method of any one of claims 409-443, wherein the immunogenic saccharide-polypeptide conjugate of the composition comprises the capsular polysaccharide at least partially chemically cross-linked to the polypeptide.

445. A kit comprising a pharmaceutical composition of any of claims 1-169 or the vaccine of any one of claims 170-261 contained in a container.

446. The kit of claim 445, further comprising instructions for use.

447. The kit of any one of claims 445-446, wherein the container is a syringe.

Petitioner Merck Ex-1015, 1711

448. The kit of any one of claims 445-446, wherein the container is a vial comprising a cap, wherein the cap comprises a rubber septum.

Petitioner Merck Ex-1015, 1712

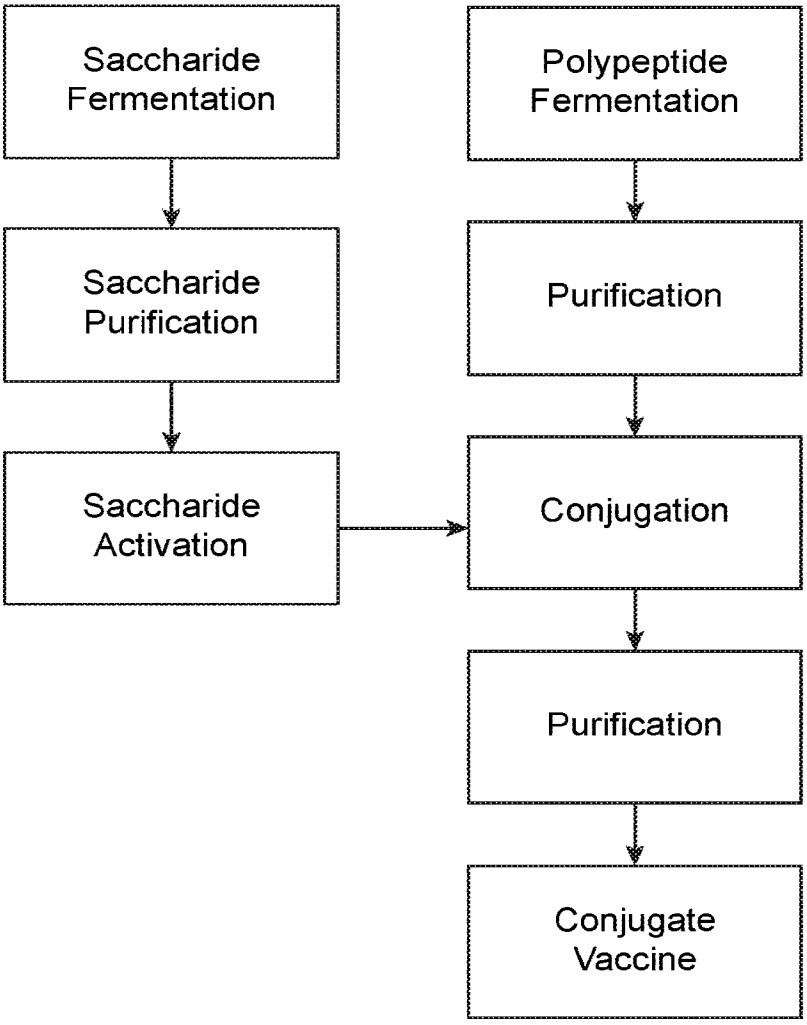

Saccharide Fermentation
Saccharide Purification
Saccharide Activation
Polypeptide Fermentation
Purification
Conjugation
Purification
Conjugate Vaccine

FIG. 1

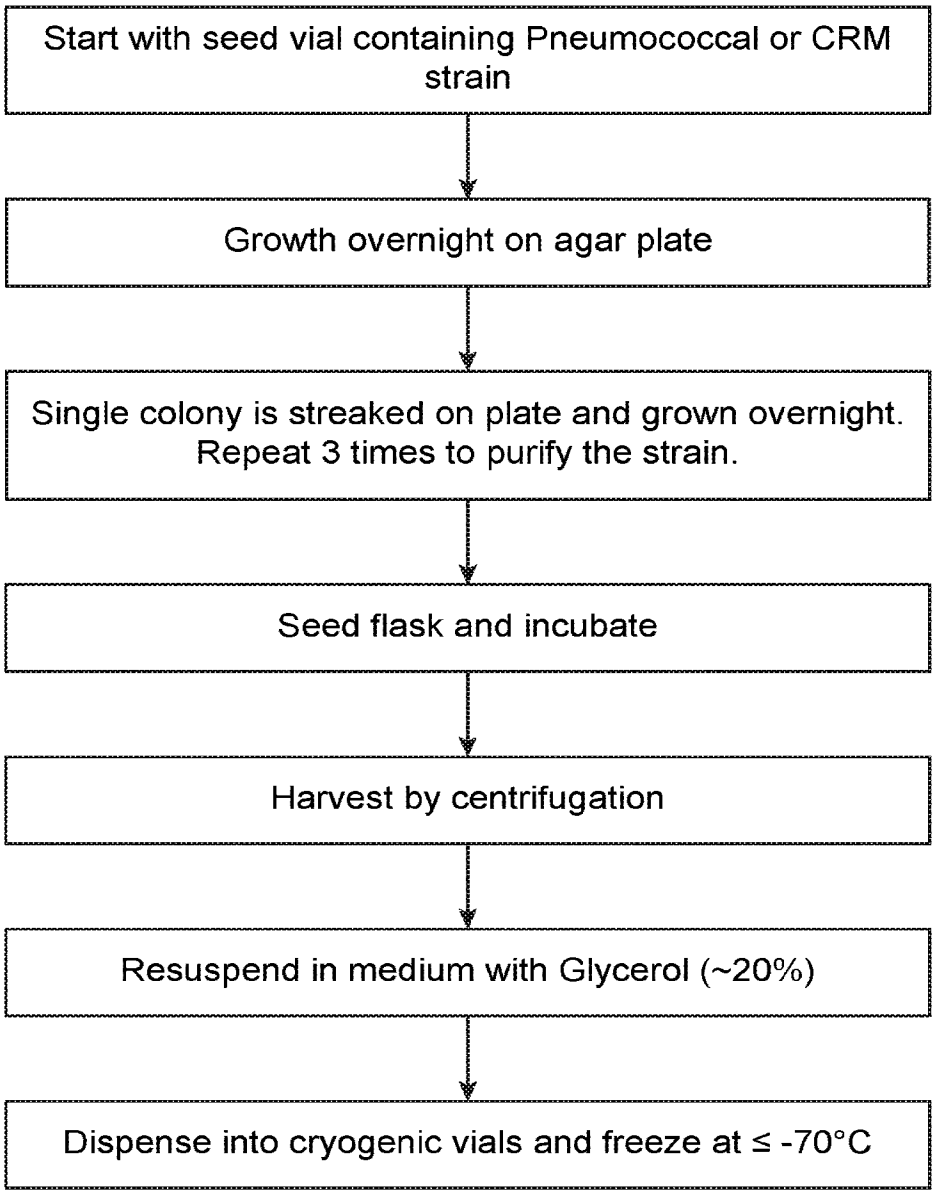

Start with seed vial containing Pneumococcal or CRM strain
Growth overnight on agar plate
Single colony is streaked on plate and grown overnight. Repeat 3 times to purify the strain.
Seed flask and incubate
Harvest by centrifugation
Resuspend in medium with Glycerol (~20%)
Dispense into cryogenic vials and freeze at ≤ -70°C

FIG. 2

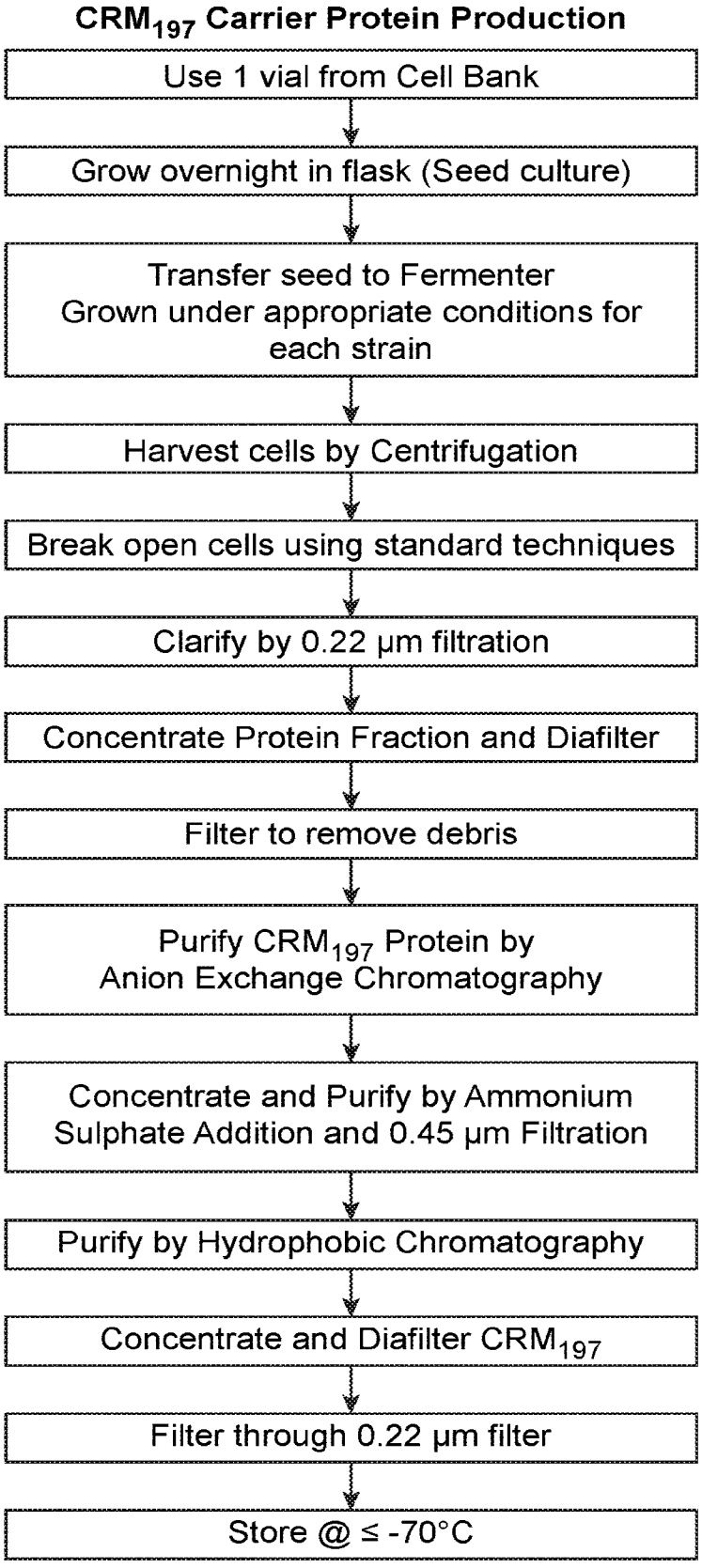

CRM197 Carrier Protein Production
Use 1 vial from Cell Bank
Grow overnight in flask (Seed culture)
Transfer seed to Fermenter
Grown under appropriate conditions for each strain
Harvest cells by Centrifugation
Break open cells using standard techniques
Clarify by 0.22 µm filtration
Concentrate Protein Fraction and Diafilter
Filter to remove debris
Purify CRM197 Protein by Anion Exchange Chromatography
Concentrate and Purify by Ammonium Sulphate Addition and 0.45 µm Filtration
Purify by Hydrophobic Chromatography
Concentrate and Diafilter CRM197
Filter through 0.22 µm filter
Store @ ≤ -70°C

FIG. 3

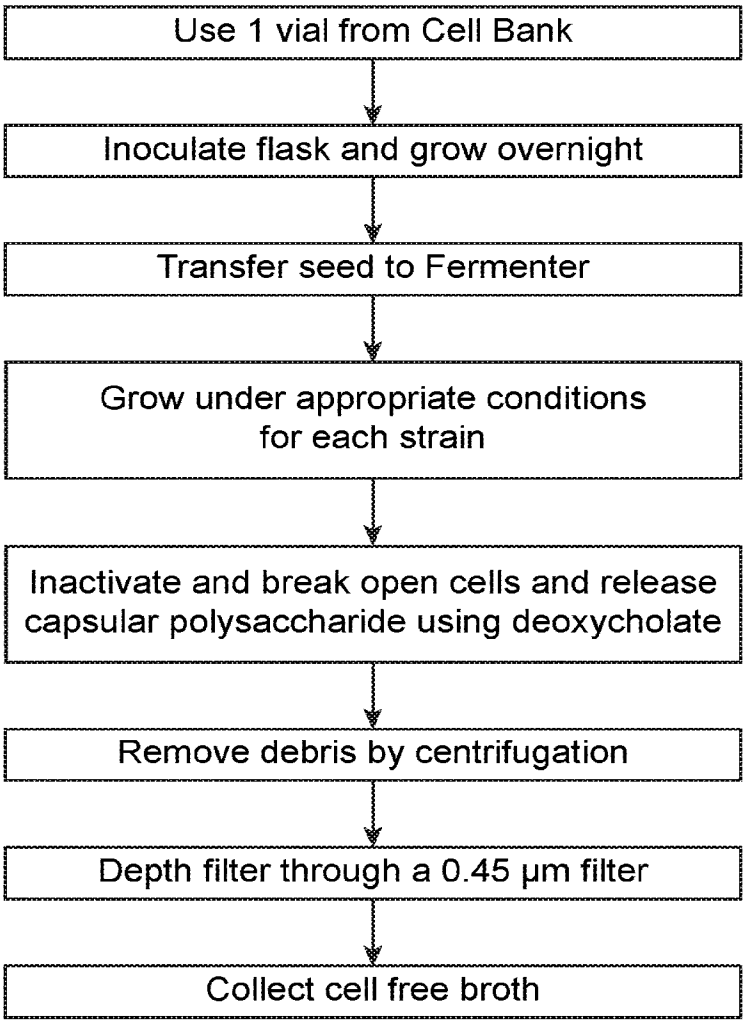

Use 1 vial from Cell Bank
Inoculate flask and grow overnight
Transfer seed to Fermenter
Grow under appropriate conditions for each strain
Inactivate and break open cells and release capsular polysaccharide using deoxycholate
Remove debris by centrifugation
Depth filter through a 0.45 µm filter
Collect cell free broth

FIG. 4

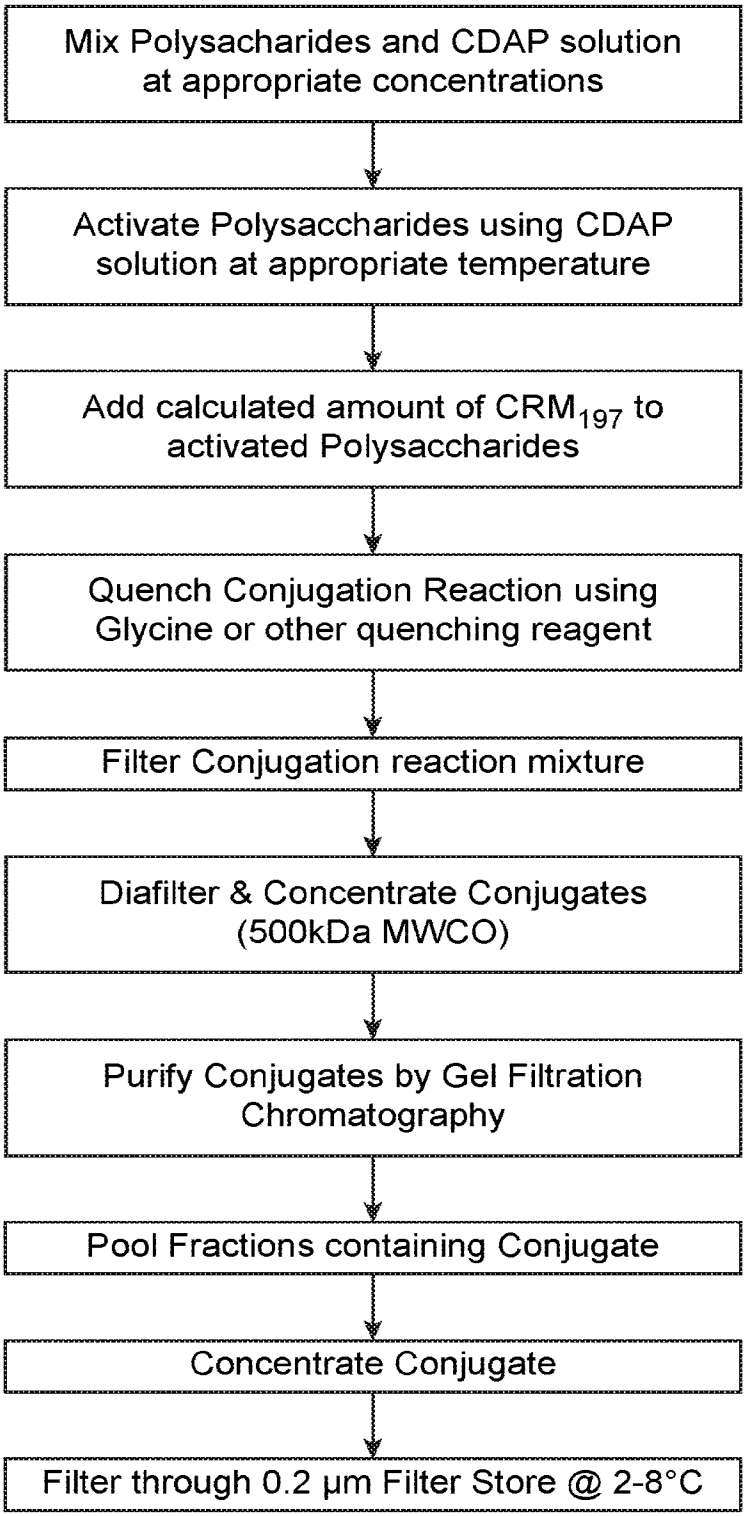

Mix Polysacharides and CDAP solution at appropriate concentrations
Activate Polysaccharides using CDAP solution at appropriate temperature
Add calculated amount of CRM_{197} to activated Polysaccharides
Quench Conjugation Reaction using Glycine or other quenching reagent
Filter Conjugation reaction mixture
Diafilter & Concentrate Conjugates (500kDa MWCO)
Purify Conjugates by Gel Filtration Chromatography
Pool Fractions containing Conjugate
Concentrate Conjugate
Filter through 0.2 µm Filter Store @ 2-8°C

FIG. 5

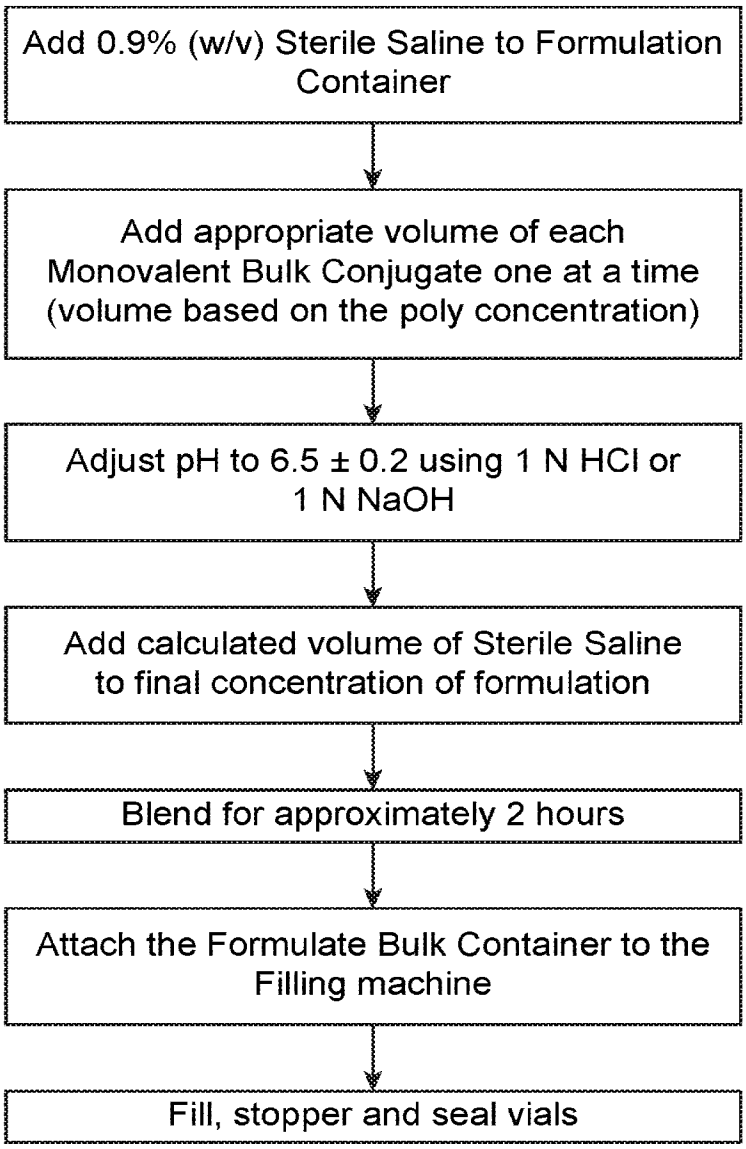

Add 0.9% (w/v) Sterile Saline to Formulation Container
Add appropriate volume of each Monovalent Bulk Conjugate one at a time (volume based on the poly concentration)
Adjust pH to 6.5 ± 0.2 using 1 N HCl or 1 N NaOH
Add calculated volume of Sterile Saline to final concentration of formulation
Blend for approximately 2 hours
Attach the Formulate Bulk Container to the Filling machine
Fill, stopper and seal vials

FIG. 6

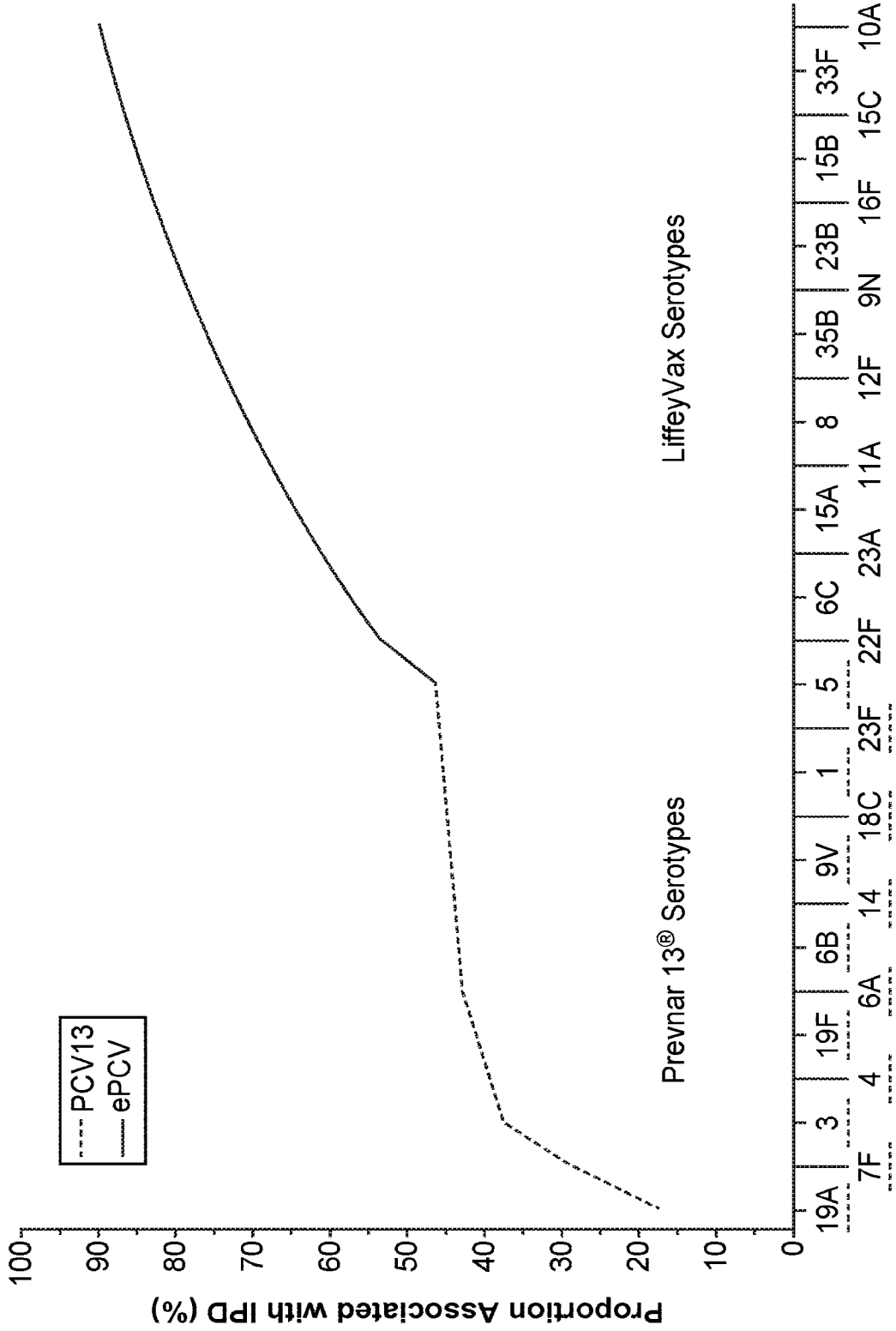

PCV13
ePCV
Proportion Associated with IPD (%)
100
90
80
70
60
50
40
30
20
10
0
Prevnar 13® Serotypes
LiffeyVax Serotypes
19A
7F
3
4
19F
6A
6B
14
9V
18C
1
23F
5
22F
6C
23A
15A
11A
8
12F
35B
9N
23B
16F
15B
15C
33F
10A
S. pneumoniae Serotypes

FIG. 7

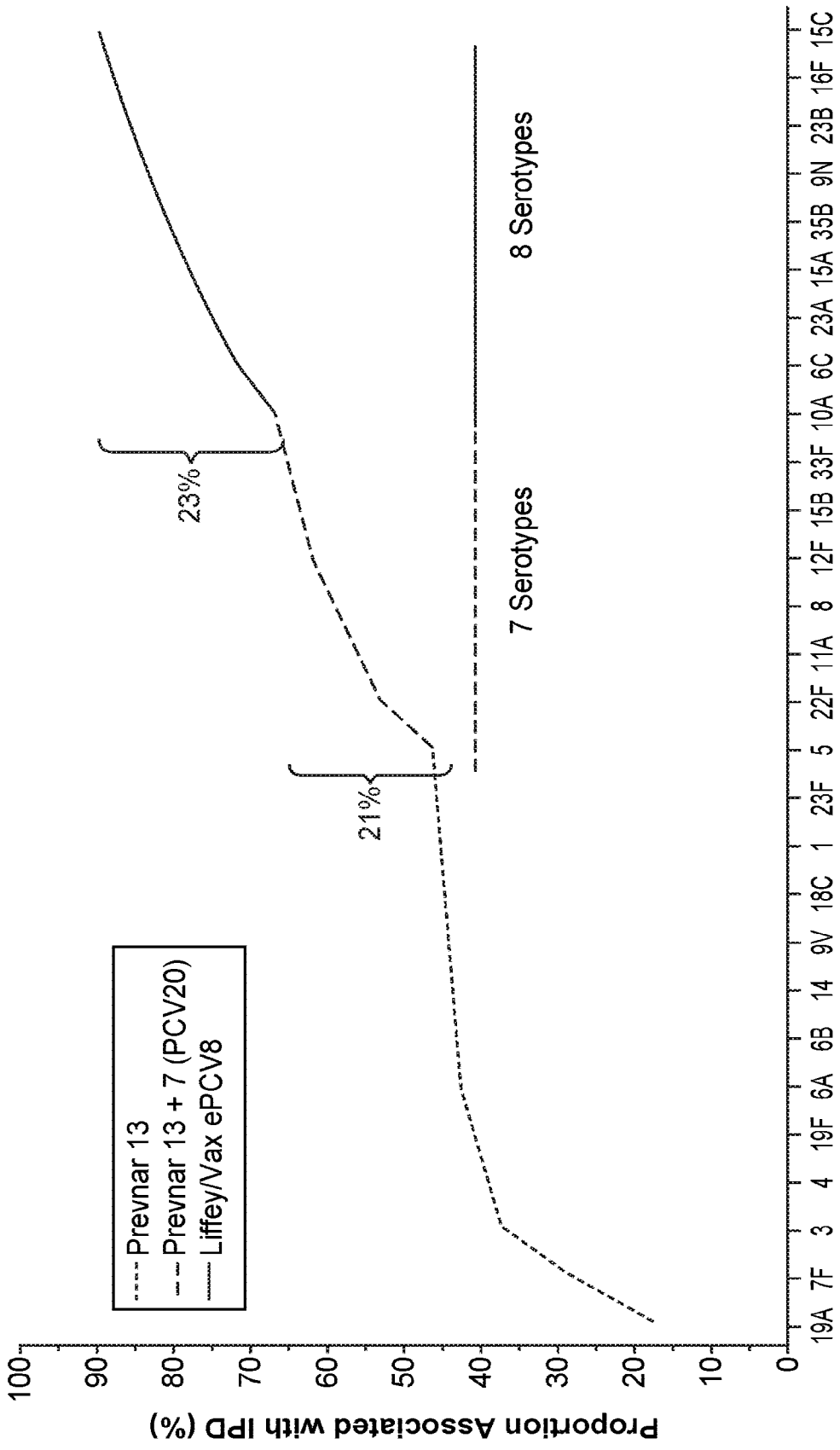

Prevnar 13
Prevnar 13 + 7 (PCV20)
Liffey/Vax ePCV8
23%
21%
7 Serotypes
8 Serotypes
Proportion Associated with IPD (%)
100
90
80
70
60
50
40
30
20
10
0
19A 7F 3 4 19F 6A 6B 14 9V 18C 1 23F 5 22F 11A 8 12F 15B 33F 10A 6C 23A 15A 35B 9N 23B 16F 15C
S. pneumoniae Serotypes

FIG. 8

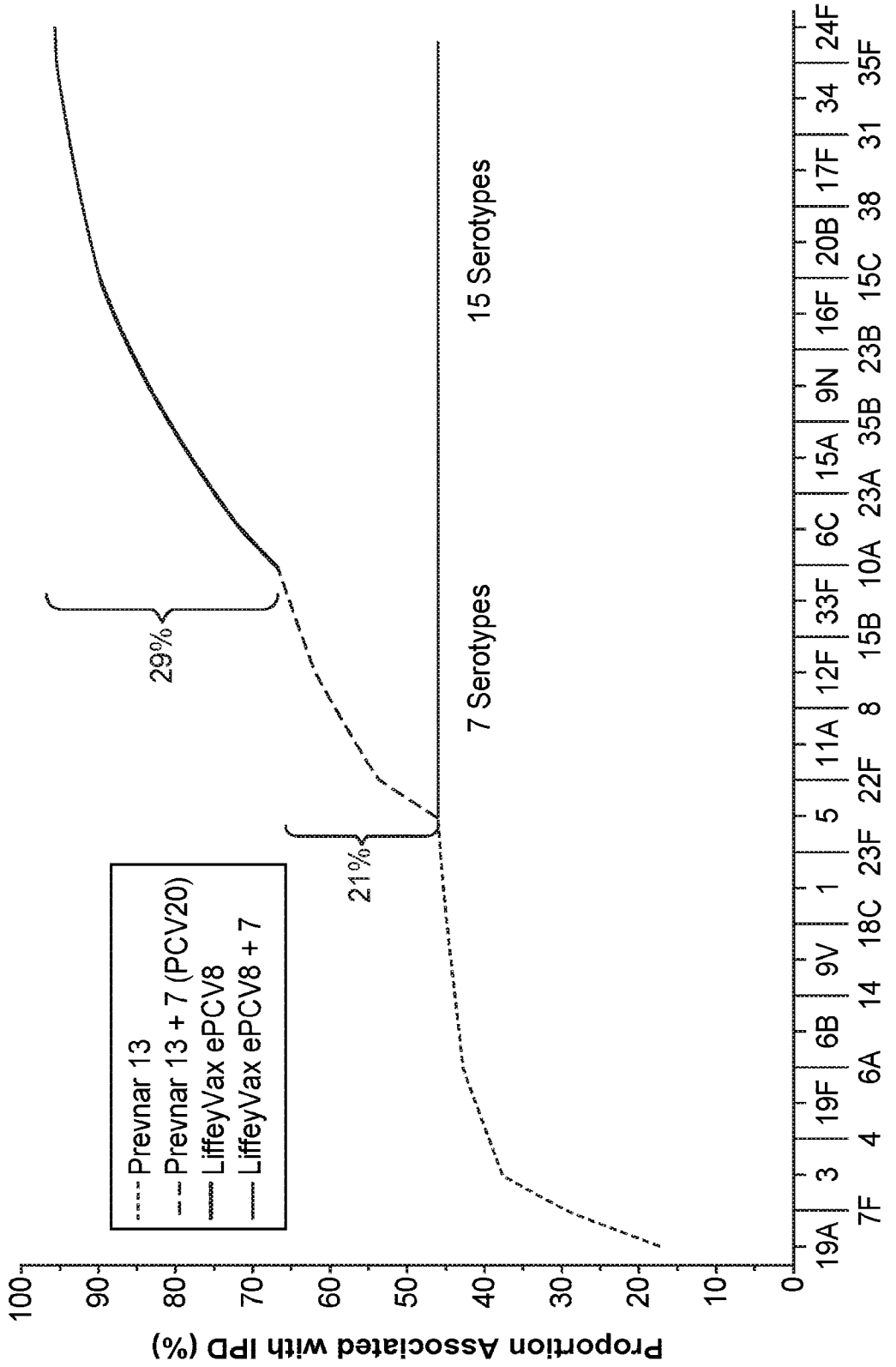

Prevnar 13
Prevnar 13 + 7 (PCV20)
LiffeyVax ePCV8
LiffeyVax ePCV8 + 7
29%
21%
7 Serotypes
15 Serotypes
Proportion Associated with IPD (%)
100
90
80
70
60
50
40
30
20
10
0
19A 3 7F 19F 4 6B 6A 9V 14 1 18C 5 23F 11A 22F 12F 8 33F 15B 6C 10A 15A 23A 9N 35B 23B 16F 15C 20B 38 17F 31 34 35F 24F
S. pneumoniae Serotypes

FIG. 9

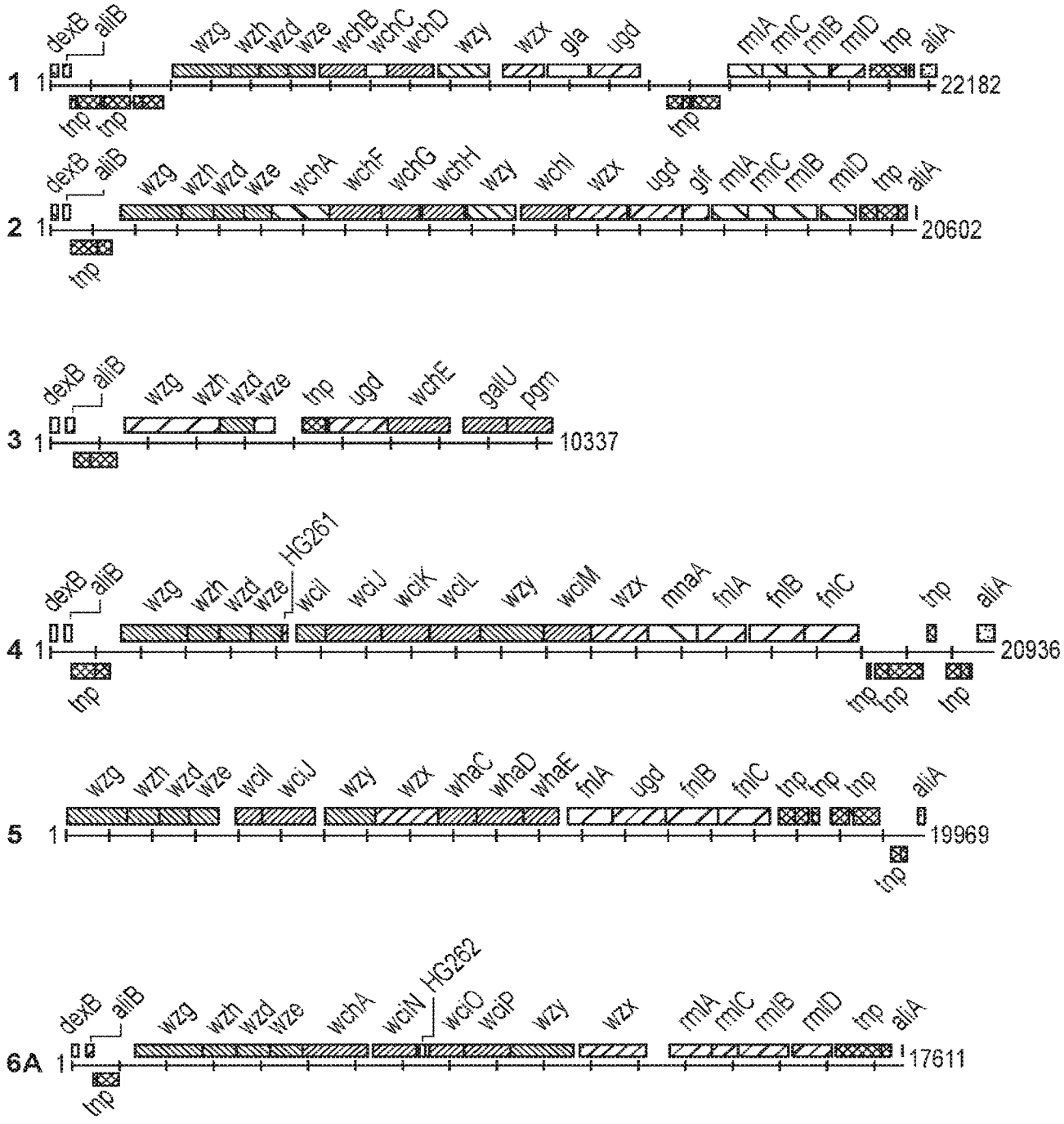

1
dexB
aliB
wzg
wzh
wzd
wze
wchB
wchC
wchD
wzy
wzx
gla
ugd
rmlA
rmlC
rmlB
rmlD
tnp
aliA
22182
2
wchA
wchF
wchG
wchH
wchI
gfi
20602
3
galU
pgm
10337
4
HG261
wcil
wciJ
wciK
wciL
wciM
nnaA
fnlA
fnlB
fnlC
20936
5
whaC
whaD
whaE
19969
6A
HG262
wciN
wciO
wciP
17611

FIG. 10A

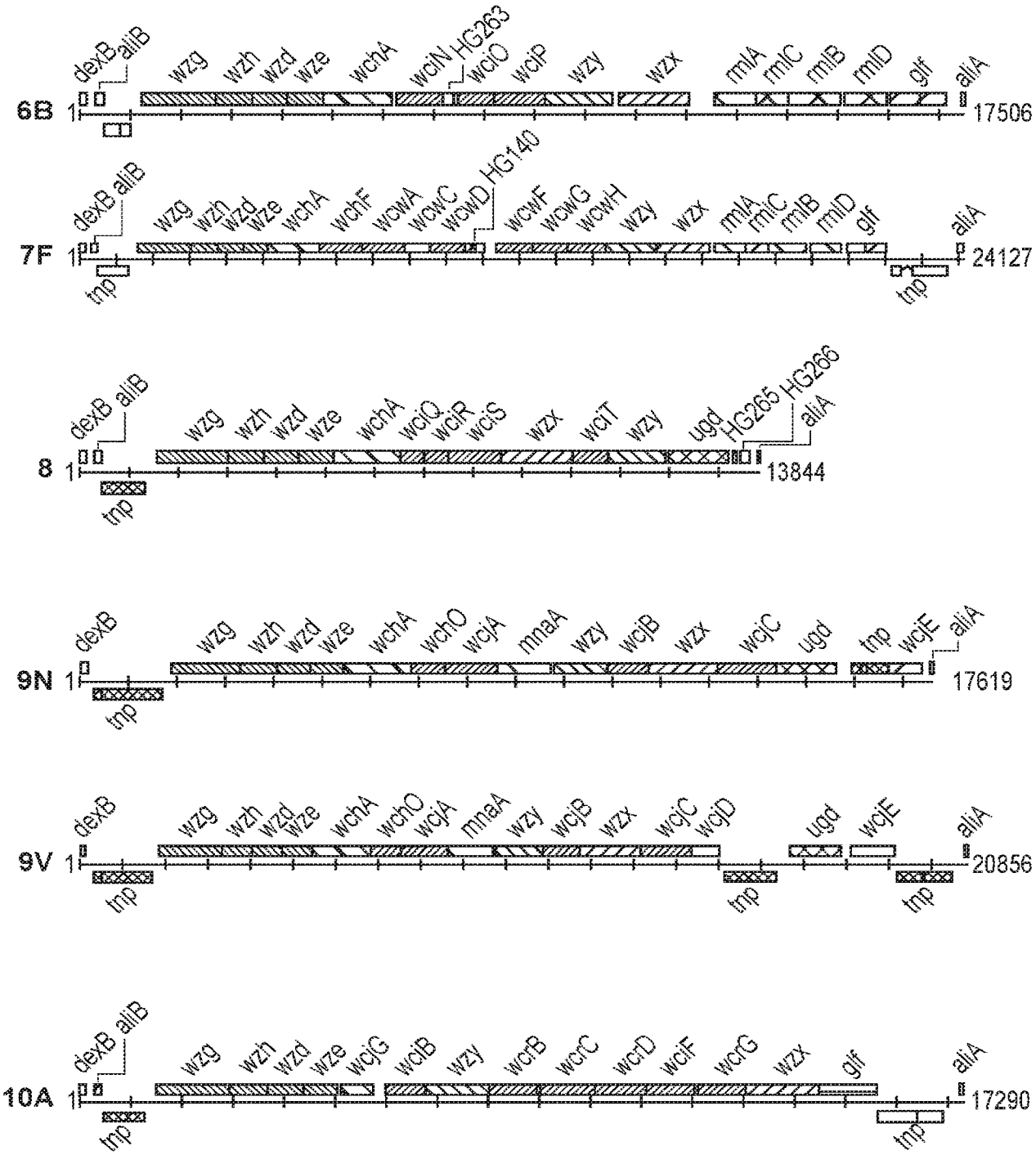

6B
dexB
aliB
wzg
wzh
wzd
wze
wchA
wciN
HG263
wciO
wciP
wzy
wzx
rmlA
rmlC
rmlB
rmlD
glf
aliA
1
17506
7F
dexB
aliB
wzg
wzh
wzd
wze
wchA
wchF
wcwA
wcwC
wcwD
HG140
wcwF
wcwG
wcwH
wzy
wzx
rmlA
rmlC
rmlB
rmlD
glf
aliA
tnp
tnp
1
24127
8
dexB
aliB
wzg
wzh
wzd
wze
wchA
wciQ
wciR
wciS
wzx
wciT
wzy
ugd
HG265
HG266
aliA
tnp
1
13844
9N
dexB
wzg
wzh
wzd
wze
wchA
wchO
wcjA
mnaA
wzy
wcjB
wzx
wcjC
ugd
tnp
wcjE
aliA
tnp
1
17619
9V
dexB
wzg
wzh
wzd
wze
wchA
wchO
wcjA
mnaA
wzy
wcjB
wzx
wcjC
wcjD
ugd
wcjE
aliA
tnp
tnp
tnp
1
20856
10A
dexB
aliB
wzg
wzh
wzd
wze
wcjG
wciB
wzy
wcrB
wcrC
wcrD
wciF
wcrG
wzx
glf
aliA
tnp
tnp
1
17290

FIG. 10B

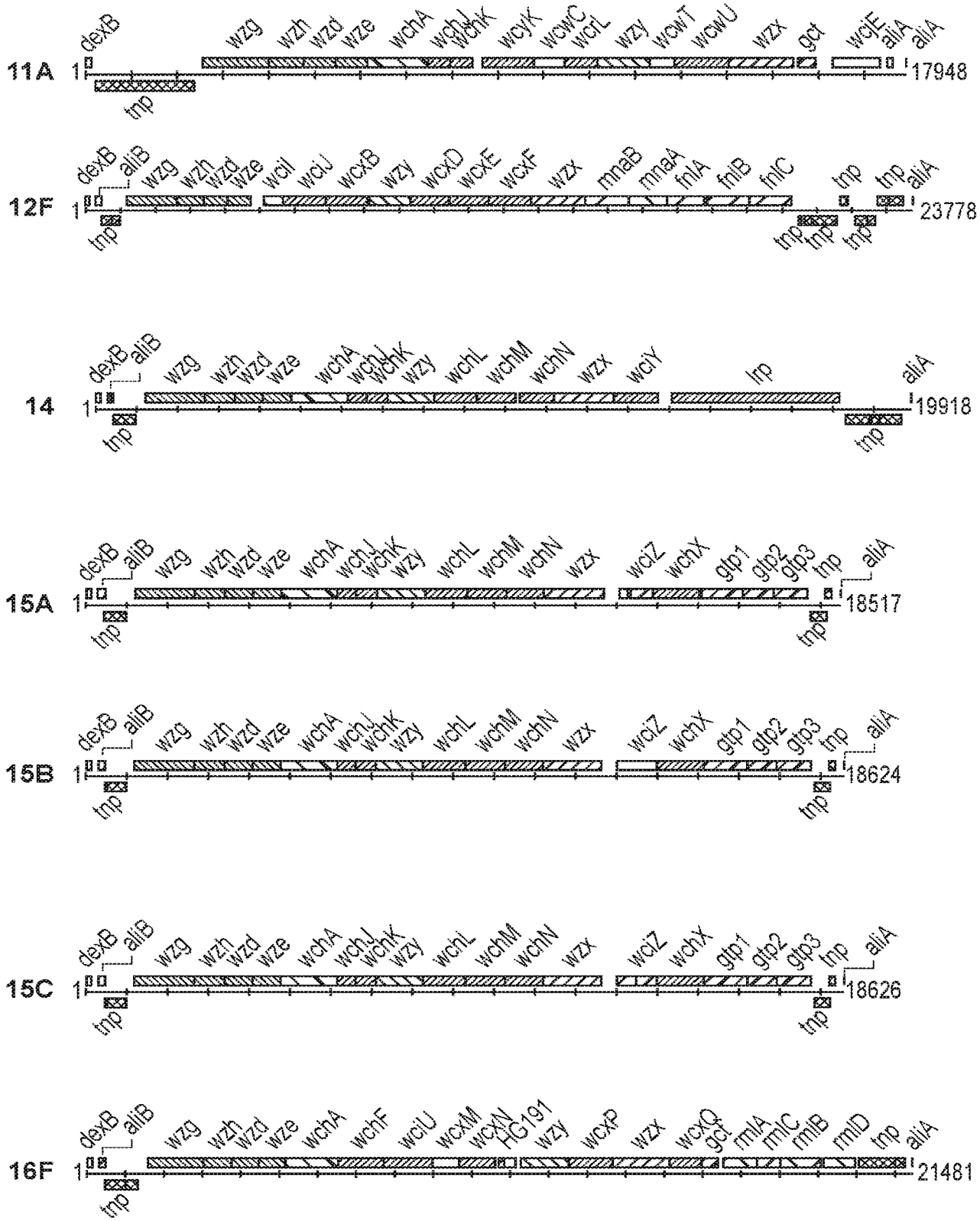

11A
dexB
wzg
wzh
wzd
wze
wchA
wchJ
wchK
wcyK
wcwC
wcrL
wzy
wcwT
wcwU
wzx
gct
wcjE
aliA
aliA
tnp
17948
12F
dexB
aliB
wzg
wzh
wzd
wze
wcil
wciJ
wcxB
wzy
wcxD
wcxE
wcxF
wzx
mnaB
mnaA
fnlA
fnlB
fnlC
tnp
tnp
aliA
tnp
tnp
tnp
tnp
23778
14
dexB
aliB
wzg
wzh
wzd
wze
wchA
wchJ
wchK
wzy
wchL
wchM
wchN
wzx
wciY
trp
aliA
tnp
tnp
19918
15A
dexB
aliB
wzg
wzh
wzd
wze
wchA
wchJ
wchK
wzy
wchL
wchM
wchN
wzx
wciZ
wchX
gtp1
gtp2
gtp3
tnp
aliA
tnp
tnp
18517
15B
dexB
aliB
wzg
wzh
wzd
wze
wchA
wchJ
wchK
wzy
wchL
wchM
wchN
wzx
wciZ
wchX
gtp1
gtp2
gtp3
tnp
aliA
tnp
tnp
18624
15C
dexB
aliB
wzg
wzh
wzd
wze
wchA
wchJ
wchK
wzy
wchL
wchM
wchN
wzx
wciZ
wchX
gtp1
gtp2
gtp3
tnp
aliA
tnp
tnp
18626
16F
dexB
aliB
wzg
wzh
wzd
wze
wchA
wchF
wciU
wcxM
wcxN
HG191
wzy
wcxP
wzx
wcxQ
gct
rmlA
rmlC
rmlB
rmlD
tnp
aliA
tnp
21481

FIG. 10C

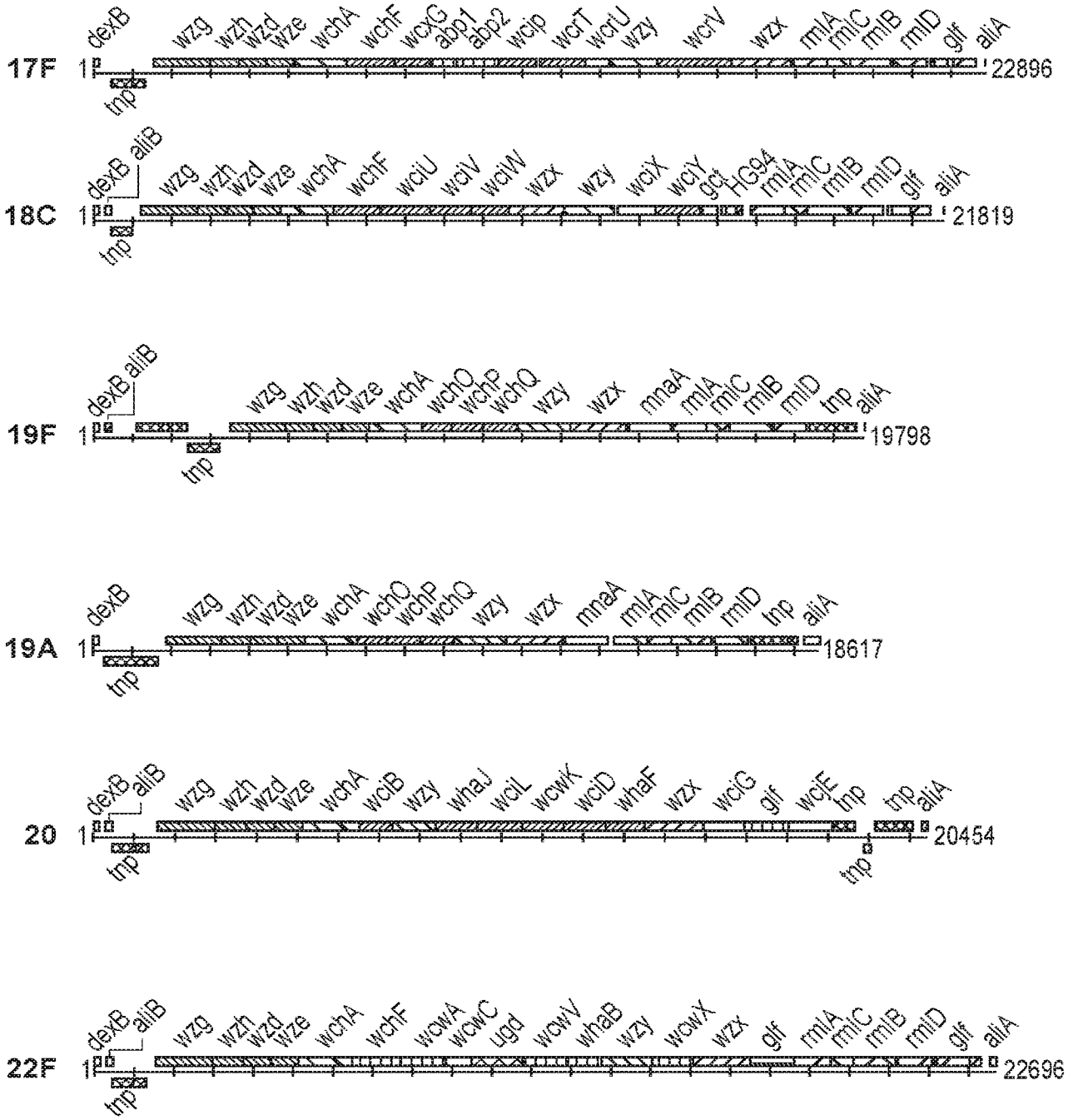

17F
dexB
wzg wzh wzd wze wchA wchF wcxG abp1 abp2 wcip wcrT wcrU wzy wcrV wzx rmlA rmlC rmlB rmlD glf aliA
1
22896
tnp
18C
dexB aliB
wzg wzh wzd wze wchA wchF wciU wciV wciW wzx wzy wciX wciY gct HG9A rmlA rmlC rmlB rmlD glf aliA
1
21819
tnp
19F
dexB aliB
wzg wzh wzd wze wchA wchO wchP wchQ wzy wzx mnaA rmlA rmlC rmlB rmlD tnp aliA
1
19798
tnp
19A
dexB
wzg wzh wzd wze wchA wchO wchP wchQ wzy wzx mnaA rmlA rmlC rmlB rmlD tnp aliA
1
18617
tnp
20
dexB aliB
wzg wzh wzd wze wchA wciB wzy whaJ wciL wcwK wciD whaF wzx wciG glf wciE tnp tnp aliA
1
20454
tnp
tnp
22F
dexB aliB
wzg wzh wzd wze wchA wchF wcwA wcwC ugd wcwV whaB wzy wcwX wzx glf rmlA rmlC rmlB rmlD glf aliA
1
22696
tnp

FIG. 10D

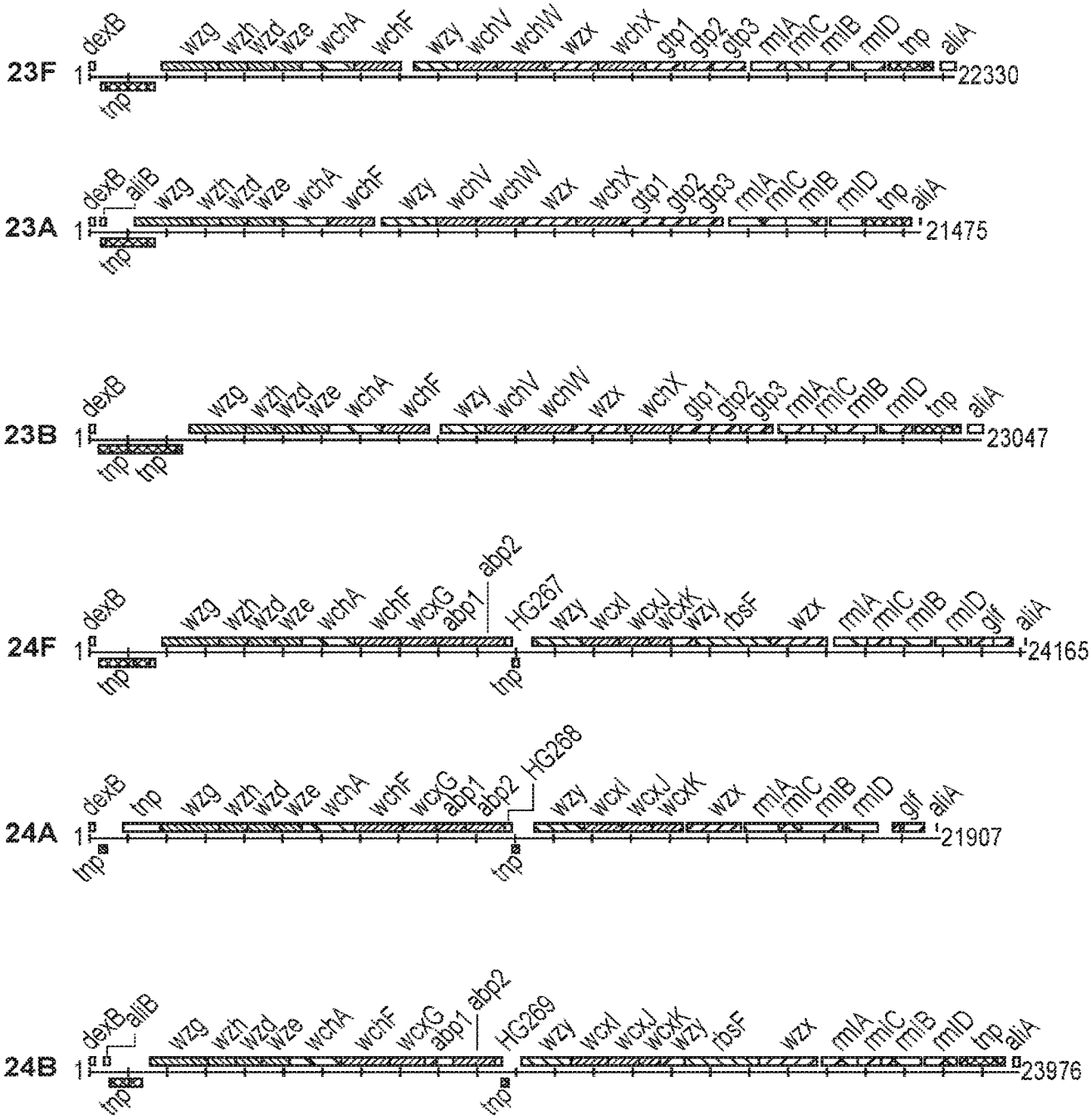

23F
dexB
wzg wzh wzd wze wchA wchF wzy wchV wchW wzx wchX glp1 glp2 glp3 rmlA rmlC rmlB rmlD tnp aliA
1
22330
tnp
23A
dexB aliB
wzg wzh wzd wze wchA wchF wzy wchV wchW wzx wchX glp1 glp2 glp3 rmlA rmlC rmlB rmlD tnp aliA
1
21475
tnp
23B
dexB
wzg wzh wzd wze wchA wchF wzy wchV wchW wzx wchX glp1 glp2 glp3 rmlA rmlC rmlB rmlD tnp aliA
1
23047
tnp tnp
24F
dexB
wzg wzh wzd wze wchA wchF wcxG abp1 abp2 HG267 wzy wcxI wcxJ wcxK wzy rbsF wzx rmlA rmlC rmlB rmlD glf aliA
1
24165
tnp tnp
24A
dexB tnp
wzg wzh wzd wze wchA wchF wcxG abp1 abp2 HG268 wzy wcxI wcxJ wcxK wzx rmlA rmlC rmlB rmlD glf aliA
1
21907
tnp tnp
24B
dexB aliB
wzg wzh wzd wze wchA wchF wcxG abp1 abp2 HG269 wzy wcxI wcxJ wcxK wzy rbsF wzx rmlA rmlC rmlB rmlD tnp aliA
1
23976
tnp tnp

FIG. 10E

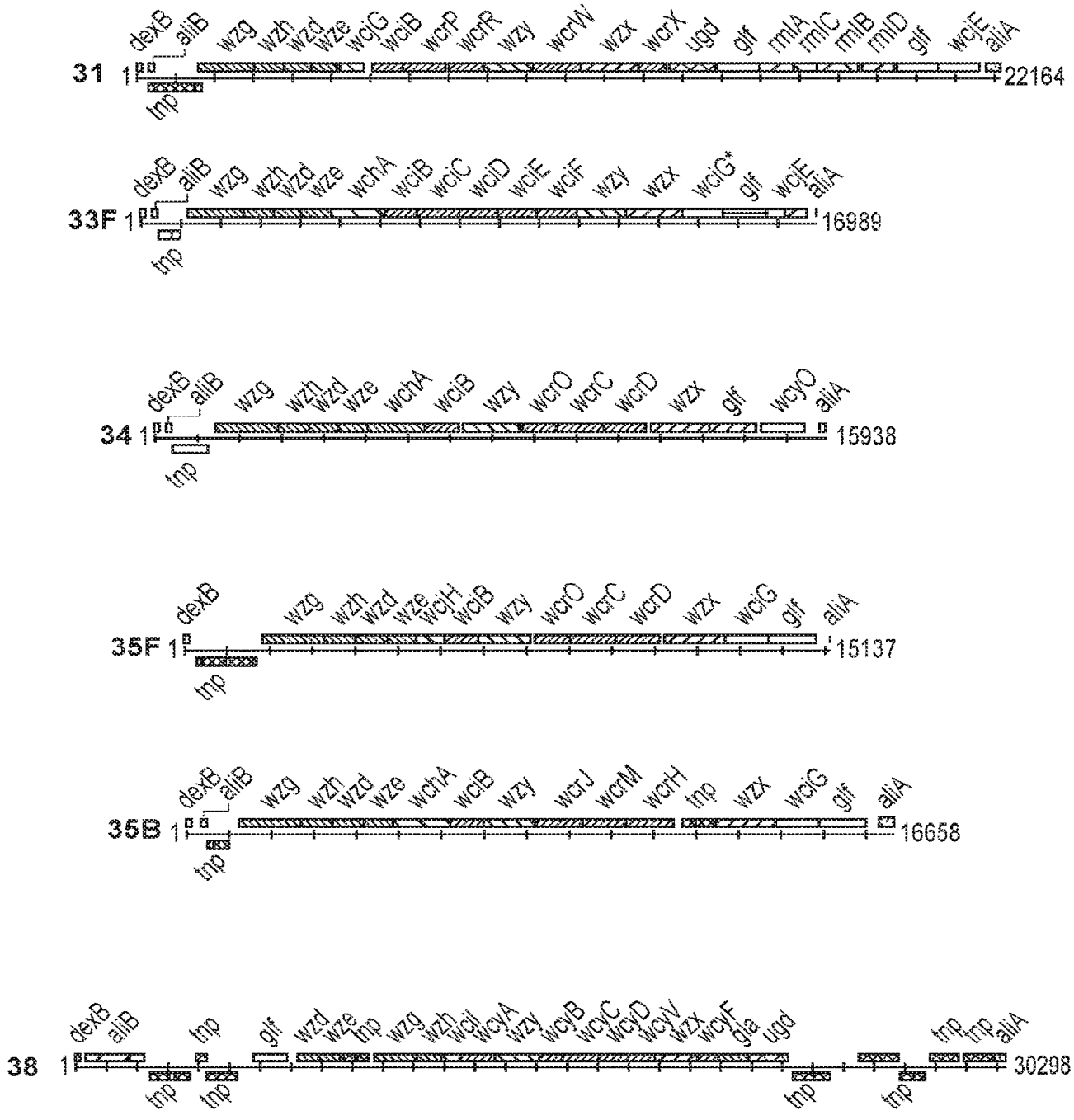

31
1
dexB
aliB
wzg
wzh
wzd
wze
wciG
wciB
wcrP
wcrR
wzy
wcrW
wzx
wcrX
ugd
glf
rmlA
rmlC
rmlB
rmlD
glf
wciE
aliA
tnp
22164
33F
1
dexB
aliB
wzg
wzh
wzd
wze
wchA
wciB
wciC
wciD
wciE
wciF
wzy
wzx
wciG*
glf
wciE
aliA
tnp
16989
34
1
dexB
aliB
wzg
wzh
wzd
wze
wchA
wciB
wzy
wcrO
wcrC
wcrD
wzx
glf
wcyO
aliA
tnp
15938
35F
1
dexB
wzg
wzh
wzd
wze
wciH
wciB
wzy
wcrO
wcrC
wcrD
wzx
wciG
glf
aliA
tnp
15137
35B
1
dexB
aliB
wzg
wzh
wzd
wze
wchA
wciB
wzy
wcrJ
wcrM
wcrH
tnp
wzx
wciG
glf
aliA
tnp
16658
38
1
dexB
aliB
tnp
tnp
glf
wzd
wze
tnp
wzg
wzh
wciI
wcyA
wzy
wcyB
wcyC
wcyD
wcyV
wzx
wcyF
gla
ugd
tnp
tnp
tnp
tnp
aliA
30298

FIG. 10F

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/54391

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 39/09, A61K 39/00 (2018.01)
CPC - A61K 39/092, A61K 47/646, A61K 2039/6087, A61K 2039/62, A61K 2039/70

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History Document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	WO 2017/067962 A1 (GLAXOSMITHKLINE BIOLOGICALS S.A.) 27 April 2017 (27.04.2017) pg 9, ln 10-15, pg 9, ln 23-26, pg 11, ln 14-20, pg 28, ln 28-30, pg 43, ln 1-2, pg 43, ln 15-20	1, 77-80 ----- 28/1, 34-46
Y	US 2017/0021006 A1 (PFIZER Inc.) 26 January 2017 (26.01.2017) Claim 1	28/1
Y	WO 2016/149771 A1 (GAMMA VACCINES PTY LIMITED) 29 September 2016 (29.09.2016) pg 18, ln 6-12	34-46

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 January 2019	11 FEB 2019
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

Petitioner Merck Ex-1015, 1728

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/54391

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☒ forming part of the international application as filed:

      ☒ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

Petitioner Merck Ex-1015, 1729

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/54391

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

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

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

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

3. ☒ Claims Nos.: 81-169, 174-448
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

- see extra sheet for Box No. III Observations where unity of invention is lacking -

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

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

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

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 28/1, 34-46, 77-80 limited to serotypes 2, 6C, 7F, 7C, 8, 9N, 10A, 11A

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

Petitioner Merck Ex-1015, 1730

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/54391

Continuation of:
Box No. III. Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I+: Claims 1-80, 170-173, drawn to a pharmaceutical composition or vaccine in unit dose form comprising a plurality of unique immunogenic saccharide-polypeptide conjugates. The plurality of unique immunogenic saccharide-polypeptide conjugates will be searched to the extent that the capsular polysaccharides encompasses eight Streptococcus pneumoniae serotypes 2, 6C, 7F, 7C, 8, 9N, 10A, 11A. It is believed that claims 1, 28(in part), 34-46, 77-80 encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass capsular polysaccharide serotypes 2, 6C, 7F, 7C, 8, 9N, 10A, 11A. Additional capsular polysaccharide serotypes will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected capsular polysaccharide serotypes. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. An exemplary election would be a pharmaceutical composition or vaccine encompasses 9 capsular polysaccharide serotypes of 6C, 15A, 15B, 15C, 17F, 20A, 20B, 23A, 23B (Claims 2, 28(in part), 34-46, 72, 74-80, 170-173).

The inventions listed as Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features

The inventions of Groups I+ each include the special technical feature of a specific set of capsular polysaccharide selected from a group of S. pneumoniae serotypes, not required by any of the other inventions of Groups I+.

Common Technical Features

The inventions of Groups I+ share the technical feature of Claims 1, 29, 34, 72, 77, 170.

However, these shared technical features do not represent a contribution over prior art in view of WO 2017/067962 A1 to Glaxosmithkline Biologicals S.A. (hereinafter 'GSK'); WO 2016/149771 A1 to Gamma Vaccines PTY Limited (hereinafter 'GVPL'); and the article "Biochemical, Genetic, and Serological Characterization of Two Capsule Subtypes among Streptococcus pneumoniae Serotype 20 Strains. DISCOVERY OF A NEW PNEUMOCOCCAL SEROTYPE" by Calix et al. (hereinafter 'Calix') (The Journal Of Biological Chemistry VOL. 287, NO. 33, pp. 27885-27894, August 10, 2012).

GSK teaches (instant claim 1) a pharmaceutical composition in unit dose form (pg 43, ln 1-2, the vaccine of the invention may be administered as a single dose.; pg 43, ln 15-20, a vaccine containing the immunogenic compositions of the invention and a pharmaceutically acceptable excipient or carrier), comprising a plurality of at least eight unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide (pg 9, ln 10-15, the invention will comprise capsular polysaccharide antigens (suitably conjugated), wherein the polysaccharides are derived from at least ten serotypes of S. pneumoniae. The number of S. pneumoniae capsular polysaccharides can range from 10 different serotypes (or valences "v") to 23 different serotypes (23v, a 23 valent composition).; pg 11, ln 14-20, Examples of carrier proteins which may be used in the present invention are DT (Diphtheria toxoid), TT (tetanus toxoid) or fragment C of TT, DT, CRM197 other DT point mutants, such as CRM176, CRM228, CRM 45.), wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique Streptococcus pneumoniae serotype selected from a group consisting of 2, 6C, 7F, 7C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, I 7F, 20A, 20B, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35B, 35F, and 38 (pg 9, ln 23-26, In one embodiment the multivalent pneumococcal vaccine of the invention will comprise polysaccharides (suitably conjugated) selected from the following serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 15C, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F.), and wherein a total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each Streptococcus pneumoniae serotype in the pharmaceutical composition in unit dose form (pg 43, ln 1-2), ranges from about 0.5 ug to about 5 ug (pg 28, ln 28-30, In the immunogenic composition of the invention contains each S. pneumoniae capsular saccharide at a dose of between 0.1-20 ug; 0.5-1.0 ug; 0,5-5 ug or 1-3 ug of saccharide.).

GSK teaches (instant claim 29) a pharmaceutical composition in unit dose form (pg 43, ln 1-2, pg 43, ln 15-20) comprising a plurality of at least 23 unique immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide (pg 9, ln 10-15, pg 11, ln 14-20), wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique Streptococcus pneumoniae serotype selected from a group consisting of 1, 2, 3, 4, 5, 6A, 6B, 7F, 7C, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, I 7F, 20A, 20B, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 35F, 34, 35B, and 38 (pg 9, ln 23-26), and wherein a total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each Streptococcus pneumoniae serotype in the pharmaceutical composition in unit dose form (pg 43, ln 1-2), ranges from about 0.5 ug to about 5 ug (pg 28, ln 28-30). GSK does not specifically teaches a composition comprising 29 unique immunogenic saccharide-polypeptide conjugates. GVPL teaches a vaccine composition comprising any one or more of S. pneumoniae serotypes (more than 29 serotypes) (pg 18, ln 6-12, the vaccines may comprise any one of more of S. pneumoniae serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 6D, 7A, 7B, 7C, 7F, 8, 9A, 9L, 9N, 9V, 10A, 10B, IOC, 10F, 11A, 11B, 11C, 11D, 11F, 12A, 12B, 12F, 13, 14, 15A, 15B, 15C, 15F, 16A, 16F, 17A, 17F, 18A, 18B, 18C, 18F, 19A, 19B, 19C, 19F, 20, 21, 22A, 22F, 23A, 23B, 23F, 24A, 24B, 24F, 25A, 25F, 27, 28A, 28F, 29, 31, 32A, 32F, 33A, 33B, 33C, 33D, 33F, 34, 35A, 35B, 35C, 35F, 36, 37, 38, 39, 40, 41A, 41F, 42, 43, 44, 45, 46, 47A, 47F, and/or 48.). It would have been obvious to one of ordinary skill in the art to have prepared a vaccine comprising 29 unique immunogenic saccharide-polypeptide conjugates, as taught by GVPL.

----continued on next sheet----

Petitioner Merck Ex-1015, 1731

Continuation of:
Box No. III. Observations where unity of invention is lacking

GSK teaches (instant claim 34) a pharmaceutical composition in unit dose form (pg 43, ln 1-2, pg 43, ln 15-20) comprising at least 2 immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide (pg 9, ln 10-15, pg 11, ln 14-20), wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique Streptococcus pneumoniae serotype group, wherein at least one additional serotype is selected from the group consisting of 1, 2, 3, 4, 5, 6A, 6B, 7F, 7C, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, I 7F, 20A, 20B, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35B, 35F, and 38 (pg 9, ln 23-26), and wherein a total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each Streptococcus pneumoniae serotype in the pharmaceutical composition in unit dose form (pg 43, ln 1-2), ranges from about 0.5 ug to about 5 ug (pg 28, ln 28-30). GSK does not specifically teaches a composition comprising serotype 6C. GVPL teaches a vaccine composition comprising any one or more of S. pneumoniae serotypes comprising 6C (pg 18, ln 6-12, the vaccines may comprise any one of more of S. pneumoniae serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 6D,.....). It would have been obvious to one of ordinary skill in the art to have prepared a vaccine comprising serotype 6C, as taught by GVPL.

GSK teaches (instant claim 72) a pharmaceutical composition in unit dose form (pg 43, ln 1-2, pg 43, ln 15-20) comprising at least 2 immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide (pg 9, ln 10-15, pg 11, ln 14-20), wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique Streptococcus pneumoniae serotype group, wherein at least one additional serotype is selected from the group consisting of 1, 2, 3, 4, 5, 6A, 6B, 6C, 7C, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, I7F, 20A, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35B, and 38 (pg 9, ln 23-26), and wherein a total amount of capsular polysaccharide, fragment thereof, or combination thereof, individually for each Streptococcus pneumoniae serotype in the pharmaceutical composition in unit dose form (pg 43, ln 1-2), ranges from about 0.5 ug to about 5 ug (pg 28, ln 28-30). GSK does not specifically teaches a composition comprising serotype 20B. Calix teaches serotype 20B (abstract, We examined the capsule structures of two serologically dissimilar serotype 20 strains, 20alpha and 20beta, by extensive biochemical analysis. 20alpha was composed of the previously described serotype 20 hexasaccharide repeat unit, whereas the 20beta was composed of a novel heptasaccharide repeat unit containing an extra branching alpha-glucose residue.). It would have been obvious to one of ordinary skill in the art to have prepared a vaccine comprising serotype 20B, which was first identified by Calix.

GSK teaches (instant claim 77) a pharmaceutical composition comprising an immunogenic saccharide-polypeptide conjugate comprising, individually, at least two unique capsular polysaccharides, fragments thereof, or combinations thereof conjugated to a polypeptide, wherein the at least two unique capsular polysaccharides, fragments thereof, or combinations thereof are from a Streptococcus pneumoniae serotype selected from a group consisting of 1, 2, 3, 4, 5, 6A, 6B, 7C, 7F, 9V, 14, 18C, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, I 7F, 20A, 20B, 22F, 23A, 23B, 24F, 24B, 31, 33F, 33B, 34, 35F, 35B, and 38 (pg 9, ln 10-15, pg 9, ln 23-26, pg 11, ln 14-20).

GSK teaches (instant claim 170) a vaccine in unit dose form (pg 43, ln 1-2, pg 43, ln 15-20) comprising at least one immunogenic saccharido polypeptide conjugate comprising a capsular polysaccharide, fragment thereof, or combination thereof conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a Streptococcus pneumoniae serotype (pg 9, ln 10-15, pg 9, ln 23-26, pg 11, ln 14-20). GSK does not specifically teaches serotypes 23A or 23B, or a combination thereof. GVPL teaches a vaccine composition comprising any one or more of S. pneumoniae serotypes comprising 23A or 23B (pg 18, ln 6-12, the vaccines may comprise any one of more of S. pneumoniae serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 6D,...23A, 23B....). It would have been obvious to one of ordinary skill in the art to have prepared a vaccine comprising serotype 23A or 23B, as taught by GVPL.

As said technical features were known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the groups.

Groups I+ therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Petitioner Merck Ex-1015, 1732

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
05 April 2018 (05.04.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/064444 A1

(51) International Patent Classification:
A61K 39/09 (2006.01) *A61P 31/04* (2006.01)
A61K 39/385 (2006.01) *A61K 39/00* (2006.01)
A61K 39/39 (2006.01)

(21) International Application Number:
PCT/US2017/054237

(22) International Filing Date:
29 September 2017 (29.09.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
201641033563 30 September 2016 (30.09.2016) IN

(71) Applicant: **BIOLOGICAL E LIMITED** [IN/IN]; 18/1 & 3, Azamabad, Hyderabad, Telangana 500 020 (IN).

(72) Inventors; and

(71) Applicants *(for US only)*: **MATUR, Ramesh, Venkat** [US/IN]; Biological E Limited, 18/1 & 3, Azamabad, Hyderabad, Telangana 500 020 (IN). **MANTENA, Narender, Dev** [US/IN]; Biological E Limited, 18/1 & 3, Azamabad, Hyderabad, Telangana 500 020 (IN).

(72) Inventors: **SRIRAMAN, Rajan**; Biological E Limited, 18/1 & 3, Azamabad, Hyderabad, Telangana 500 020 (IN). **CHAKKA, Deviprasanna**; Biological E Limited, 18/1 & 3, Azamabad, Hyderabad, Telangana 500 020 (IN). **SUREDDI, Satyam, Naidu**; Biological E Limited, 18/1 & 3, Azamabad, Hyderabad, Telangana 500 020 (IN). **BURKI, Rajendar**; Biological E Limited, 18/1 & 3, Azamabad, Hyderabad, Telangana 500 020 (IN). **GANTI, Sreenivasa, Rao**; Biological E Limited, 18/1 & 3, Azamabad, Hyderabad, Telangana 500 020 (IN). **DATLA, Mahima**; Biological E Limited, 18/1 & 3, Azamabad, Hyderabad, Telangana 500 020 (IN).

(74) Agent: **FOURNIER, David, B.** et al.; Perkins Coie LLP, P.O. Box 1247, Seattle, WA 98111-1247 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(54) Title: MULTIVALENT PNEUMOCOCCAL VACCINE COMPOSITIONS COMPRISING POLYSACCHARIDE-PROTEIN CONJUGATES

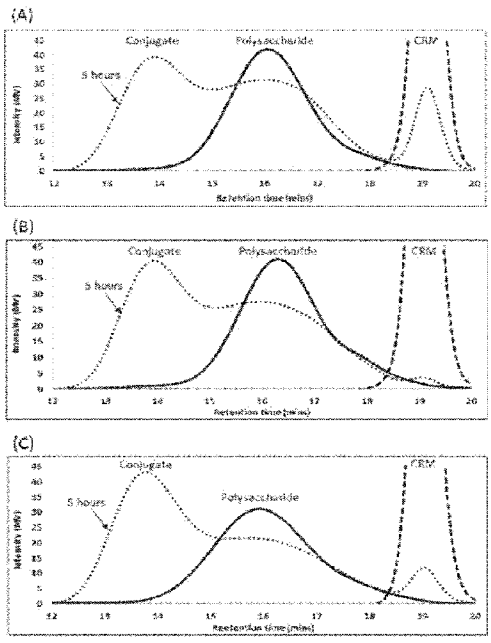


FIG. 1

(57) Abstract: The present disclosure relates to multivalent pneumococcal vaccine compositions comprising capsular pneumococcal polysaccharide serotypes each individually conjugated to carrier proteins. When conjugated, the combination of the capsular pneumococcal polysaccharide serotype and the carrier protein is referred to herein as a polysaccharide-protein conjugate. The pneumococcal vaccine compositions may further comprise one or more of the following; a pharmaceutically acceptable carrier, a pharmaceutically acceptable diluent, a buffer, a preservative, a stabilizer, an adjuvant, and/or a lyophilization excipient. Methods of making and administering the pneumococcal vaccine compositions described herein are also provided.

[Continued on next page]

WO 2018/064444 A1

Petitioner Merck Ex-1015, 1733

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

Petitioner Merck Ex-1015, 1734

MULTIVALENT PNEUMOCOCCAL VACCINE COMPOSITIONS COMPRISING POLYSACCHARIDE-PROTEIN CONJUGATES

CROSS-REFERENCE TO RELATED APPLICATION

[0001] The present application claims priority to Indian Provisional Application No. 201641033563 filed on September 30, 2016, and incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] The present disclosure relates to multivalent pneumococcal vaccine compositions comprising capsular pneumococcal polysaccharide of one or more *Streptococcus pneumoniae* serotypes conjugated to one or more carrier proteins. When conjugated, the capsular pneumococcal polysaccharide and the carrier protein is referred to herein as a polysaccharide-protein conjugate.

BACKGROUND

[0003] *Streptococcus pneumoniae* ("pneumococcus") is a gram-positive bacteria that causes invasive diseases, such as pneumonia, bacteremia and meningitis, and diseases associated with colonization, such as acute otitis media (e.g., colonization of middle ear). These pneumococcus-induced diseases result in morbidity and mortality, particularly in persons less than 24 months old and greater than 60 years old. The rate of pneumococcal pneumonia in the U.S. for persons over 60 years of age is estimated to be 3 to 8 per 100,000. In 20% of cases, pneumococcal pneumonia leads to bacteremia and meningitis collectively having a mortality rate close to 30% despite antibiotic treatment.

[0004] Proteins such as pneumolysin and the pneumococcal surface protein A (PspA) have been evaluated for their suitability as carrier protein candidates in pneumococcal vaccines. While both are partially protective in mice (Paton et al. "Effect of immunization with pneumolysin on survival time of mice challenged with Streptococcus pneumoniae." Infect Immun. 1983 May; 40(2): 548–552 and McDaniel et al. "PspA, a surface protein of Streptococcus pneumoniae, is capable of eliciting protection against pneumococci of more than one capsular type" Infect Immun. 1991

Petitioner Merck Ex-1015, 1735

Jan; 59(1): 222–228.), there are disadvantages to their use as immunogens in vaccines. Pneumolysin, although well conserved among pneumococci, has toxic effects in its native state (AlonsoDeVelasco et al. "Streptococcus pneumoniae: Virulence factors, pathogenesis, and vaccines." Microbiol Rev. 1995 Dec; 59(4): 591–603.). On the other hand, PspA is serologically and structurally heterogeneous. (Crain et al. "Pneumococcal surface protein A) is serologically highly variable and is expressed by all clinically important capsular serotypes of Streptococcus pneumoniae." Infect Immun. 1990 Oct; 58(10): 3293–3299). Its use in vaccine formulations would require multiple PspA types, thus increasing the complexity of vaccine preparation.

[0005] Pneumococcal surface adhesion A ("PsaA") is a multi-functional lipoprotein and is involved in host cell adherence and colonization. It is a highly conserved surface protein and 97% homologous across known serotypes of *S. pneumoniae*. PsaA is immunogenic and anti-PsaA antibodies are known to increase during natural nasopharyngeal colonization of pneumococci.

[0006] Pneumococcal vaccines may be administered to prevent infections. Current vaccines include multivalent pneumococcal polysaccharide vaccines (comprises pneumococcal polysaccharides from two or more serotypes) and pneumococcal conjugate vaccines. The protective efficacy of the pneumococcal polysaccharide vaccine is known to be related to the concentration of antibody generated against a capsular polysaccharide. Pneumococcus cells are encapsulated with a polysaccharide giving rise to more than 90 different pneumococcus serotypes. The capsule is the principal virulence determinant for pneumococci - it not only protects the cell's inner surface from complement mediated cell lysis, it is also poorly immunogenic.

[0007] Merck's Pneumovax®23 is a multivalent pneumococcal polysaccharide vaccine and contains unconjugated capsular polysaccharides from 23 pneumococcal serotypes including serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F. In addition to Pneumovax®23, the multivalent pneumococcal polysaccharide vaccines that have been licensed thus far proved valuable in preventing pneumococcal disease in adults, particularly, the elderly

Petitioner Merck Ex-1015, 1736

and those at high-risk. However, infants and young children respond poorly to these unconjugated pneumococcal polysaccharide vaccines.

[0008] Prevnar®-7 is a pneumococcal polysaccharide-protein conjugate vaccine and includes the seven most frequently isolated polysaccharide serotypes (e.g., 4, 6B, 9V, 14, 18C, 19F, and 23F conjugated to CRM_{197}). Since use of Prevnar®-7 began in the United States in 2000, there has been a significant reduction in invasive pneumococcal disease (IPD) in children. A 13-valent conjugate vaccine Prevenar-13®, containing thirteen serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F conjugated to CRM_{197}, was developed and approved due to the limitations in serotype coverage with Prevnar®-7 in certain regions of the world.

[0009] Synflorix® is a pneumococcal vaccine that includes ten polysaccharide serotypes – serotypes 1, 4, 5, 6B, 7, 9, 14, 23F – conjugated to protein D (PD), serotype 18C conjugated to tetanus toxoid (TT) and serotype 19F conjugated to diphtheria toxoid (DT). Each of the serotype polysaccharides are coupled utilizing 1-cyano-4-dimethylamino-pyridinium tetrafluoroborate (CDAP) under controlled pH.

[0010] Despite these vaccines, there is a need for additional multivalent pneumococcal vaccines comprising alternative polysaccharide serotypes and carrier proteins, as well as simple and efficient production thereof.

[0011] Pneumococcal vaccines have been described in additional references. For example, U.S. Patent No. 5,360,897 discloses an immunogenic conjugate comprising a reductive amination product of an intact capsular polymer of the bacterial pathogen *S. pneumoniae* having at least two carbonyl groups and a bacterial toxin or toxoid, said conjugate comprising a cross-linked conjugate in which there is a direct covalent linkage between the capsular polymer and the toxin or toxoid.

[0012] U.S. Patent No. 5,693,326 provides a generalized method for preparing a conjugate vaccine wherein for activating viral, fungal or bacterial polysaccharides, an organic cyanylating agent is used selected from the group 1-cyano-4-(dimethylamino)-pyridinium tetrafluoroborate, N-cyanotriethyl-ammonium tetrafluoroborate, and p-nitrophenylcyanate, to form an activated carbohydrate and is subsequently coupled to the protein or carrier protein.

Petitioner Merck Ex-1015, 1737

[0013] U.S. Patent No. 5,854,416 discloses amino acid and DNA sequences of 37-kDa protein from *S. pneumonia* known as PsaA (Pneumococcal surface adhesion A) and U.S. Patent No. 7,862,823 discloses a multivalent conjugate vaccine composition comprising pneumococcal capsular polysaccharides with at least two different carrier proteins, such as DT and TT.

[0014] U.S. Patent No. 7,955,605 describes a process of making immunogenic conjugate consisting 19A where the activated serotype 19A polysaccharide and carrier protein are re-suspended in dimethyl sulfoxide (DMSO) to form a conjugate.

[0015] U.S. Patent No. 8,192,746 discloses a 15-valent pneumococcal polysaccharide-protein conjugate vaccine composition having capsular polysaccharides from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F conjugated to CRM_{197}.

[0016] U.S. Patent No. 8,465,749 provides a method for preparing a conjugate vaccine by reacting a polysaccharide with CDAP and reacting a protein with hydrazine or adipic acid dihydrazide with specific pH range.

[0017] U.S. Patent No. 8,557,250 B2 discloses a method comprising contacting a mixture of a plurality of cyanate activated immunogenic distinct polysaccharides with at least one hydrazide activated protein.

[0018] U.S. Patent No. 8,808,708, 7,955,605 and U.S. Patent No. 8,603,484 describe a 13-valent immunogenic composition consisting polysaccharide-protein conjugates where serotypes consist of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, and carrier protein CRM_{197}.

[0019] U.S. Patent Publication No. 2009/0017059 A1 discloses an immunogenic composition wherein serotypes 19A and 19F are conjugated to different bacterial toxoids including tetanus toxoid, diphtheria toxoid, pertussis toxoid, bacterial cytolysins and/or pneumolysin.

[0020] U.S. Patent Publication No. 2010/0074922 A1 discloses an immunogenic composition containing 10 or more serotypes wherein 19F capsular saccharide is conjugated to DT, serotype 18C capsular saccharide is conjugated to tetanus toxoid and serotypes 1, 4, 5, 6B, 7F, 9V, 14 and 23F capsular saccharides are conjugated to Protein D isolated from *Haemophilus influenzae*.

Petitioner Merck Ex-1015, 1738

[0021] U.S. Patent Publication No. 2010/0239604 describes an immunogenic composition comprising multivalent *S. pneumoniae* capsular saccharide conjugates from serotypes 19A and 19F wherein serotype 19A is conjugated to a first bacterial toxoid and 19F is conjugated to a second bacterial toxoid and 2-9 of the *S. pneumoniae* capsular saccharides are conjugated to protein D.

[0022] U.S. Patent Publication No. 2012/321658 A1 discloses an immunogenic composition wherein serotypes 1, 3, 19A and 19F linked to protein carrier(s) either directly or indirectly through a chemistry other than reductive amination, and one or more different saccharides is/are selected from a second group consisting of serotypes 4, 5, 6A, 6B, 7F, 9V, 14, 18C and 23F which is/are linked to a protein carrier(s) by reductive amination.

[0023] IN 140/DEL/2011 provides a *S. pneumonia* vaccine comprising either of (a) 7 or more (b) 10 or more polysaccharides from different serotypes conjugated to at least 2 or more carrier proteins selected from a group comprising DT, diphtheria toxoid, CRM_{197}, and tetanus toxoid.

[0024] WO Publication No. 2013/191459 A1 discloses a conjugated 15 valent composition comprising different serotypes of *S. pneumoniae* derived from a capsular polysaccharide 1, 2, 3, 4, 5, 6A, 6B, 7F, 9N, 9V, 14, 18C, 19A, 19F and 23F conjugated to CRM_{197}.

[0025] WO Publication No. 2014/092377 A1 discloses a 13 valent composition wherein 12 serotypes are selected from 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F and the last serotype is either 12 or 9N conjugated to CRM_{197}.

[0026] WO Publication No. 2014/092378 A1 describes an immunogenic conjugate composition where 12 serotypes are selected from 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F and remaining one from 22F or 33F conjugated to CRM_{197}.

[0027] WO 2016207905 A2 discloses a multivalent Pneumococcal conjugate vaccine (PCV) composition comprising: 1) at least 12 capsular polysaccharides selected from serotypes 1, 3, 4, 5, 6B, 7F, 9N, 9V, 15B, 14, 18C, 19A, 19F, 22F, 23F and 33F of S. pneumoniae activated with CDAP and conjugated to carrier protein

Petitioner Merck Ex-1015, 1739

CRM197, and 2) a pharmaceutically acceptable carrier, wherein the composition does not contain capsular polysaccharide from serotype 6A.

[0028] Chinese Patent Application Publication No. CN 101590224 describes a 14 valent pneumococcal polysaccharide-protein conjugate vaccine containing serotypes 1, 2, 4, 5, 6A, 6B, 7F, 9N, 9V, 14, 18C, 19A, 19F and 23F conjugated to CRM_{197}.

[0029] Chinese Patent Application Publication No. CN 103623401 discloses a 14 multivalent pneumococcal capsular polysaccharide - protein conjugate composition wherein said 14 different serotype are 1, 3, 4, 5, 6A, 6B, 9V, 14,18C, 19A, 19F, 22F, 23F and 33F conjugated to CRM_{197}.

[0030] Chinese Patent Application Publication No. CN 103656632 discloses a multivalent pneumococcal capsular polysaccharide composition containing serotype 6A and at least one extra serotype selected from the group consisting of 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F conjugated to CRM_{197}.

[0031] Chinese Patent Application Publication No. CN 103656631 provides a multivalent pneumococcus capsular polysaccharide-protein conjugate composition and a preparation method thereof. The conjugate composition is prepared from capsular polysaccharides of pneumococcus of 24 different serotypes and a carrier protein in a covalent linkage manner, wherein the 24 different serotypes are 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F conjugated to CRM_{197}.

[0032] Chinese Patent Application Publication No. CN 104069488 discloses a multivalent pneumococcus capsular polysaccharides of 14 different serotypes and carrier protein, wherein the 14 serotypes include 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F conjugated to CRM_{197}.

[0033] Deborah et al, (1996, Volume 21, Issue 1, Pages 17-22) describes PsaA as having significant homology with fimbrial adhesion proteins. Immunization of CBA/CaHNJ Xid mice with PsaA using either complete Freund's or TiterMax™ adjuvants significantly protected mice against heterologous intravenous challenge with type 3 pneumococcal strain WU2 at doses up to 45 times the LD_{50}.

Petitioner Merck Ex-1015, 1740

[0034] Miyaji E N et al, (2001, Vaccine; 20 (5-6): 805-12) discloses *S. pneumoniae* as one of the most important human pathogens. DNA vaccine vectors containing either the full-length PsaA or a truncated PspA gene were constructed. Both constructs showed transient expression of the antigens in vertebrate cells and induced significant antibody response to the pneumococcal antigens in BALB/c mice injected intramuscularly.

[0035] Wuorimaa et al. (2001, The Paediatric Infectious Disease Journal, Volume 20(3), pp 272-277) discloses a study to assess the tolerability and immunogenicity in healthy toddlers of an 11-valent pneumococcal conjugate vaccine that uses both TT and DT as carriers.

[0036] Gatchalian et al. (2001, 17th Annual Meeting of the Eur. Soc. Paed. Inf. Dis (ESPID), poster number 4, P1A Poster Session 1, Istanbul Turkey) discloses an opsanophagocytic assay (OPA)results from infants who had received doses of the 11-valent vaccine failed to show antibody responses for serotype 3 at levels comparable to other tested serotypes.

[0037] Anderson P et al, (2003, Vaccine; 21 (13-14):1554-9) discloses a comparative study of tetravalent conjugate vaccines with each polysaccharide types 6A, 14, 19F, and 23F separately coupled to tetanus toxoid or diphtheria CRM_{197} or a mixture of halved doses of polysaccharide types 6A, 14, 19F, and 23F separately coupled to tetanus toxoid and diphtheria CRM_{197}.

[0038] Nurkka et al. (2004, Ped. Inf. Dis. J., 23:1008-1014) discloses a study of the immunogenicity and safety of an 11-valent pneumococcal protein D conjugate vaccine where no priming effect was observed for serotype 3 in infants who had received three doses of the vaccine followed by a booster dose of either the same vaccine or a pneumococcal polysaccharide vaccine.

[0039] The above mentioned references disclose, amongst other compositions, methods, and the like, multivalent pneumococcal vaccines comprising polysaccharides from one or more serotypes as well as conjugation of these polysaccharides with carrier proteins such as CRM_{197}, protein D, DT, and TT. In view of the different serotypes that are prevalent across various regions, there is a need for additional multivalent pneumococcal vaccines comprising novel conjugates of

Petitioner Merck Ex-1015, 1741

polysaccharide serotypes with improved immune response, as well as simple and efficient production thereof.

SUMMARY

[0040] In several embodiments, the present disclosure provides a pneumococcal vaccine composition, the composition comprising two or more capsular pneumococcal polysaccharide serotypes each individually conjugated to pneumococcal surface adhesion protein A (PsaA) or combination of PsaA and CRM_{197} as carrier proteins.

[0041] In one embodiment, the present disclosure provides a pneumococcal vaccine composition that is a 10 valent, 14 valent, 15 valent, 17 valent, 18 valent, 19 valent, 20 valent, 22 valent, 23 valent, 24 valent, or 25 valent pneumococcal vaccine composition.

[0042] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising pneumococcal polysaccharides that are each serotypes selected from pneumococcal serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39, and 45.

[0043] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising pneumococcal polysaccharides from each serotypes selected from pneumococcal serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39, and 45 conjugated with pneumococcal surface adhesion protein A (PsaA) as a carrier protein.

[0044] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising pneumococcal polysaccharides from serotypes selected from 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39, and 45 conjugated with pneumococcal surface adhesion protein A (PsaA) or combination of PsaA and CRM_{197} as carrier proteins.

[0045] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising pneumococcal polysaccharides from serotypes selected from 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B,

Petitioner Merck Ex-1015, 1742

15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39, and 45 wherein at least 3 pneumococcal polysaccharides are conjugated with pneumococcal surface adhesion protein A (PsaA).

[0046] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising pneumococcal polysaccharides from serotypes 3, 6A, 6B conjugated with pneumococcal surface adhesion protein A (PsaA).

[0047] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising at least 10 pneumococcal polysaccharides selected from serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39 and 45 and the carrier proteins comprise PsaA, or combination of PsaA and CRM_{197}.

[0048] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising at least 14 pneumococcal polysaccharide conjugates.

[0049] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising at least 17 pneumococcal polysaccharide conjugates.

[0050] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising at least 19 pneumococcal polysaccharide conjugates.

[0051] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising at least 20 pneumococcal polysaccharide conjugates.

[0052] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising at least 22 pneumococcal polysaccharide conjugates.

[0053] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising at least 24 pneumococcal polysaccharide conjugates.

[0054] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising pneumococcal polysaccharides of two or more serotypes and a carrier protein, wherein the serotypes are selected from 3, 5, 6A, 6B, 9V and 18C, and the carrier protein is PsaA.

[0055] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising pneumococcal polysaccharides of two or more

Petitioner Merck Ex-1015, 1743

serotypes and a carrier protein, wherein the serotypes are selected from 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A and 22F and the carrier protein is PsaA.

[0056] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising pneumococcal polysaccharides of two or more serotypes and a carrier protein, wherein the serotypes are selected from 1, 3, 4, 5, 6A, 6B, 7F, 9V, 10A, 12F, 14, 15A, 15B, 18C, 19F, 19A, 22F, 23F, 33F, 34, 35, 38 and 45, and the carrier protein is PsaA.

[0057] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising pneumococcal polysaccharides of one or more serotypes and a carrier protein, wherein the serotypes are 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39 and 45, and the carrier protein is PsA.

[0058] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising pneumococcal polysaccharides of one or more serotypes and a carrier protein wherein the pneumococcal polysaccharides are each individually conjugated to PsaA or combination of PsaA and CRM_{197}.

[0059] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising at least six pneumococcal polysaccharides each individually conjugated to PsaA, and one or more pneumococcal polysaccharides each individually conjugated to CRM_{197}.

[0060] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising at least five pneumococcal polysaccharides each individually conjugated to PsaA, and at least five pneumococcal polysaccharides each individually conjugated to CRM_{197}.

[0061] In another embodiment, the present disclosure provides a 14 valent pneumococcal vaccine comprising at least five pneumococcal polysaccharides each individually conjugated to PsaA, and at least five pneumococcal polysaccharides each individually conjugated to CRM_{197}.

[0062] In another embodiment, the present disclosure provides a 17 valent pneumococcal vaccine comprising at least five serotypes of pneumococcal

Petitioner Merck Ex-1015, 1744

polysaccharides each individually conjugated to PsaA, and at least five serotypes of pneumococcal polysaccharides each individually conjugated to CRM_{197}.

[0063] In another embodiment, the present disclosure provides a 20 valent pneumococcal vaccine comprising at least five serotypes of pneumococcal polysaccharides each individually conjugated to PsaA, and at least five serotypes of pneumococcal polysaccharides each individually conjugated to CRM_{197}.

[0064] In another embodiment, the present disclosure provides a 22 valent pneumococcal vaccine comprising at least five serotypes of pneumococcal polysaccharides each individually conjugated to PsaA, and at least five serotypes of pneumococcal polysaccharides each individually conjugated to CRM_{197}.

[0065] In another embodiment, the present disclosure provides a 24 valent pneumococcal vaccine comprising at least five serotypes of pneumococcal polysaccharides each individually conjugated to PsaA, and at least five serotypes of pneumococcal polysaccharides each individually conjugated to CRM_{197}.

[0066] In another embodiment, the present disclosure provides a 14 valent pneumococcal vaccine comprising pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F, wherein at least serotypes 3, and 6B are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F are conjugated to CRM_{197}.

[0067] In another embodiment, the present disclosure provides a 14 valent pneumococcal vaccine comprising pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F, wherein at least serotypes 3, and 6A are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F are conjugated to CRM_{197}.

[0068] In another embodiment, the present disclosure provides a 15 valent pneumococcal vaccine comprising pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F wherein at least serotypes 3, 6A and 6B are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F are conjugated to CRM_{197}.

[0069] In another embodiment, the present disclosure provides a 17 valent pneumococcal vaccine comprising pneumococcal polysaccharide serotypes 1, 3, 4, 5,

Petitioner Merck Ex-1015, 1745

6A, 6B, 7F, 9V, 12F,14, 18C, 19A, 19F, 22F, 23F, 33F and 35B wherein at least serotypes 3, 6A and 6B are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 12F, 14, 18C, 19A, 19F, 22F, 23F, 33F and 35B are conjugated to CRM_{197}.

[0070] In another embodiment, the present disclosure provides a 20 valent pneumococcal vaccine comprising pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 35B and 45 wherein at least serotypes 3, 6A and 6B are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 35B and 45 are conjugated to CRM_{197}.

[0071] In another embodiment, the present disclosure provides a 22 valent pneumococcal vaccine comprising pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 10A, 12F, 14, 15A, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38 wherein at least serotypes 3, 6A and 6B are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 10A, 12F, 14, 15A, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38 are conjugated to CRM_{197}.

[0072] In another embodiment, the present disclosure provides a 22 valent pneumococcal vaccine comprising pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 10A, 12F, 14, 15A, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38 wherein serotypes 1, 3, 6A, 10A, 12F, 15A 15B, 22F, 34, 35B, 38 are conjugated to PsaA and serotypes 14, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F and 33F are conjugated to CRM_{197}.

[0073] In another embodiment, the present disclosure provides a 24 valent pneumococcal vaccine comprising pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 12F, 14, 15A, 15B, 16F, 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38 wherein at least serotypes 3, 6A and 6B are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 8, 9V, 10A, 12F, 14, 15A, 15B, 16F, 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38 are conjugated to CRM_{197}.

[0074] In another embodiment, the present disclosure provides a 24 valent pneumococcal vaccine comprising pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 12F, 14, 15A, 15B, 16F 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38 wherein serotypes 1, 3, 6A, 8, 10A, 12F, 15A 15B, 16F 22F, 34, 35, 38

Petitioner Merck Ex-1015, 1746

are conjugated to PsaA and one or more serotypes 14, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F and 33F are conjugated to CRM_{197}.

[0075] In another embodiment, the present disclosure provides a pneumococcal vaccine composition formulated into a dosage unit.

[0076] In another embodiment, the present disclosure provides a pneumococcal vaccine composition formulated into a dosage unit wherein the dosage unit comprises about 0.1 µg to about 50 µg of each polysaccharide, about 0.1 µg to about 10 µg, or about 1 µg to about 5 µg of each polysaccharide, wherein each polysaccharide is each individually conjugated to the carrier protein from about 1.5 µg to about 5 µg of carrier protein.

[0077] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising a pharmaceutically acceptable diluent, buffer, preservative, stabilizer, adjuvant, and/or a lyophilization excipient.

[0078] In another embodiment, the present disclosure provides a pneumococcal vaccine composition formulated into a dosage unit that is supplied as a unit dose vial, a multiple dose vial, or a pre-filled syringe.

[0079] In another embodiment, the present disclosure provides a pneumococcal vaccine composition as a single 0.5 mL dose, the single dose comprising about 2.2 to 4.4 µg of one or more pneumococcal polysaccharides; about 1 µg to about 10 µg of PsaA conjugated to each of the one or more pneumococcal polysaccharides; about 1 µg to about 10 µg of CRM_{197} conjugated to each of the one or more pneumococcal polysaccharides; about 0.2 mg to about 1 mg of aluminum phosphate adjuvant; and an excipient.

[0080] In another embodiment, the present disclosure provides a 13 valent pneumococcal vaccine comprising pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F and 33F each individually conjugated to PsaA or combination of PsaA and CRM_{197}, wherein the pneumococcal vaccine composition is about a 0.5 mL dose formulated as a sterile liquid comprising about 2.2 µg to about 4.4 µg of each polysaccharide, about 25 µg to about 30 µg PsaA and CRM_{197}, about 0.125 mg of elemental aluminum as about 0.5 mg aluminum phosphate, sodium chloride, and a L-histidine buffer.

Petitioner Merck Ex-1015, 1747

[0081] In another embodiment, the present disclosure provides a 14 valent pneumococcal vaccine comprising pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F each individually conjugated to PsaA or combination of PsaA and CRM_{197}, wherein the pneumococcal vaccine composition is about a 0.5 mL dose formulated as a sterile liquid comprising, about 2.2 µg to about 4.4 µg of each polysaccharide, about 30 µg to about 35 µg PsaA and CRM_{197}, about 0.125 mg of elemental aluminum as about 0.5 mg aluminum phosphate, sodium chloride, and a L-histidine buffer.

[0082] In another embodiment, the present disclosure provides a 14 valent pneumococcal vaccine comprising pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F each individually conjugated to PsaA or combination of PsaA and CRM_{197}, wherein the pneumococcal vaccine composition is about a 0.5 mL dose formulated as a sterile liquid comprising, about 2.2 to 4.4 µg of each polysaccharide, about 30 µg to about 35 µg PsaA and CRM_{197}, about 0.125 mg of elemental aluminum as about 0.5 mg aluminum phosphate, sodium chloride, and a L-histidine buffer.

[0083] In another embodiment, the present disclosure provides a 15 valent pneumococcal vaccine comprising pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V,14, 18C, 19A, 19F, 22F, 23F and 33F wherein at least serotypes 3, 6A and 6B are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F are conjugated to CRM_{197}, wherein the pneumococcal vaccine composition is about a 0.5 mL dose formulated as a sterile liquid comprising, about 2.2 µg to about 4.4 µg of each polysaccharide, about 5 µg to about 20 µg of PsaA, about 20 µg to about 40 µg of CRM_{197}, about 0.125 mg of elemental aluminum as about 0.5 mg aluminum phosphate, sodium chloride, and a L-histidine buffer.

[0084] In another embodiment, the present disclosure provides a 17 valent pneumococcal vaccine comprising pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 12F,14, 18C, 19A, 19F, 22F, 23F, 33F and 35B wherein at least serotypes 3, 6A and 6B are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 12F,14, 18C, 19A, 19F, 22F, 23F, 33F and 35B are conjugated to CRM_{197}, wherein the pneumococcal vaccine composition is about a 0.5 mL dose formulated as a sterile liquid comprising, about 2.2 µg to about 4.4 µg of each polysaccharide, about

Petitioner Merck Ex-1015, 1748

5 µg to about 20 µg of PsaA, about 20 µg to about 40 µg of CRM_{197}, about 0.125 mg of elemental aluminum as about 0.5 mg aluminum phosphate, sodium chloride, and a L-histidine buffer.

[0085] In another embodiment, the present disclosure provides a 20 valent pneumococcal vaccine comprising pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 35B and 45 wherein at least serotypes 3, 6A and 6B are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 35B and 45 are conjugated to CRM_{197}, wherein the pneumococcal vaccine composition is about a 0.5 mL dose formulated as a sterile liquid comprising, about 2.2 µg to about 4.4 µg of each polysaccharide, about 5 µg to about 20 µg of PsaA, about 20 µg to about 50 µg of CRM_{197}, about 0.125 mg of elemental aluminum as about 0.5 mg aluminum phosphate, sodium chloride, and a L-histidine buffer.

[0086] In another embodiment, the present disclosure provides a 22 valent pneumococcal vaccine comprising pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 10A, 12F, 14, 15A, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38 wherein at least serotypes 3, 6A and 6B are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 10A, 12F, 14, 15A, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38 are conjugated to CRM_{197}, wherein the pneumococcal vaccine composition is about a 0.5 mL dose formulated as a sterile liquid comprising, about 2.2 µg to about 4.4 µg of each polysaccharide, about 5 µg to about 20 µg of PsaA, about 20 µg to about 50 µg of CRM_{197}, about 0.125 mg of elemental aluminum as about 0.5 mg aluminum phosphate, sodium chloride, and a L-histidine buffer.

[0087] In another embodiment, the present disclosure provides a 22 valent pneumococcal vaccine comprising pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 10A, 12F, 14, 15A, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38 wherein serotypes 1, 3, 6A, 10A, 12F, 15A 15B, 22F, 34, 35B, 38 are conjugated to PsaA and serotypes 14, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F and 33F are conjugated to CRM_{197}, wherein the pneumococcal vaccine composition is about a 0.5 mL dose formulated as a sterile liquid comprising, about 2.2 µg to about 4.4 µg of each polysaccharide, about 20 µg to about 40 µg of PsaA, about 20 µg to about 40 µg

Petitioner Merck Ex-1015, 1749

of CRM_{197}, about 0.125 mg of elemental aluminum as about 0.5 mg aluminum phosphate, sodium chloride, and a L-histidine buffer.

[0088] In another embodiment, the present disclosure provides a 24 valent pneumococcal vaccine comprising pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 12F, 14, 15A, 15B, 16F, 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38 wherein at least serotypes 3, 6A and 6B are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 8, 9V, 10A, 12F, 14, 15A, 15B, 16F, 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38 are conjugated to CRM_{197}, wherein the pneumococcal vaccine composition is about a 0.5 mL dose formulated as a sterile liquid comprising, about 2.2 µg to about 4.4 µg of each polysaccharide, about 5 µg to about 20 µg of PsaA, about 20 µg to about 50 µg of CRM_{197}, about 0.125 mg of elemental aluminum as about 0.5 mg aluminum phosphate, sodium chloride, and a L-histidine buffer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0089] Figure 1: An SEC-HPLC chromatogram illustrates conjugation reaction kinetics of serotype 7F (A), serotype 14 (B), serotype 19F (C), serotype 3 (D), serotype 6A (E), and serotype 6B (F).

[0090] Figure 2: An SEC-HPLC chromatogram illustrates conjugation reaction kinetics of serotype 5 (A), serotype 9V (B), serotype 18C (C), serotype 3 (D), serotype 6A (E), and serotype 6B (F).

[0091] Figure 3: Immune response to different serotypes in rabbits immunized with a composition of the present disclosure as described in Example 3.

[0092] Figure 4: Immune response to different serotypes in rabbits immunized with Prevnar 13®.

[0093] Figure 5: Immune response to different serotypes in rabbits immunized with another composition of the present disclosure as described in Example 4.

DETAILED DESCRIPTION

[0094] In an embodiment, the present disclosure provides a pneumococcal vaccine composition comprising pneumococcal polysaccharides where one or more of the pneumococcal polysaccharides are native pneumococcal polysaccharides.

Petitioner Merck Ex-1015, 1750

[0095] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising pneumococcal polysaccharides where one or more of the pneumococcal polysaccharides are fragmented, each fragmented pneumococcal polysaccharide having an average molecular weight less than that of a native pneumococcal polysaccharide.

[0096] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising pneumococcal polysaccharides where each of the pneumococcal polysaccharides is activated with 1-cyano-4-dimethylamino-pyridinium tetrafluoroborate (CDAP) to form a cyanate ester prior to conjugation to the carrier protein.

[0097] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising pneumococcal polysaccharides where one or more of the pneumococcal polysaccharides are directly coupled to an amino group of the carrier protein or are coupled to the amino group by a spacer.

[0098] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising pneumococcal polysaccharides wherein the spacer is cystamine, cysteamine, hexane diamine, adipic acid dihydrazide (ADH), EDAC or EDC.

[0099] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising pneumococcal polysaccharides of one or more serotypes and a carrier protein wherein the PsaA carrier protein is a modified PsaA and does not include wild-type hydrophobic N-terminal leader peptide.

[0100] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising pneumococcal polysaccharides of one or more serotypes and a carrier protein wherein the PsaA carrier protein includes 290 amino acids.

[0101] The present disclosure provides a pneumococcal vaccine composition comprising two or more capsular pneumococcal polysaccharide serotypes each individually conjugated to a carrier protein, referred to herein as polysaccharide-protein conjugates and/or conjugates. When included in the pneumococcal vaccine composition described herein, pneumococcal vaccine is a multivalent pneumococcal

Petitioner Merck Ex-1015, 1751

polysaccharide-protein conjugate vaccine (also referred to herein as multivalent conjugate vaccine, conjugate vaccine, and/or polysaccharide-protein conjugate vaccine). In addition to the multivalent conjugate vaccine, the present disclosure provides a process for preparing and/or administering the same to a subject in need thereof.

[0102] In some embodiments, the pneumococcal vaccine composition is a multivalent immunogenic composition comprising one or more conjugates. For example, the conjugates may include two or more pneumococcal polysaccharides, each of the pneumococcal polysaccharides selected from pneumococcal polysaccharides of serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39, and 45.

[0103] In some embodiments, the pneumococcal vaccine composition is multivalent and comprises five pneumococcal polysaccharides (5 valent), ten pneumococcal polysaccharides (10 valent), eleven pneumococcal polysaccharides (11 valent), twelve pneumococcal polysaccharides (12 valent), thirteen pneumococcal polysaccharides (13 valent), fourteen pneumococcal polysaccharides (14 valent), fifteen pneumococcal polysaccharides (15 valent), sixteen pneumococcal polysaccharides (16 valent), seventeen pneumococcal polysaccharides (17 valent), eighteen pneumococcal polysaccharides (18 valent), nineteen pneumococcal polysaccharides (19 valent), twenty pneumococcal polysaccharides (20 valent), twenty-one pneumococcal polysaccharides (21 valent), twenty-two pneumococcal polysaccharides (22 valent), twenty-three pneumococcal polysaccharides (23 valent), twenty-four pneumococcal polysaccharides (24 valent), twenty-five pneumococcal polysaccharides (25 valent), twenty-six pneumococcal polysaccharides (26 valent), twenty-seven pneumococcal polysaccharides (27 valent), twenty-eight pneumococcal polysaccharides (28 valent), twenty-nine pneumococcal polysaccharides (29 valent), or thirty pneumococcal polysaccharides (30 valent). In other embodiments, the pneumococcal vaccine composition is a 10 valent, 14 valent, 15 valent, 17 valent, 18 valent, 19 valent, 20 valent, 22 valent, 23 valent, 24 valent or 25 valent pneumococcal vaccine composition.

Petitioner Merck Ex-1015, 1752

[0104] Surprisingly, the multivalent pneumococcal conjugate vaccine compositions of the present disclosure offer an improved immune response compared to multivalent pneumococcal vaccines comprising pneumococcal polysaccharides not conjugated to carrier proteins. More specifically, the multivalent pneumococcal conjugate vaccine compositions of the present disclosure were surprisingly most effective when the pneumococcal polysaccharides from one or more serotypes of *Streptococcus. pneumoniae* are conjugated to PsaA and/or CRM_{197}.

[0105] Carrier proteins are non-toxic and non-reactogenic proteins that are obtainable in a sufficient amount and purity. In some embodiments, the present disclosure provides a pneumococcal conjugate vaccine composition comprising one or more carrier proteins conjugated to one or more *S. pneumoniae* polysaccharides (also referred to herein as "pneumococcal polysaccharides"). By conjugating a pneumococcal polysaccharide to a carrier protein, the pneumococcal polysaccharide has increased immunogenicity compared to an unconjugated pneumococcal polysaccharide. Carrier proteins useful with the present disclosure should be amenable to standard conjugation procedures.

[0106] CRM_{197} is a variant of diphtheria toxin and is non-toxic for use in vaccines. CRM_{197} may be isolated from cultures of *Corynebacterium diphtheriae* strain C7 (β197) grown in casamino acids and yeast extract-based medium. CRM_{197} may be prepared recombinantly in accordance with the methods described in U.S. Pat. No. 5,614,382. Alternatively, CRM_{197} may be prepared recombinantly in accordance with the methods known in the literature or according to the method disclosed in PCT publication WO 2016/079755. CRM_{197} may be purified by ultrafiltration, ammonium sulphate precipitation, and ion-exchange chromatography or other methods well known in art.

[0107] In some embodiments, the pneumococcal polysaccharides of the present disclosure are conjugated to one or more carrier proteins. For example, a pneumococcal polysaccharide is each individually conjugated to a carrier protein. In other embodiments, more than one pneumococcal polysaccharide is conjugated to a carrier protein. For example, two pneumococcal polysaccharides, three pneumococcal polysaccharides, four pneumococcal polysaccharides, five pneumococcal polysaccharides, six pneumococcal polysaccharides, seven

Petitioner Merck Ex-1015, 1753

pneumococcal polysaccharides, eight pneumococcal polysaccharides, nine pneumococcal polysaccharides, or ten pneumococcal polysaccharides are conjugated to a carrier protein. In some embodiments, a pneumococcal polysaccharide is conjugated to more than one carrier protein. For example, a pneumococcal polysaccharide is conjugated to one carrier protein, two carrier proteins, three carrier proteins, and/or four carrier proteins.

[0108] In some embodiments, the carrier protein is PsaA. In additional embodiments, a combination of the carrier protein used, which includes two or more carrier proteins, such as PsaA and CRM_{197} which are each individually conjugated to each pneumococcal polysaccharide. In further embodiments, the carrier protein is two carrier proteins and includes PsaA and CRM_{197}.

[0109] In some embodiments, the carrier protein is selected from one or more of the following carrier proteins, PsaA, CRM_{197}, inactivated bacterial toxins such as tetanus toxoid, pertussis toxoid; cholera toxoid, exotoxin A from *Pseudomonas aeruginosa*, bacterial outer membrane proteins such as outer membrane complex c (OMPC), porins, transferrin binding proteins, pneumolysin, PspA, C5a peptidase from Group A or Group B streptococcus, or *Haemophilus influenzae* protein D, ovalbumin, keyhole limpet hemocyanin, (KLH), bovine serum albumin (BSA) and purified protein derivative of tuberculin (PPD).

[0110] Furthermore, one or more of the conjugates may include native (e.g., wild-type) carrier proteins and/or one or more of the conjugates may include carrier proteins modified from their native form to a non-native form (e.g., engineered to lack one or more amino acids). In some embodiments, carrier proteins may be engineered to eliminate one or more protein domains, such as a leader peptide, or other domains that might have properties which are undesirable for conjugates of the present disclosure. For example, PsaA may be a 290 amino acid carrier protein engineered to lack a hydrophobic N-terminal leader peptide having hydropathy index of 2.052.

[0111] In some embodiments, the present disclosure provides a pneumococcal polysaccharide-protein conjugate vaccine composition comprising pneumococcal polysaccharides (e.g., capsular pneumococcal polysaccharides) selected from serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B,

Petitioner Merck Ex-1015, 1754

35F, 38, 39 and 45. The selected pneumococcal polysaccharides are each individually conjugated to carrier protein PsaA or a first portion of the selected pneumococcal polysaccharides are conjugated to PsaA and a second portion of the selected pneumococcal polysaccharides are conjugated to CRM_{197}. In any of these embodiments, the pneumococcal polysaccharide-protein conjugate vaccine composition is an immunogenic multivalent pneumococcal polysaccharide-protein conjugate composition, such as a 10 valent, 13 valent, 14 valent, 15 valent, 17 valent, 18 valent, 19 valent, 20 valent, 22 valent, 23 valent, 24 valent or 25 valent immunogenic multivalent pneumococcal polysaccharide-protein conjugate composition.

[0112] In some embodiments, the present disclosure provides a pneumococcal polysaccharide-protein conjugate vaccine composition comprising pneumococcal polysaccharides (e.g., capsular pneumococcal polysaccharides) selected from serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39 and 45. The selected pneumococcal polysaccharides are each individually conjugated to carrier protein PsaA. In other embodiments, a first portion of the selected pneumococcal polysaccharides are conjugated to PsaA and a second portion of the selected pneumococcal polysaccharides are conjugated to CRM_{197}. In any of these embodiments, the pneumococcal polysaccharide-protein conjugate vaccine composition is an immunogenic multivalent pneumococcal polysaccharide-protein conjugate composition, such as a 10 valent, 13 valent, 14 valent, 15 valent, 17 valent, 18 valent, 19 valent, 20 valent, 22 valent, 23 valent, 24 valent or 25 valent immunogenic multivalent pneumococcal polysaccharide-protein conjugate composition.

[0113] In further embodiments, the present disclosure provides a pneumococcal polysaccharide-protein conjugate vaccine composition comprising pneumococcal polysaccharides (e.g., capsular pneumococcal polysaccharides) selected from serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39 and 45. In these embodiments, at least three of the selected pneumococcal polysaccharides are each individually conjugated to carrier protein PsaA and additional pneumococcal polysaccharides are each individually conjugated

Petitioner Merck Ex-1015, 1755

to carrier protein CRM_{197}. In any of these embodiments, the pneumococcal polysaccharide-protein conjugate vaccine composition is an immunogenic multivalent pneumococcal polysaccharide-protein conjugate composition, such as a 10 valent, 13 valent, 14 valent, 15 valent, 17 valent, 18 valent, 19 valent, 20 valent, 22 valent, 23 valent, 24 valent or 25 valent immunogenic multivalent pneumococcal polysaccharide-protein conjugate composition.

[0114] In further embodiments, the present disclosure provides a pneumococcal polysaccharide-protein conjugate vaccine composition comprising pneumococcal polysaccharides (e.g., capsular pneumococcal polysaccharides) selected from serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39 and 45. In these embodiments, at least a first five of the selected pneumococcal polysaccharides are each individually conjugated to carrier protein PsaA and at least a second five polysaccharides are each individually conjugated to carrier protein CRM_{197}. The first five selected pneumococcal polysaccharides are selected from serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39 and 45 and the second five selected from serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39 and 45. In other embodiments, a first portion of the selected pneumococcal polysaccharides are conjugated to PsaA and a second portion of the selected pneumococcal polysaccharides are conjugated to CRM_{197}. In any of these embodiments, the pneumococcal polysaccharide-protein conjugate vaccine composition is an immunogenic multivalent pneumococcal polysaccharide-protein conjugate composition, such as a 10 valent, 14 valent, 15 valent, 17 valent, 18 valent, 19 valent, 20 valent, 22 valent, 23 valent, 24 valent or 25 valent immunogenic multivalent pneumococcal polysaccharide-protein conjugate composition.

[0115] In further embodiments, the present disclosure provides a 14 valent pneumococcal polysaccharide-protein conjugate vaccine composition comprising at least three pneumococcal polysaccharides (e.g., capsular pneumococcal polysaccharides) selected from serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B,

Petitioner Merck Ex-1015, 1756

23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39 and 45, and are conjugated to PsaA. Moreover, the 14 valent pneumococcal polysaccharide-protein conjugate vaccine composition further comprises at least five pneumococcal polysaccharides selected from serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39 and 45, and are conjugated to CRM_{197}.

[0116] In further embodiments, the present disclosure provides a 15 valent pneumococcal polysaccharide-protein conjugate vaccine composition comprising at least three pneumococcal polysaccharides (e.g., capsular pneumococcal polysaccharides) selected from serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39 and 45, and are conjugated to PsaA. Moreover, the 15 valent pneumococcal polysaccharide-protein conjugate vaccine composition further comprises at least five pneumococcal polysaccharides selected from serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39 and 45, and are conjugated to CRM_{197}.

[0117] In some embodiments, the present disclosure provides a 17 valent pneumococcal polysaccharide-protein conjugate vaccine composition comprising at least three pneumococcal polysaccharides (e.g., capsular pneumococcal polysaccharides) selected from serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39 and 45, and are conjugated to PsaA. Moreover, the 17 valent pneumococcal polysaccharide-protein conjugate vaccine composition further comprises at least five pneumococcal polysaccharides selected from serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39 and 45, and are conjugated to CRM_{197}.

[0118] In other embodiments, the present disclosure provides a 20 valent pneumococcal polysaccharide-protein conjugate vaccine composition comprising at least three pneumococcal polysaccharides (e.g., capsular pneumococcal polysaccharides) selected from serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A,

Petitioner Merck Ex-1015, 1757

11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39 and 45, and are conjugated to PsaA. Moreover, the 20 valent pneumococcal polysaccharide-protein conjugate vaccine composition further comprises at least five pneumococcal polysaccharides selected from serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39 and 45, and are conjugated toCRM_{197}.

[0119] In additional embodiments, the present disclosure provides a 22 valent pneumococcal polysaccharide-protein conjugate vaccine composition comprising at least five pneumococcal polysaccharides (e.g., capsular pneumococcal polysaccharides) selected from serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39 and 45, and are conjugated to PsaA . Moreover, the 22 valent pneumococcal polysaccharide-protein conjugate vaccine composition further comprises at least five pneumococcal polysaccharides selected from serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39 and 45, and are conjugated to CRM_{197}.

[0120] In some embodiments, the present disclosure provides a 24 valent pneumococcal polysaccharide-protein conjugate vaccine composition comprising at least five pneumococcal polysaccharides (e.g., capsular pneumococcal polysaccharides) selected from serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39 and 45, and are conjugated to PsaA. Moreover, the 24 valent pneumococcal polysaccharide-protein conjugate vaccine composition further comprises at least five pneumococcal polysaccharides selected from serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39 and 45, and are conjugated to CRM_{197}.

[0121] In further embodiments, the present disclosure provides a 25 valent pneumococcal polysaccharide-protein conjugate vaccine composition comprising at least five pneumococcal polysaccharides (e.g., capsular pneumococcal

Petitioner Merck Ex-1015, 1758

polysaccharides) selected from serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39 and 45, and are conjugated to PsaA . Moreover, the 25 valent pneumococcal polysaccharide-protein conjugate vaccine composition further comprises at least five pneumococcal polysaccharides selected from serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39 and 45, and are conjugated to CRM_{197}.

[0122] In other embodiments, the present disclosure provides a 14 valent pneumococcal polysaccharide-protein conjugate vaccine composition comprising pneumococcal polysaccharides (e.g., capsular pneumococcal polysaccharides) selected from serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F. Of the selected serotypes, at least serotype 3, and serotype 6B are conjugated to PsaA, and each of one or more serotypes 1, 4, 5, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F are conjugated to CRM_{197}.

[0123] In other embodiments, the present disclosure provides a 14 valent pneumococcal polysaccharide-protein conjugate vaccine composition comprising pneumococcal polysaccharides (e.g., capsular pneumococcal polysaccharides) selected from serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F. Of the selected serotypes, at least serotype 3, and serotype 6A are conjugated to PsaA, and each of one or more serotypes 1, 4, 5, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F are conjugated to CRM_{197}.

[0124] In additional embodiments, the present disclosure provides a 15 valent pneumococcal polysaccharide-protein conjugate vaccine composition comprising pneumococcal polysaccharides (e.g., capsular pneumococcal polysaccharides) selected from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V,14, 18C, 19A, 19F, 22F, 23F and 33F. Of the selected serotypes, at least serotypes 3, 6A, and 6B are conjugated to PsaA, and each of one or more serotypes 1, 4, 5, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F are conjugated to CRM_{197}.

[0125] In some embodiments, the present disclosure provides a 17 valent pneumococcal polysaccharide-protein conjugate vaccine composition comprising pneumococcal polysaccharides (e.g., capsular pneumococcal polysaccharides)

Petitioner Merck Ex-1015, 1759

selected from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 12F,14, 18C, 19A, 19F, 22F, 23F, 33F and 35B. Of the selected serotypes, at least serotypes 3, 6A, and 6B are conjugated to PsaA, and each of one or more serotypes 1, 4, 5, 7F, 9V, 12F,14, 18C, 19A, 19F, 22F, 23F, 33F and 35B are conjugated to CRM_{197}.

[0126] In some embodiments, the present disclosure provides a 20 valent pneumococcal polysaccharide-protein conjugate vaccine composition comprising pneumococcal polysaccharides (e.g., capsular pneumococcal polysaccharides) selected from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 35B and 45. Of the selected serotypes, at least serotypes 3, 6A, and 6B are conjugated to PsaA, and each of one or more serotypes 1, 4, 5, 7F, 9V, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 35B and 45 are conjugated to CRM_{197}.

[0127] In other embodiments, the present disclosure provides a 22 valent pneumococcal polysaccharide-protein conjugate vaccine composition comprising pneumococcal polysaccharides (e.g., capsular pneumococcal polysaccharides) selected from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 10A, 12F, 14, 15A, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 34,35B and 38. Of the selected serotypes, at least serotypes 3, 6A, and 6B are conjugated to PsaA, and each of one or more serotypes 1, 4, 5, 7F, 9V, 10A, 12F, 14, 15A, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38 are conjugated to CRM_{197}.

[0128] In other embodiments, the present disclosure provides a 22 valent pneumococcal polysaccharide-protein conjugate vaccine composition comprising pneumococcal polysaccharides (e.g., capsular pneumococcal polysaccharides) selected from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 10A, 12F, 14, 15A, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38. Of the selected serotypes, serotypes 1, 3, 6A, 10A, 12F, 15A 15B, 22F, 34, 35, and 38 are conjugated to PsaA, and each of serotypes 14, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F and 33F are conjugated to CRM_{197}.

[0129] In other embodiments, the present disclosure provides a 24 valent pneumococcal polysaccharide-protein conjugate vaccine composition comprising pneumococcal polysaccharides (e.g., capsular pneumococcal polysaccharides) selected from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 12F, 14, 15A, 15B, 16F, 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38. Of the selected serotypes, serotypes

Petitioner Merck Ex-1015, 1760

1, 3, 6A, 8, 10A, 12F, 15A 15B, 16F, 22F, 34, 35, and 38 are conjugated to PsaA, and each of serotypes 14, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F and 33F are conjugated to CRM_{197}.

[0130] The pneumococcal polysaccharide-protein conjugate compositions of the present disclosure further comprise one or more of the following: a pharmaceutically acceptable carrier, a pharmaceutically acceptable diluent, a buffer, a preservative, a stabilizer, an adjuvant, and/or a lyophilization excipient. For example, the pneumococcal polysaccharide-protein conjugate compositions of the present disclosure may comprise a pharmaceutically acceptable carrier. In some embodiments, the pneumococcal polysaccharide-protein conjugate compositions of the present disclosure comprise at least 10 pneumococcal polysaccharides selected from serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39 and 45. The selected serotypes are each individually conjugated to PsaA or a combination of PsaA and CRM_{197}, and a pharmaceutically acceptable carrier.

[0131] In some embodiments, the pneumococcal polysaccharides useful in the compositions of the present disclosure may be extracted from one or more microorganisms (e.g. Streptococcus pneumoniae) according to conventional methods. For example, pneumococcal polysaccharides may be prepared according to known procedures. Furthermore, purification of the pneumococcal polysaccharides may be performed according to the procedure described in PCT publication WO 2016/174683 A1.

[0132] The extracted pneumococcal polysaccharides may be purified according to conventional methods and may be used in its native form. In other embodiments, the extracted and purified pneumococcal polysaccharides may be fragmented to obtain one or more portions of the pneumococcal polysaccharide, each portion of the pneumococcal polysaccharide having an average molecular weight less than that of the extracted and purified pneumococcal polysaccharides.

[0133] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising pneumococcal polysaccharides, each pneumococcal polysaccharide having a molecular between about 150 kDa and 450 kDa.

Petitioner Merck Ex-1015, 1761

[0134] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising one or more capsular pneumococcal polysaccharide serotype each individually conjugated to a carrier protein, such as a polysaccharide-protein conjugate wherein each polysaccharide-protein conjugate has a molecular weight of about 1,500 kDa to about 15,000 kDa.

[0135] In other embodiments, the extracted and purified pneumococcal polysaccharides may be activated prior to conjugation to one or more carrier proteins. For example, the extracted and purified pneumococcal polysaccharides may be activated (e.g., chemically) prior to conjugation to one or more carrier proteins. Each activated pneumococcal polysaccharide may be each individually conjugated to a carrier protein forming a polysaccharide-protein conjugate (e.g., a glycoconjugate). In other embodiments, one or more of the activated pneumococcal polysaccharides may be conjugated to an individual carrier protein and/or an activated pneumococcal polysaccharide may be conjugated to an individual carrier protein. The conjugates may be prepared by known techniques.

[0136] In some embodiments, the pneumococcal polysaccharides may be chemically activated and subsequently conjugated to carrier proteins according to known techniques, such as those described in U.S. Pat. Nos. 4,365,170, 4,673,574 and 4,902,506. For example, pneumococcal polysaccharides can be activated by oxidation of a terminal hydroxyl group to an aldehyde with an oxidizing agent, such as periodate (e.g., sodium periodate, potassium periodate, or periodic acid) by random oxidative cleavage of one or more vicinal hydroxyl groups of the carbohydrates and formation of one or more reactive aldehyde groups.

[0137] The pneumococcal polysaccharides may also be activated by CDAP (1-cyano-4-dimethylamino-pyridinium tetrafluoroborate) and subsequently conjugated to one or more carrier proteins such as PsaA, CRM_{197}, PspA, or combination thereof. In other embodiments, pneumococcal polysaccharides activated with CDAP to form a cyanate ester may be directly conjugated to one or more carrier proteins or conjugated using a spacer (e.g., linker). The spacer may couple to an amino group on the carrier protein. In some embodiments, the spacer may be cystamine or cysteamine, which generates a thiolated polysaccharide that may be coupled to the carrier protein through a thioether linkage to a maleimide-activated carrier protein

Petitioner Merck Ex-1015, 1762

(e.g., using GMBS) or a haloacetylated carrier protein (e.g., using iodoacetimide, ethyl iodoacetimide HCl, SIAB, SIA, SBAP, and/or N-succinimidyl bromoacetate. In other embodiments, the cyanate ester is coupled using hexane diamine or adipic acid dihydrazide (ADH) and an amino-derivitized saccharide is conjugated to a carrier protein using carbodiimide (e.g. EDAC or EDC) chemistry via a carboxyl group on the protein carrier. Such conjugates are described in International Patent Application Publication No. WO 93/15760, International Patent Application Publication No. WO 95/08348, International Patent Application Publication No. WO 96/29094, and Chu et al., 1983, Infect. Immunity 40:245-256.

[0138] Other suitable activation and/or coupling techniques for use with the polysaccharide-protein conjugates and vaccine compositions of the present disclosure include use of carbodiimides, hydrazides, active esters, norborane, p-nitrobenzoic acid, N-hydroxysuccinimide, S—NHS, EDC, TSTU, and other methods described in International Patent Application Publication No. WO 98/42721. For example, conjugation may involve a carbonyl linker which may be formed by reaction of a free hydroxyl group of the saccharide with CDI (See Bethell et al., 1979, J. Biol. Chem. 254:2572-4; Hearn et al., 1981, J. Chromatogr. 218:509-18) followed by coupling with a protein to form a carbamate linkage. In some embodiments, the anomeric terminus may be reduced to a primary hydroxyl group, optional protection/deprotection of the primary hydroxyl group, reaction of the primary hydroxyl group with CDI to form a CDI carbamate intermediate and coupling the CDI carbamate intermediate with an amino group on a protein.

[0139] For example, another suitable activation and/or coupling techniques for use with the polysaccharide-protein conjugates and vaccine compositions of the present disclosure include the following method: sized pneumococcal polysaccharides (e.g., about 6 mL of sized polysaccharide at a concentration of about 10 mg/mL) and CDAP (e.g., about 100 mg/mL in acetonitrile (w/v)) can be mixed in a glass vial in a ratio of about 1 to about 1 (e.g., by stirring for about 1 minute). The pH of the polysaccharide solution may be adjusted as necessary (e.g., to about 9.25 with about 0.2M triethylamine and stirred for 3 min at room temperature). In addition, PsaA (e.g., about 4 mL of a solution having a concentration of about 15 mg/mL) may be added slowly to the activated pneumococcal polysaccharides (e.g., in a ratio of about 1 to about 1 (Ps: Carrier protein)). The pH of the reaction may be adjusted (e.g., to about

Petitioner Merck Ex-1015, 1763

9.05 using 0.2M trimethylamine) and the reaction may be continued (e.g., by stirring for 5 hours at room temperature). The reaction mixture may be quenched (e.g., by addition of an excess concentration of glycine).

[0140] In some embodiments, the reaction mixture may be diafiltered using a membrane (e.g., a 100 K MWCO membrane) and may be purified by size-exclusion chromatography. The diafiltered and purified fractions may be analyzed using SEC-MALLS, and an anthrone method. The analyzed fractions containing conjugates may be pooled and sterile filtered (e.g., using 0.2 μm filters).

[0141] Following conjugation of pneumococcal polysaccharides to one or more carrier proteins, the polysaccharide-protein conjugates may be purified (e.g., enriched with respect to the amount of polysaccharide-protein conjugate) by a variety of techniques. These techniques include, but are not limited to concentration/diafiltration operations, precipitation/elution, column chromatography, and depth filtration. For example, after the conjugates are purified, the conjugates may be compounded to formulate the pneumococcal polysaccharide-protein conjugate compositions of the present disclosure, which may be used as vaccines.

[0142] In some embodiments, the present disclosure provides a method for preparing a polysaccharide-protein conjugate of the pneumococcal vaccine composition described herein wherein the method further comprises formulating the polysaccharide-protein conjugate into the pneumococcal vaccine composition including an adjuvant, an excipient, and a buffer.

[0143] In some embodiments, the present disclosure provides a method for preparing a polysaccharide-protein conjugate of the pneumococcal vaccine composition described herein wherein the adjuvant is aluminum phosphate.

[0144] In some embodiments, the present disclosure provides a method of treating a subject in need thereof comprising, administering a pneumococcal vaccine composition described herein to the subject in need thereof.

[0145] In some embodiments, the subject has a disease mediated by *streptococcus pneumoniae,* such as invasive pneumococcal disease (IPD).

[0146] In one embodiment, the subject is a human, such as an infant (less than about 1 year of age), a toddler (about 12 months to about 24 months of age), a young

Petitioner Merck Ex-1015, 1764

child (about 2 years to about 5 years of age), an older child (about 5 years to about 13 years of age), an adolescent (about 13 years to about 18 years of age), an adult (about 18 years to about 65 years of age), or an elder (more than about 65 years of age).

[0147] In some embodiments, the present disclosure provides a method of inducing an immune response to an *S. pneumoniae* capsular polysaccharide conjugate comprising administering an immunologically effective amount of the pneumococcal vaccine composition described herein to a subject.

[0148] In one embodiment, method of inducing an immune response to an *S. pneumoniae* capsular polysaccharide conjugate, comprising administering the pneumococcal vaccine composition described herein to the subject systemically, subcutaneously, and/or mucousally.

[0149] In some embodiments, an amount of each conjugate in a dose of the vaccine compositions of the present disclosure is an amount sufficient to induce an immunoprotective response, such as an immunoprotective response without significant, adverse effects. While the amount of each conjugate may vary depending upon the pneumococcal serotype, each dose of the vaccine compositions may comprise about 0.1 µg to about 50 µg of each pneumococcal polysaccharide, about 0.1 µg to about 10 µg, or about 1 µg to about 5 µg of each pneumococcal polysaccharide conjugated to each carrier protein comprising about 1.5 µg to about 5 µg of carrier protein.

[0150] In another embodiment, the present disclosure provides a pneumococcal vaccine composition comprising pneumococcal polysaccharides and carrier proteins, the pneumococcal vaccine composition having a percent ratio of protein to polysaccharide (protein/PS) of about 0.5 to about 2.0 protein/PS, preferably, 0.7 to 1.2.

[0151] In some embodiments, the present disclosure provides pneumococcal polysaccharide-protein conjugate vaccine compositions comprising pneumococcal polysaccharides having molecular weights ranging between about 100 kDa to about 400 kDa, about 125 kDa to about 425 kDa, about 150 kDa to about 450 kDa, about 175 kDa to about 475 kDa, about 200 kDa to about 500 kDa, about 250 kDa to about 550 kDa, or about 300 kDa to about 600 kDa.

Petitioner Merck Ex-1015, 1765

[0152] In other embodiments, the present disclosure provides pneumococcal polysaccharide-protein conjugate vaccine compositions comprising one or more polysaccharide-protein conjugates having a molecular weight ranging between about 1,000 kDa to about 10,000 kDa, about 1,500 kDa to about 15,000 kDa, about 2,000 kDa to about 20,000 kDa, about 2,500 kDa to about 25,000 kDa, or about 3,000 kDa to about 30,000 kDa.

[0153] The pneumococcal polysaccharide-protein conjugate vaccine compositions of the present disclosure may be manufactured using known methods. For example, the pneumococcal polysaccharide-protein conjugate vaccine compositions may be formulated with a pharmaceutically acceptable diluent or vehicle, e.g. water or a saline solution. In addition, the pneumococcal polysaccharide-protein conjugate vaccine compositions may further include one or more of the following: a buffer, a preservative or a stabilizer, polysorbate, an adjuvant such as an aluminum compound, e.g. an aluminium hydroxide, an aluminium phosphate or an aluminium hydroxyphosphate, and/or a lyophilization excipient. Inclusion of any one of the above compounds in the pneumococcal polysaccharide-protein conjugate vaccine compositions of the present disclosure may be selected as a function of the mode and route of administration to a subject in need thereof and may further be based on standard pharmaceutical practices.

[0154] In some embodiments, the present disclosure provides a method for preparing a fourteen valent pneumococcal polysaccharide-protein conjugate composition comprising pneumococcal polysaccharides selected from serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F, wherein at least serotypes 3, and 6B are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F are conjugated to CRM_{197}. The method for preparing the fourteen valent pneumococcal polysaccharide-protein conjugate composition comprises the steps of;

(a) individually conjugating one or more of the fourteen pneumococcal polysaccharides (e.g., activated utilizing CDAP) to an immunogenic carrier protein, such as PsaA and/or CRM_{197},

(b) diafiltering and purifying the conjugates using size exclusion chromatography,

Petitioner Merck Ex-1015, 1766

(c) analyzing the purified fractions using SEC-MALLS, pooling fractions containing each of the fourteen conjugates, and filter sterilizing the monovalent conjugate fractions, and

(d) formulating the fourteen conjugates (e.g., about 2.2 to 4.4 µg for each serotype, about 5 µg to about 10 µg of PsaA, and about 15 µg to about 36 µg of CRM_{197}), an adjuvant (such as aluminum phosphate), an excipient, and buffer into the fourteen valent pneumococcal polysaccharide-protein conjugate composition.

In some embodiments, the fourteen valent pneumococcal polysaccharide-protein conjugate composition may be filtered (e.g., aseptically).

[0155] In some embodiments, the present disclosure provides a method for preparing a fourteen valent pneumococcal polysaccharide-protein conjugate composition comprising pneumococcal polysaccharides selected from serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F, wherein at least serotypes 3, and 6A are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F are conjugated to CRM_{197}. The method for preparing the fourteen valent pneumococcal polysaccharide-protein conjugate composition comprises the steps of;

(a) individually conjugating one or more of the fourteen pneumococcal polysaccharides (e.g., activated utilizing CDAP) to an immunogenic carrier protein, such as PsaA and/or CRM_{197},

(b) diafiltering and purifying the conjugates using size exclusion chromatography,

(c) analyzing the purified fractions using SEC-MALLS, pooling fractions containing each of the fourteen conjugates, and filter sterilizing the monovalent conjugate fractions, and

(d) formulating the fourteen conjugates (e.g., about 2.2 to 4.4µg for each serotype, about 5 µg to about 10 µg of PsaA, and about 15 µg to about 36 µg of CRM_{197}), an adjuvant (such as aluminum phosphate), an excipient, and buffer into the fourteen valent pneumococcal polysaccharide-protein conjugate composition.

Petitioner Merck Ex-1015, 1767

In some embodiments, the fourteen valent pneumococcal polysaccharide-protein conjugate composition may be filtered (e.g., aseptically).

[0156] In some embodiments, the present disclosure provides a method for preparing a fifteen valent pneumococcal polysaccharide-protein conjugate composition comprising pneumococcal polysaccharides selected from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V,14, 18C, 19A, 19F, 22F, 23F and 33F wherein at least serotypes 3, 6A and 6B are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F are conjugated to CRM_{197}. The method for preparing the fifteen valent pneumococcal polysaccharide-protein conjugate composition comprises the steps of;

(a) individually conjugating one or more of the fifteen pneumococcal polysaccharides (e.g., activated utilizing CDAP) to an immunogenic carrier protein, such as PsaA and/or CRM_{197},

(b) diafiltering and purifying the conjugates using size exclusion chromatography,

(c) analyzing the purified fractions using SEC-MALLS, pooling fractions containing each of the fifteen conjugates, and filter sterilizing the monovalent conjugate fractions, and

(d) formulating the fifteen conjugates (e.g., about 2.2 to 4.4 µg for each serotype, about 5 µg to about 20 µg of PsaA, and about 20 µg to about 40 µg of CRM_{197}), an adjuvant (such as aluminum phosphate), an excipient, and buffer into the fifteen valent pneumococcal polysaccharide-protein conjugate composition.

In some embodiments, the fifteen valent pneumococcal polysaccharide-protein conjugate composition may be filtered (e.g., aseptically).

[0157] In some embodiments, the present disclosure provides a method for preparing a seventeen valent pneumococcal polysaccharide-protein conjugate composition comprising pneumococcal polysaccharides selected from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 12F,14, 18C, 19A, 19F, 22F, 23F, 33F and 35B wherein at least serotypes 3, 6A and 6B are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 12F,14, 18C, 19A, 19F, 22F, 23F, 33F and 35B are conjugated to CRM_{197}.

Petitioner Merck Ex-1015, 1768

The method for preparing the seventeen valent pneumococcal polysaccharide-protein conjugate composition comprises the steps of;

(a) individually conjugating one or more of the seventeen pneumococcal polysaccharides (e.g., activated utilizing CDAP) to an immunogenic carrier protein, such as PsaA and/or CRM_{197},

(b) diafiltering and purifying the conjugates using size exclusion chromatography,

(c) analyzing the purified fractions using SEC-MALLS, pooling fractions containing each of the seventeen conjugates, and filter sterilizing the monovalent conjugate fractions, and

(d) formulating the seventeen conjugates (e.g., about 2.2 to 4.4 µg for each serotype, about 5 µg to about 20 µg of PsaA, and about 20 µg to about 40 µg of CRM_{197}), an adjuvant (such as aluminum phosphate), an excipient, and buffer into the seventeen valent pneumococcal polysaccharide-protein conjugate composition.

In some embodiments, the seventeen valent pneumococcal polysaccharide-protein conjugate composition may be filtered (e.g., aseptically).

[0158] In some embodiments, the present disclosure provides a method for preparing a twenty valent pneumococcal polysaccharide-protein conjugate composition comprising pneumococcal polysaccharides selected from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 35B and 45 wherein at least serotypes 3, 6A and 6B are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 35B and 45 are conjugated to CRM_{197}. The method for preparing the twenty valent pneumococcal polysaccharide-protein conjugate composition comprises the steps of;

(a) individually conjugating one or more of the twenty pneumococcal polysaccharides (e.g., activated utilizing CDAP) to an immunogenic carrier protein, such as PsaA and/or CRM_{197},

(b) diafiltering and purifying the conjugates using size exclusion chromatography,

Petitioner Merck Ex-1015, 1769

(c) analyzing the purified fractions using SEC-MALLS, pooling fractions containing each of the twenty conjugates, and filter sterilizing the monovalent conjugate fractions, and

(d) formulating the twenty conjugates (e.g., about 2.2 to 4.4 μg for each serotype, about 5 μg to about 20 μg of PsaA, and about 20 μg to about 50 μg of CRM_{197}), an adjuvant (such as aluminum phosphate), an excipient, and buffer into the twenty valent pneumococcal polysaccharide-protein conjugate composition.

In some embodiments, the twenty valent pneumococcal polysaccharide-protein conjugate composition may be filtered (e.g., aseptically).

[0159] In some embodiments, the present disclosure provides a method for preparing a twenty-two valent pneumococcal polysaccharide-protein conjugate composition comprising one or more pneumococcal polysaccharides selected from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 10A, 12F, 14, 15A, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38wherein at least serotypes 3, 6A and 6B are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 10A, 12F, 14, 15A, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38 are conjugated to CRM_{197}. The method for preparing the twenty-two valent pneumococcal polysaccharide-protein conjugate composition comprises the steps of;

(a) individually conjugating one or more of the twenty-two pneumococcal polysaccharides (e.g., activated utilizing CDAP) to an immunogenic carrier protein, such as PsaA and/or CRM_{197},

(b) diafiltering and purifying the conjugates using size exclusion chromatography,

(c) analyzing the purified fractions using SEC-MALLS, pooling fractions containing each of the twenty-two conjugates, and filter sterilizing the monovalent conjugate fractions, and

(d) formulating the twenty-two conjugates (e.g., about 2.2 to 4.4 μg for each serotype, about 5 μg to about 20 μg of PsaA, and about 20 μg to about 50 μg of CRM_{197}), an adjuvant (such as aluminum phosphate),

Petitioner Merck Ex-1015, 1770

an excipient, and buffer into the twenty-two valent pneumococcal polysaccharide-protein conjugate composition.

In some embodiments, the twenty-two valent pneumococcal polysaccharide-protein conjugate composition may be filtered (e.g., aseptically).

[0160] The compositions of the present disclosure may be formulated into a unit dose, for example, a unit dose vial, into a multiple dose, for example, a multiple dose vial, or a pre-filled syringe. The compositions of the present disclosure may further comprise of one or more preservative(s) selected from thiomersal, 2-phenoxyethanol and the like, in an amount which may range from about 4 mg/mL to about 20 mg/mL.

[0161] In some embodiments, the present disclosure also provides an immunogenic composition (e.g., a vaccine), such as a pneumococcal polysaccharide-protein conjugate composition, administered as a single dose of about 0.5 mL formulated to contain at least the following: about 2.2 to 4.4 µg of two or more pneumococcal polysaccharide serotypes, about 1 µg to about 10 µg of PsaA per serotype, about 1 µg to about 10 µg of CRM_{197} for each serotype, about 0.2 mg to about 1 mg of an adjuvant (e.g., aluminum phosphate), and one or more excipients (e.g., sodium chloride, and/or a buffer).

[0162] In other embodiments, the present disclosure also provides a thirteen valent immunogenic composition (e.g., a vaccine) in a sterile liquid formulation, such as a thirteen valent pneumococcal polysaccharide-protein conjugate composition, administered as a single dose of about 0.5 mL formulated to contain at least the following: pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F and 33F each individually conjugated to PsaA or combination of PsaA and CRM_{197}.

[0163] The thirteen valent vaccine may be further formulated into one or more doses of about 0.5 mL dose, each 0.5 mL dose comprising about 2.2 µg to about 4.4 µg of each of the thirteen serotypes, about 25 µg to about 30 µg PsaA and CRM_{197}, about 0.125 mg of an adjuvant (e.g., elemental aluminum such as about 0.5 mg aluminum phosphate), sodium chloride, and L-histidine buffer.

[0164] In some embodiments, the present disclosure also provides a fourteen valent immunogenic composition (e.g., a vaccine) in a sterile liquid formulation, such

Petitioner Merck Ex-1015, 1771

as a fourteen valent pneumococcal polysaccharide-protein conjugate composition, administered as a single dose of about 0.5 mL formulated to contain at least the following: pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F each individually conjugated to PsaA or combination of PsaA and CRM_{197}.

[0165] In some embodiments, the present disclosure also provides a fourteen valent immunogenic composition (e.g., a vaccine) in a sterile liquid formulation, such as a fourteen valent pneumococcal polysaccharide-protein conjugate composition, administered as a single dose of about 0.5 mL formulated to contain at least the following: pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F each individually conjugated to PsaA or combination of PsaA and CRM_{197}.

[0166] The fourteen valent vaccine may be further formulated into one or more doses of about 0.5 mL dose, each 0.5 mL dose comprising about 2.2 µg to about 4.4 µg of each of the fourteen serotypes, about 20 µg to about 35 µg PsaA and CRM_{197}, about 0.125 mg of an adjuvant (e.g., elemental aluminum such as about 0.5 mg aluminum phosphate), sodium chloride, and L-histidine buffer.

[0167] In other embodiments, the present disclosure also provides a fifteen valent immunogenic composition (e.g., a vaccine) in a sterile liquid formulation, such as a fifteen valent pneumococcal polysaccharide-protein conjugate composition, administered as a single dose of about 0.5 mL formulated to contain at least the following: pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V,14, 18C, 19A, 19F, 22F, 23F and 33F, wherein at least serotypes 3, 6A and 6B are each individually conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F are each individually conjugated to CRM_{197}.

[0168] The fifteen valent vaccine may be further formulated into one or more doses of about 0.5 mL dose, each 0.5 mL dose comprising about 2.2 µg to about 4.4 µg of each of the fifteen serotypes, about 5 µg to about 20 µg PsaA, about 20 µg to 40 µg of CRM_{197}, about 0.125 mg of an adjuvant (e.g., elemental aluminum such as about 0.5 mg aluminum phosphate), sodium chloride, and L-histidine buffer.

[0169] In additional embodiments, the present disclosure also provides a seventeen valent immunogenic composition (e.g., a vaccine) in a sterile liquid

Petitioner Merck Ex-1015, 1772

formulation, such as a seventeen valent pneumococcal polysaccharide-protein conjugate composition, administered as a single dose of about 0.5 mL formulated to contain at least the following: pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 12F,14, 18C, 19A, 19F, 22F, 23F, 33F and 35B, wherein at least serotypes 3, 6A and 6B are each individually conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 12F,14, 18C, 19A, 19F, 22F, 23F, 33F and 35B are each individually conjugated to CRM_{197}.

[0170] The seventeen valent vaccine may be further formulated into one or more doses of about 0.5 mL dose, each 0.5 mL dose comprising about 2.2 µg to about 4.4 µg of each of the seventeen serotypes, about 5 µg to about 20 µg PsaA, about 20 µg to 40 µg of CRM_{197}, about 0.125 mg of an adjuvant (e.g., elemental aluminum such as about 0.5 mg aluminum phosphate), sodium chloride, and L-histidine buffer.

[0171] In some embodiments, the present disclosure also provides a twenty valent immunogenic composition (e.g., a vaccine) in a sterile liquid formulation, such as a twenty valent pneumococcal polysaccharide-protein conjugate composition, administered as a single dose of about 0.5 mL formulated to contain at least the following: pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 35B and 45, wherein at least serotypes 3, 6A and 6B are each individually conjugated to PsaA and one ore more serotypes 1, 4, 5, 7F, 9V, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 35B and 45 are each individually conjugated to CRM_{197}.

[0172] The twenty valent vaccine may be further formulated into one or more doses of about 0.5 mL dose, each 0.5 mL dose comprising about 2.2 µg to about 4.4 µg of each of the twenty serotypes, about 5 µg to about 20 µg PsaA, about 20 µg to 50 µg of CRM_{197}, about 0.125 mg of an adjuvant (e.g., elemental aluminum such as about 0.5 mg aluminum phosphate), sodium chloride, and L-histidine buffer.

[0173] In some embodiments, the present disclosure also provides a twenty-two valent immunogenic composition (e.g., a vaccine) in a sterile liquid formulation, such as a twenty-two valent pneumococcal polysaccharide-protein conjugate composition, administered as a single dose of about 0.5 mL formulated to contain at least the following: pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 10A, 12F, 14, 15A, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38, wherein at least

Petitioner Merck Ex-1015, 1773

serotypes 3, 6A and 6B are each individually conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 10A, 12F, 14, 15A, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38 are each individually conjugated to CRM_{197}.

[0174] The twenty-two valent vaccine may be further formulated into one or more doses of about 0.5 mL dose, each 0.5 mL dose comprising about 2.2 µg to about 4.4 µg of each of the twenty-two serotypes, about 5 µg to about 20 µg PsaA, about 20 µg to 50 µg of CRM_{197}, about 0.125 mg of an adjuvant (e.g., elemental aluminum such as about 0.5 mg aluminum phosphate), sodium chloride, and L-histidine buffer.

[0175] In some embodiments, the present disclosure also provides a twenty-four valent immunogenic composition (e.g., a vaccine) in a sterile liquid formulation, such as a twenty-four valent pneumococcal polysaccharide-protein conjugate composition, administered as a single dose of about 0.5 mL formulated to contain at least the following: pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 12F, 14, 15A, 15B, 16F, 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38, wherein at least serotypes 3, 6A and 6B are each individually conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 8, 9V, 10A, 12F, 14, 15A, 15B, 16F, 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38 are each individually conjugated to CRM_{197}.

[0176] The twenty-four valent vaccine may be further formulated into one or more doses of about 0.5 mL dose, each 0.5 mL dose comprising about 2.2 µg to about 4.4 µg of each of the twenty-two serotypes, about 5 µg to about 20 µg PsaA, about 20 µg to 50 µg of CRM_{197}, about 0.125 mg of an adjuvant (e.g., elemental aluminum such as about 0.5 mg aluminum phosphate), sodium chloride, and L-histidine buffer.

[0177] Compositions of the present disclosure may be administered to a subject in need thereof by any number of conventional routes used in the field of vaccines. For example, compositions of the present disclosure may be administered systemically, such as parenterally (e.g. subcutaneously, intramuscularly, intradermally and/or intravenously) or mucosally (e.g., orally and/or nasally).

[0178] In some embodiments, the present disclosure also provides methods of inducing an immune response in a subject in need thereof to one or more *s. pneumoniae* capsular polysaccharides conjugated to one or more carrier proteins. The methods for inducing the immune response comprise administering an

Petitioner Merck Ex-1015, 1774

immunologically effective amount of the compositions described herein to the subject in need thereof.

[0179] According to the methods of the present disclosure, the subject to whom the compositions described herein is a human, such as an infant (less than about 1 year of age), a toddler (about 12 months to about 24 months of age), a young child (about 2 years to about 5 years of age), an older child (about 5 years to about 13 years of age), an adolescent (about 13 years to about 18 years of age), an adult (about 18 years to about 65 years of age), or an elder (more than about 65 years of age).

[0180] As used herein, an "effective amount" of the compositions described in the present disclosure refers to an amount required to elicit an immune response in the subject to which the composition was administered. The immune response is characterized by the presence of one or more *S. pneumoniae* antigen-specific antibodies in the host that significantly reduce the likelihood or severity of infection of *S. pneumoniae* during a subsequent challenge.

EXAMPLES

[0181] The following examples are provided to illustrate the disclosure and are merely for illustrative purpose only and should not be construed to limit the scope of the disclosure.

Example 1: Conjugation of individual pneumococcal polysaccharide to carrier protein to form Polysaccharide-PsaA Conjugates

A) *PsaA Preparation:*

[0182] The PsaA gene was PCR amplified from *Streptococcus pneumoniae* Serotype 4, without its hydrophobic leader peptide sequence. The gene was sequence verified and cloned into *E. coli* using a vector constructed in-house (pBE66) for higher expression.

[0183] Glycerol stock culture encoding the PSaA gene was revived on a 20 mL LB Media containing 1 mL of Glycerol Stock in a 150 mL conical flask. The culture was incubated for about 6 hrs at 37° C under 200 rpm to a final OD_{600nm} of 3.5 OD. The revived culture was transferred to 1L seed culture in a 5 L conical flask. The culture was grown for about 10 hrs at 37° C under 200 rpm to a final OD 600nm of 3.

Petitioner Merck Ex-1015, 1775

[0184] The seed culture was transferred aseptically to a 20 L fermenter containing the following media components, HyPeptone 6 g/L , Yeast extract 12/L, di Potassium Hydrogen ortho phosphate 13.5 g/L , ammonium phosphate di basic 4 g/L , Citric acid 1.7 g/L , $MgSO_4.7H_2O$ 1.2 g/L , Glucose 4 g/L , thamine HCL 10 mg/L along with 1 mL/L trace elements (e.g., trace elements for 100mL composition $FeCl_3$ 2.7 g, $ZnCl_2$ 0.2g, $CoCl_2.6H_2O$ 0.2g, $Na_2MoO_4.2H_2O$ 0.2 g, $CuSO_4$ $5H_2O$ 0.1 g, Boric Acid 0.05 g, $CaCl_2$ $2H_2O$ 0.1g, Conc., HCL 10mL.) The initial fermentation started with OD $_{600nm}$ 0.2 OD. The pH was maintained at 7± 0.2 throughout the fermentation with 20% ortho-phosphoric acid and 12.5 % ammonium hydroxide.

[0185] When the glucose level falls below 0.5 g/L the feed batch was initiated at a steady rate of 3 – 4 g/L/hr, the DO% was maintained > 20% throughout the fermentation with oxygen enrichment.

[0186] Cells were grown in the fermentor and the cell pellet was harvested by centrifugation. The cells were lysed using cell-disruption device (Panda). The lysate was centrifuged at 10000g, the clarified supernatant was subject to purification.

[0187] PsaA purification was performed similar to the procedure described in Larentis et.al, 2011 (Protein expression and Purification 78 (2011) 38). Purification was further optimized by using mixed mode chromatography (Ceramic Hydroxyapatite Type-II) after DEAE to achieve higher purity of PsaA.

[0188] *Anion exchange chromatography:* 30 mL of DEAE Sepharose (GE) resin was packed in XK16/20 column. The resin was washed with 5 column volumes of sterile distilled water followed by 10 column volumes of 20mM Tris, 1mM EDTA, pH 8.0 (Equilibration buffer). 30 mL of supernatant was diluted to 100 mL with equilibration buffer and loaded onto column and flow through was collected. The column was washed with 5 volumes of equilibration buffer. PsaA was eluted with 12 volumes of linear gradient of (0-100%B). (Buffer A containing 20 mM Tris, 1 mM EDTA pH 8.0; Buffer B-20 mM Tris, 1 mM EDTA, 250 mM NaCl pH 8.0.) This was followed by washing the columns with 20 mM Tris, 1mM EDTA, 1 M NaCl pH8.0.

[0189] *Mixed mode Chromatography:* 25ml of Ceramic Hydroxyapatite Type II (CHT-II) was packed in column. The resin was washed with volumes of sterile distilled water followed by 10 volumes of 20 mM Tris pH 6.8. Elution fractions from DEAE resin that showed clear major visible band of approximately 37 KD good

Petitioner Merck Ex-1015, 1776

concentration of PsaA on SDS PAGE were pooled and loaded onto CHT-II resin. The flow through was collected and the column was washed with 5 column volumes of equilibration buffer. Protein was eluted with 5 column volumes step gradients of (15%B, 20%B, 50%B and 100%B). Buffer A contains 20 mM Tris pH 6.8, while the Buffer B contains 250 mM Phosphate buffer pH 6.8.

[0190] All the elution fractions showing a clean band at the expected size of PsaA were pooled, concentrated by 10 kDa MWCO cassette and diafiltered against 20mM Phosphate buffer pH 7.5. The purified protein was loaded on SDS-PAGE gel to assess purity.

B) *Activation and Conjugation of Pneumococcal Polysaccharide Serotype 3 To PsaA*

[0191] The size reduced polysaccharide of serotype 3 (concentration of 5 mg/mL) and 1.5 mL of CDAP (100 mg/mL in acetonitrile (w/v)) was mixed in a glass bottle in the ratio of 1:0.5 (PS: CDAP) and stirred for 1 min. The pH of the polysaccharide solution was adjusted to 9.0 with 3.5 mL of 0.2M triethylamine and stirred for 1 min at room temperature (RT). 210 mg of PsaA (14.0 mL of 15.0 mg/mL concentration) was added slowly to the activated polysaccharide in a ratio of 1:0.7 (Ps: Carrier protein).

[0192] The pH of the reaction was adjusted to about 9.01 with 0.7 mL of 0.2M triethylamine and the reaction was continued under stirring for 5 hours at room temperature followed by quenching of the reaction by adding excess concentration of glycine (100 mM). The conjugation kinetics of reactions were monitored using SEC-HPLC at each hour of the reaction.

[0193] The reaction mixture was diafiltered and concentrated using 100 kDa MWCO TFF membrane. Concentrate was purified by size-exclusion chromatography. The fractions were analyzed by SEC-MALLS, anthrone method and fractions containing conjugates were pooled and sterile filtered with 0.2 µm filters.

C) *Activation and Conjugation of Pneumococcal Polysaccharide Serotype 6A To PsaA*

[0194] The size reduced polysaccharide Type 6A (concentration of 14.6 mg/mL) and 400 µL of CDAP (100 mg/mL in Acetonitrile (w/v)) was mixed in a glass bottle in

Petitioner Merck Ex-1015, 1777

the ratio of 1: 1 (PS:CDAP) and stirred for 1 min. The pH of the polysaccharide solution was adjusted to 9.5 with 800 µL of 0.2M triethylamine and stirred for 1 min at room temperature (RT). 40 mg of PsaA (3.78 mL of 11.0 mg/mL concentration) was added slowly to the activated polysaccharide in a ratio of 1:1 (Ps: Carrier protein).

[0195] The pH of the reaction was adjusted to about 9.01 with 0.7mL of 0.2M triethylamine and the reaction was continued under stirring for 5 hours at room temperature followed by quenching of the reaction by adding excess concentration of glycine (100 mM). The conjugation kinetics of reactions were monitored using SEC-HPLC at each hour of the reaction.

[0196] The reaction mixture was diafiltered and concentrated using 100 kDa MWCO TFF membrane. Concentrate was purified by size-exclusion chromatography. The fractions were analyzed by SEC-MALLS, anthrone method and fractions containing conjugates were pooled and sterile filtered with 0.2µm filters.

D) *Activation And Conjugation Of Pneumococcal Polysaccharide Serotype 6B To PsaA*

[0197] The size reduced polysaccharide Type 6B (concentration of 14.97 mg/mL) and 4.0 mL of CDAP (100 mg/mL in acetonitrile (w/v)) was mixed in a glass bottle in the ratio of 1: 2 (PS: CDAP) and stirred for 1 min. The pH of the polysaccharide solution was adjusted to 9.1 with 8.0 mL of 0.2M Triethylamine and stirred for 1 min at room temperature (RT). 340 mg of PsaA (22.66 mL of 15.0 mg/mL concentration) was added slowly to the activated polysaccharide in a ratio of 1:1.7 (Ps: Carrier protein).

[0198] The pH of the reaction was adjusted to about 9.01 with 0.7mL of 0.2M triethylamine and the reaction was continued under stirring for 5 hours at room temperature followed by quenching of the reaction by adding excess concentration of glycine (100 mM). The conjugation kinetics of reactions were monitored using SEC-HPLC at each hour of the reaction.

[0199] The reaction mixture was diafiltered and concentrated using 100 kDa MWCO TFF membrane. Concentrate was purified by size-exclusion chromatography. The fractions were analyzed by SEC-MALLS, anthrone method and fractions containing conjugates were pooled and sterile filtered with 0.2µm filters.

Petitioner Merck Ex-1015, 1778

[0200] SEC-HPLC chromatogram for conjugation reaction kinetics of Serotype 3 (D), 6A (E) and 6B (F) were performed. The following symbols were used for all three chromatograms; polysaccharide (solid line), PsaA (dashed line), 3 or 5 hour reaction (dotted line). As shown in Figure 2 for all the chromatograms, the consumption of PsaA is indicated based on the reduction or disappearing the peak belongs PsaA at retention time of about 19 minutes. The conjugation is confirmed based on the formation of a new peak at about 13.5 minutes to about 14 minutes.

[0201] Conjugates of pneumococcal polysaccharides from serotype 5, 9V, 12F, 10A, 15B, 18C and 45 with PsaA were prepared using the procedure similar to the one described above. SEC-HPLC chromatogram for conjugation reaction kinetics of Serotype 5 (A), 9V (B) and 18C (C) was carried out. As shown in Figure 2, all three chromatograms Polysaccharide (solid line), PsaA (dashed line), 3 or 5 hour reaction (dotted line). In all the chromatograms the consumption of PsaA is indicated based on the reduction or disappearing the peak belongs PsaA at retention time of about 19 mins. The conjugation is confirmed based on the formation of a new peak at about 13.5 minutes to about 14 minutes.

Example 2: Preparation of Pneumococcal Capsular Polysaccharide-CRM_{197} Conjugates

A) *Activation of Polysaccharide and Conjugation With Carrier Protein:*

[0202] Sized polysaccharide (6.0 mL of Ps, concentration of 10 mg/mL) and CDAP (100 mg/mL in Acetonitrile (w/v)) was mixed in a glass vial in the ratio of 1:1 and stirred for 1 min. The pH of the polysaccharide solution was adjusted to 9.25 with 0.2M triethylamine and stirred for 3 min at room temperature (RT). CRM_{197} (4.0 mL of conc. 15.0 mg/mL) was added slowly to the activated polysaccharide in a ratio of 1:1 (Ps: Carrier protein).

[0203] The pH of the reaction were adjusted to about 9.05 with 0.2M triethylamine and the reaction was continued under stirring for 5 hours at room temperature and finally the reaction was quenched by adding excess concentration of glycine.

[0204] The reaction mixture was diafiltered using 100 K MWCO membrane and purified by size-exclusion chromatography. The fractions were analyzed by SEC-

Petitioner Merck Ex-1015, 1779

MALLS, anthrone method and fractions containing conjugates were pooled and sterile filtered with 0.2μ filters. This material is called monovalent conjugate bulk.

[0205] The reaction kinetics of the conjugates prepared from serotypes 7F (A), 14 (B) and 19F (C) with CRM_{197} were prepared and the reaction kinetics are shown in Figure 1. In all three chromatograms polysaccharide (solid line), CRM_{197} (dashed line), 5 hour reaction (dotted line). In all the chromatograms the consumption of CRM_{197} is indicated based on the reduction or disappearing the peak belongs CRM_{197} at retention time of about 19 minutes. The conjugation is confirmed based on the formation of a new peak at about 13.5 minutes to about 14 minutes.

[0206] The reaction kinetics of the conjugates prepared from serotypes 3 (D), 6A (E) and 6B (F) with CRM_{197} were prepared and the reaction kinetics are shown in Figure 1. In all three chromatograms polysaccharide (solid line), CRM_{197} (dashed line), 5 hour reaction (dotted line). In all the chromatograms the consumption of CRM_{197} is indicated based on the reduction or disappearing the peak belongs CRM_{197} at retention time of about 19 minutes. The conjugation is confirmed based on the formation of a new peak at about 13.5 minutes to about 14 minutes.

Example 3: Formulation of Pneumococcal Capsular Polysaccharide-protein conjugate vaccine

[0207] A 15 valent conjugated vaccine was formulated as 0.5 mL dose containing 2.2 μg of each pneumococcal polysaccharide from serotypes 1, 4, 5, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F & 33F conjugated to ~28 μg CRM_{197} Protein and 2.2 μg of each polysaccharide from serotypes 3, 6A and 6B conjugated to about 7 μg PsaA Protein. All the conjugates were adsorbed on to aluminum phosphate gel equivalent to 0.5 mg Al^{3+} per dose of 0.5 mL. The 0.9% W/V saline was used as diluent and vehicle for the formulation and the final formulation pH was adjusted to pH 6 using 1N hydrochloric acid. For effective adsorption post adjusting the pH, the formulation was mixed for 2 hours under constant stirring. After 2 hours of blending, the formulated blend was aseptically filled at 0.58 mL fill volume per vial into the 3 mL sterile nonsiliconized vials, closed with sterile 13 mm rubber stoppers and sealed with 13 mm sterile pink colored flip off aluminum seals, followed by optical inspection and labelling of filled vials. From the lot, some vials randomly picked were sent for

Petitioner Merck Ex-1015, 1780

analyzing the appearance, pH, Osmolality, total poly and protein content (µg/SHD), %Adsorption, aluminum content (mg/SHD).

Example 4: Formulation of Pneumococcal Capsular Polysaccharide-protein conjugate vaccine

[0208] A 15 valent conjugated vaccine was formulated as 0.5 mL dose containing 2.2 µg of each polysaccharide from serotypes 1, 4, 5, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F & 33F conjugated to ~28 µg CRM_{197} protein and 4.4 µg of each polysaccharide from serotypes 3, 6A and 6B conjugated to ~14 µg PsaA Protein. All the conjugates were adsorbed on to aluminum phosphate gel equivalent to 0.5 mg Al^{3+} per dose of 0.5 mL. The 0.9% w/v saline was used as diluent and vehicle for the formulation and the final formulation pH was adjusted to pH 6 using 1N hydrochloric acid. For effective adsorption post adjusting the pH, the formulation was mixed for 2 hours under constant stirring. After 2 hours of blending, the formulated blend was aseptically filled at 0.58 mL fill volume per vial into the 3 mL sterile nonsiliconized vials, closed with sterile 13 mm rubber stoppers and sealed with 13 mm sterile pink colored flip off aluminum seals, followed by optical inspection and labelling of filled vials. From the lot, some vials randomly picked were sent for analyzing the appearance, pH, Osmolality, Total poly and protein content (µg/SHD), % Adsorption, aluminum content (mg/SHD).

A) *Immunization of Rabbits With the Formulated Vaccine*

[0209] Healthy rabbits 1.5 to 2 kg each were bred and reared in a specific pathogen free contained facility. Rabbits were immunized with the aforementioned formulation with the following schedule.

[0210] Group 1 consisted of 7 rabbits that were immunized with the 15 valent conjugate vaccine (Example 3). The 15 valent vaccine comprised of 2.2µg each of the *S. pneumoniae* polysaccharides of serotypes 1, 4, 5, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F conjugated to CRM_{197} and 2.2µg each *S. pneumoniae* polysaccharides of serotypes 3, 6A and 6B conjugated to PsaA. Rabbits were immunized on days 1, 15 and 29; blood samples were collected on days 0, 15 and 36. Serum was separated from the blood sample and stored at -80°C.

Petitioner Merck Ex-1015, 1781

[0211] Group 2 consists of 7 rabbits that were immunized with the 13 valent conjugate vaccine – Prevnar13®. Rabbits were immunized on days 1, 15 and 29; blood samples were collected on days 0, 12, 26 and 40. Data from day 12 and day 40 was used to plot for comparison with the PsaA study (Figure 4). Serum was separated from the blood sample and stored at -80°C.

[0212] Group 3 consists of 7 rabbits that were immunized with the 15 valent conjugate vaccine (Example 4). The 15 valent vaccine comprised of 2.2 µg of polysaccharide for each serotypes 1, 4, 5, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F & 33F conjugated to ~28 µg CRM_{197} protein and 4.4 µg of each polysaccharide for Serotypes 3, 6A and 6B conjugated to ~14 µg PsaA protein. Rabbits were immunized on days 1, 15 and 29; blood samples were collected on days 0, 15 and 36. Serum was separated from the blood sample and stored at -80°C. Serum obtained from the immunized rabbits were analyzed for serotype specific immune response using ELISA.

[0213] The ELISA was performed as per the WHO suggested protocol. Briefly, Maxisorp™ ELISA plates were coated with PnCPS of given serotype (1µg/50µL/well using PBS; sterile endotoxin free, with 0.02% sodium azide). Plates were placed in a box with moistened paper towels for humidification and incubated at 37°C ± 2°C for 5hrs, the plates were then stored at 5°C ± 3°C until use.

[0214] The test sera were pre-adsorbed to CWPS MIti™ to eliminate background reactivity originating from cell-wall polysaccharide. To achieve this 2µL of test and positive control serum were diluted using 998µL preadsorption solution (1mL-1µL CWPS Multi™ in 999µL of 10% SuperBlock™ in PBST) to get final dilution of 1:500. The diluted samples were incubated at room temperature (25°C ± 5°C) for 1 hr with continuous shaking. The unbound PnCPS were removed by flicking the plate and the free sites in the wells were blocked by adding 200µL of blocker (20% SuperBlock™ in PBS). The plate were incubated at room temperature (25°C ± 5°C) for 1 hr without shaking.

B) *Test Samples and Controls Addition*

[0215] 50µL diluent (10% SuperBlock™ in PBST) were added to all wells except A1 to A12. Following this 100µL/well preadsorbed test sera samples were added to A1 to A10, control sera samples were added to A11 and A12. Two fold serial dilution

Petitioner Merck Ex-1015, 1782

of test samples was performed by transferring 50µL from 1st to 2nd and so on i.e. from A1-A10 to H1-H10. Similarly, serial dilution of control samples (007SP) from A11 and 12 to E11 and E12 were performed. F11 and F12 to H11 and H12 without dilution were set up as blank.

[0216] The plates were incubated at room temperature (25°C ± 5°C) for 2 hrs without shaking. Following the incubation step the contents were discarded and the plates were washed thrice with PBST (~250µL/well) manually or with plate washer.

C) *Primary Antibody Addition*

[0217] 50µL/well recombinant protein A/G peroxidase (diluted 1:20000 using 10% SuperBlock™ in PBST) was added to all wells and the plates were incubated for 1hr at room temperature (25°C ± 5°C) without shaking. Following this, the plates were washed thrice with PBST (250µL/well) manually or with plate washer.

D) *Development and Reading*

[0218] Chromogenic reaction was developed by adding 50µL/well TMB substrate and incubated for 15mins at room temperature (25°C ± 5°C) without shaking. The reaction was stopped by adding 50µL/well 1.25M Sulphuric acid. The OD at 450nm was measured.

E) *Titer Estimation*

[0219] Antibody titer in the immunized animals were assigned as inverse of dilution factor. The highest dilution showing OD_{450nm} as twice the pre-immune titer (approximately 0.2) was reported as titer. The titer of serum antibody to each serotype was plotted and compared with different treatment groups.

[0220] The immune response data of animals from Group 1 shows dose dependent rise in serotype specific rise in serum antibody titer i.e. the level of antibody titer increased with each subsequent dose in the vaccinated animals. The immune response to Serotype 3 (Figure 5) was about 1:10000 when the animals were immunized with conjugates of PsaA containing 4.4 µg of polysaccharide (group 3). Further, the serum antibody titer to serotypes 3, 6A and 6B were at least twice as much when compared to the immune response obtained from Prevnar®13 immunized rabbits. The serum IgG titer after first immunization in rabbits with Prevnar®13 does not show rise to the same extent as observed with the 15 valent formulation of the

Petitioner Merck Ex-1015, 1783

present disclosure (Figure 3 & 4). Even though the concentration of polysaccharide for serotype 6B in Prevnar®13 is twice as much (4.4µg), when compared to the concentration of serotype 3 polysaccharide conjugated to PsaA (Figure 3), is twice the level of IgG response. The titer of Serotype 3 antibody barely reaches 8000 in formulations containing 2.2 µg of Serotype 3 conjugated to CRM_{197}. This titer shows a notable improvement (16000) when conjugated to 4.4 µg of PsaA.. This is an improvement in the immune response due to conjugation of serotype 3, 6A and 6B polysaccharides to PsaA. Serum antibody titer to serotype 14 in Prevnar®13 vaccinated animals were lower when compared to the formulations of the present disclosure. IgG response to other serotypes in animal vaccinated either with the vaccine formulations of the present disclosure or with Prevnar®13 were similar. Serotypes 3, 6A and 6B titers were improved upon conjugation to PsaA even at 2.2 µg concentration.

[0221] The use of numerical values specified in this application, unless expressly indicated otherwise, are stated as approximations through the minimum and maximum values specified within the stated ranges, and preceded by the word "about." The disclosure of ranges is intended as a continuous range including every value between the minimum and maximum values recited as well as any ranges that may be formed through such values. The numerical values presented in this application represent various embodiments of the present disclosure.

[0222] Throughout this disclosure, the singular terms "a," "an," and "the" include plural referents unless the context clearly indicates otherwise. Similarly, unless the word "or" is expressly limited to mean only a single item exclusive from the other items in reference to a list of two or more items, then the use of "or" in such a list is to be interpreted as including (a) any single item in the list, (b) all of the items in the list, or (c) any combination of the items in the list. Additionally, the terms "comprising" and the like are used throughout this disclosure to mean including at least the recited feature(s) such that any greater number of the same feature(s) and/or one or more additional types of features are not precluded. Reference herein to "one embodiment," "an embodiment," or similar formulations means that a particular feature of a composition, a composition, a method, or a characteristic described in connection with the embodiment may be included in at least one embodiment of the present technology. Thus, the appearances of such phrases or formulations herein are not

Petitioner Merck Ex-1015, 1784

necessarily all referring to the same embodiment. Furthermore, various particular features, compositions, methods, or characteristics may be combined in any suitable manner in one or more embodiments.

[0223] This disclosure is not intended to be exhaustive or to limit the present technology to the precise forms disclosed herein. Although specific embodiments are disclosed herein for illustrative purposes, various equivalent modifications are possible without deviating from the present technology, as those of ordinary skill in the relevant art will recognize. In some cases, well-known structures and functions have not been shown and/or described in detail to avoid unnecessarily obscuring the description of the embodiments of the present technology. Although steps of methods may be presented herein in a particular order, in alternative embodiments the steps may have another suitable order. Similarly, certain embodiments of the present technology disclosed in the context of particular embodiments may be combined or eliminated in other embodiments. Furthermore, while advantages associated with certain embodiments may have been disclosed in the context of those embodiments, other embodiments may also exhibit such advantages, and not all embodiments need necessarily exhibit such advantages or other advantages disclosed herein to fall within the scope of the present technology. Accordingly, this disclosure and associated technology may encompass other embodiments not expressly shown and/or described herein.

[0224] From the foregoing, it will be appreciated that specific embodiments of the disclosure have been described herein for purposes of illustration, but that various modifications may be made without deviating from the scope of the disclosure. Accordingly, the disclosure is not limited except as by the appended claims.

Petitioner Merck Ex-1015, 1785

CLAIMS

What is claimed is:

1. A pneumococcal vaccine composition, the composition comprising two or more capsular pneumococcal polysaccharide serotypes each individually conjugated to a carrier protein pneumococcal surface adhesion protein A (PsaA) or combination of PsaA and CRM_{197} as a carrier proteins.

2. The pneumococcal vaccine composition of claim 1 wherein the pneumococcal vaccine composition is a 10 valent, 13 valent, 14 valent, 15 valent, 17 valent, 18 valent, 19 valent, 20 valent, 22 valent, 23 valent, 24 valent or 25 valent pneumococcal vaccine composition.

3. The pneumococcal vaccine composition of claims 1 or 2 wherein each of the pneumococcal polysaccharides include one or more serotypes selected from 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39 and 45.

4. The pneumococcal vaccine composition of any one of the preceding claims having a percent ratio of carrier protein to pneumococcal polysaccharide (protein/PS) of about 0.5 to about 2.0 protein/PS.

5. The pneumococcal vaccine composition of any one of the preceding claims wherein the pneumococcal vaccine composition further comprises a pharmaceutically acceptable carrier.

6. The pneumococcal vaccine composition of any one of the preceding claims wherein the pneumococcal polysaccharides comprise at least 10 pneumococcal polysaccharides, each pneumococcal polysaccharide selected from serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B,

Petitioner Merck Ex-1015, 1786

35F, 38, 39 and 45 and the carrier proteins comprise PsaA, or a combination of PsaA and CRM_{197}.

7. The pneumococcal vaccine composition of any one of the preceding claims wherein the pneumococcal vaccine composition comprises at least 14 pneumococcal polysaccharides.

8. The pneumococcal vaccine composition of any one of the preceding claims wherein the pneumococcal vaccine composition comprises at least 17 pneumococcal polysaccharides.

9. The pneumococcal vaccine composition of any one of the preceding claims wherein the pneumococcal vaccine composition comprises at least 19 pneumococcal polysaccharides.

10. The pneumococcal vaccine composition of any one of the preceding claims wherein the pneumococcal vaccine composition comprises at least 20 pneumococcal polysaccharides.

11. The pneumococcal vaccine composition of any one of the preceding claims wherein the pneumococcal vaccine composition comprises at least 22 pneumococcal polysaccharides.

12. The pneumococcal vaccine composition of any one of the preceding claims wherein the pneumococcal vaccine composition comprises at least 24 pneumococcal polysaccharides.

13. The pneumococcal vaccine composition of any one of the preceding claims wherein each of the pneumococcal polysaccharides are selected from serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 20A, 20B, 22F, 23A, 23B, 23F, 24B, 24F, 31, 33F, 34, 35B, 35F, 38, 39 and 45, and the carrier protein is PsA.

Petitioner Merck Ex-1015, 1787

14. The pneumococcal vaccine composition of any one of the preceding claims wherein the pneumococcal vaccine composition is a 14 valent pneumococcal vaccine composition comprising pneumococcal polysaccharides selected from serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F, wherein at least serotypes 3, and 6B are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F are conjugated to CRM_{197}.

15. The pneumococcal vaccine composition of any one of the preceding claims wherein the pneumococcal vaccine composition is a 14 valent pneumococcal vaccine composition comprising pneumococcal polysaccharides selected from serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F, wherein at least serotypes 3, and 6A are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F are conjugated to CRM_{197}.

16. The pneumococcal vaccine composition of any one of the preceding claims wherein the pneumococcal vaccine composition is a 15 valent pneumococcal vaccine composition comprising pneumococcal polysaccharides selected from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V,14, 18C, 19A, 19F, 22F, 23F and 33F wherein at least serotypes 3, 6A and 6B are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F are conjugated to CRM_{197}.

17. The pneumococcal vaccine composition of any one of the preceding claims wherein the pneumococcal vaccine composition is a 17 valent pneumococcal vaccine composition comprising pneumococcal polysaccharides selected from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 12F,14, 18C, 19A, 19F, 22F, 23F, 33F and 35B wherein at least serotypes 3, 6A and 6B are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 12F,14, 18C, 19A, 19F, 22F, 23F, 33F and 35B are conjugated to CRM_{197}.

18. The pneumococcal vaccine composition of any one of the preceding claims wherein the pneumococcal vaccine composition is a 20 valent pneumococcal vaccine composition comprising pneumococcal polysaccharides selected from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F,

Petitioner Merck Ex-1015, 1788

33F, 35B and 45 wherein at least serotypes 3, 6A and 6B are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 35B and 45 are conjugated to CRM_{197}.

19. The pneumococcal vaccine composition of any one of the preceding claims wherein the pneumococcal vaccine composition is a 22 valent pneumococcal vaccine comprising pneumococcal polysaccharides selected from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 10A, 12F, 14, 15A, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B, and 38 wherein at least serotypes 3, 6A and 6B are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 10A, 12F, 14, 15A, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38 are conjugated to CRM_{197}.

20. The pneumococcal vaccine composition of any one of the preceding claims wherein the pneumococcal vaccine composition is a 22 valent pneumococcal vaccine comprising pneumococcal polysaccharides selected from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 10A, 12F, 14, 15A, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38 wherein serotypes 1, 3, 6A, 10A, 12F, 15A 15B, 22F, 34, 35B, 38 are conjugated to PsaA and serotypes 14, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F and 33F are conjugated to CRM_{197}.

21. The pneumococcal vaccine composition of any one of the preceding claims wherein the pneumococcal vaccine composition is a 24 valent pneumococcal vaccine comprising pneumococcal polysaccharides selected from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A,12F, 14, 15A, 15B, 16F, 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38 wherein at least serotypes 3, 6A and 6B are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 8, 9V, 10A, 12F, 14, 15A, 15B, 16F, 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38 are conjugated to CRM_{197}.

22. The pneumococcal vaccine composition of any one of the preceding claims wherein the pneumococcal vaccine composition is a 24 valent pneumococcal vaccine comprising pneumococcal polysaccharides selected from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 12F, 14, 15A, 15B, 16F 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38 wherein serotypes 1, 3, 6A, 8, 10A, 12F, 15A 15B, 16F 22F, 34, 35B, 38

Petitioner Merck Ex-1015, 1789

are conjugated to PsaA and serotypes 14, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F and 33F are conjugated to CRM_{197}.

23. The pneumococcal vaccine composition comprising pneumococcal polysaccharides of two or more serotypes and a carrier protein, wherein the serotypes are selected from 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A and 22F and the carrier protein is PsaA.

24. The pneumococcal vaccine composition comprising pneumococcal polysaccharides of two or more serotypes and a carrier protein, wherein the serotypes are selected from 1, 3, 4, 5, 6A, 6B, 7F, 9V, 10A, 12F, 14, 15A, 15B, 18C, 19F, 19A, 22F, 23F, 33F, 34, 35, 38 and 45, and the carrier protein is PsaA.

25. The pneumococcal vaccine composition of any one of the preceding claims wherein the pneumococcal vaccine composition is formulated into a dosage unit.

26. The pneumococcal vaccine composition of any one of the preceding claims wherein the dosage unit comprises about 0.1 µg to about 50 µg of each pneumococcal polysaccharide, about 0.1 µg to about 10 µg, or about 1 µg to about 5 µg of each pneumococcal polysaccharide, wherein each pneumococcal polysaccharide is each individually conjugated to the carrier protein from about 1.5 µg to about 5 µg of carrier protein.

27. The pneumococcal vaccine composition of any one of the preceding claims further comprising a pharmaceutically acceptable diluent, buffer, preservative, stabilizer, adjuvant, and/or a lyophilization excipient.

28. The pneumococcal vaccine composition of any one of the preceding claims wherein the dosage unit is supplied as a unit dose vial, a multiple dose vial, or a pre-filled syringe.

Petitioner Merck Ex-1015, 1790

29. The pneumococcal vaccine composition of any one of the preceding claims wherein the pneumococcal vaccine composition is a single 0.5 mL dose comprising:

about 2.2 to 4.4 µg of one or more pneumococcal polysaccharides;

about 1 µg to about 10 µg of PsaA conjugated to each of the one or more pneumococcal polysaccharides;

about 1 µg to about 10 µg of CRM_{197} conjugated to each of the one or more pneumococcal polysaccharides;

about 0.2 mg to about 1 mg of aluminum phosphate adjuvant; and

an excipient.

30. The pneumococcal vaccine composition of any one of the preceding claims wherein the pneumococcal vaccine composition is a 13 valent pneumococcal vaccine composition comprising:

pneumococcal polysaccharide selected from serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F and 33F, each pneumococcal polysaccharide each individually conjugated to PsaA or combination of PsaA CRM_{197},

wherein the pneumococcal vaccine composition is about a 0.5 mL dose formulated as a sterile liquid comprising:

about 2.2 µg to about 4.4 µg of each pneumococcal polysaccharide,

about 25 µg to about 30 µg PsaA and CRM_{197},

about 0.125 mg of elemental aluminum as about 0.5 mg aluminum phosphate,

sodium chloride, and

a L-histidine buffer.

31. The pneumococcal vaccine composition of any one of the preceding claims wherein the pneumococcal vaccine composition is a 14 valent pneumococcal vaccine composition comprising:

pneumococcal polysaccharides selected from serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F, each pneumococcal

Petitioner Merck Ex-1015, 1791

polysaccharide each individually conjugated to PsaA or combination of PsaA CRM_{197},

wherein the pneumococcal vaccine composition is about a 0.5 mL dose formulated as a sterile liquid comprising:

about 2.2 µg to about 4.4 µg of each pneumococcal polysaccharide,

about 20 µg to about 35 µg PsaA and CRM_{197},

about 0.125 mg of elemental aluminum as about 0.5 mg aluminum phosphate,

sodium chloride, and

a L-histidine buffer.

32. The pneumococcal vaccine composition of any one of the preceding claims wherein the pneumococcal vaccine composition is a 14 valent pneumococcal vaccine composition comprising:

pneumococcal polysaccharides selected from serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F, each pneumococcal polysaccharide each individually conjugated to PsaA or combination of PsaA CRM_{197},

wherein the pneumococcal vaccine composition is about a 0.5 mL dose formulated as a sterile liquid comprising:

about 2.2 to 4.4 µg of each pneumococcal polysaccharide,

about 20 µg to about 35 µg PsaA and CRM_{197},

about 0.125 mg of elemental aluminum as about 0.5 mg aluminum phosphate,

sodium chloride, and

a L-histidine buffer.

33. The pneumococcal vaccine composition of any one of the preceding claims wherein the pneumococcal vaccine composition is a 15 valent pneumococcal vaccine composition comprising:

pneumococcal polysaccharides selected from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V,14, 18C, 19A, 19F, 22F, 23F and 33F wherein at least serotypes 3,

Petitioner Merck Ex-1015, 1792

6A and 6B are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F are conjugated to CRM_{197},

wherein the pneumococcal vaccine composition is about a 0.5 mL dose formulated as a sterile liquid comprising:

about 2.2 µg to about 4.4 µg of each pneumococcal polysaccharide,

about 5 µg to about 20 µg of PsaA;

about 20 µg to about 40 µg of CRM_{197},

about 0.125 mg of elemental aluminum as about 0.5 mg aluminum phosphate,

sodium chloride, and

a L-histidine buffer.

34. The pneumococcal vaccine composition of any one of the preceding claims wherein the pneumococcal vaccine composition is a 17 valent pneumococcal vaccine composition comprising:

pneumococcal polysaccharides selected from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 12F,14, 18C, 19A, 19F, 22F, 23F, 33F and 35B wherein at least serotypes 3, 6A and 6B are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 12F, 14, 18C, 19A, 19F, 22F, 23F, 33F and 35B are conjugated to CRM_{197},

wherein the pneumococcal vaccine composition is about a 0.5 mL dose formulated as a sterile liquid comprising:

about 2.2 µg to about 4.4 µg of each pneumococcal polysaccharide,

about 5 µg to about 20 µg of PsaA,

about 20 µg to about 40 µg of CRM_{197},

about 0.125 mg of elemental aluminum as about 0.5 mg aluminum phosphate,

sodium chloride, and

a L-histidine buffer.

Petitioner Merck Ex-1015, 1793

35. The pneumococcal vaccine composition of any one of the preceding claims wherein the pneumococcal vaccine composition is a 20 valent pneumococcal vaccine composition comprising:

pneumococcal polysaccharides selected from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 35B and 45 wherein at least serotypes 3, 6A and 6B are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 35B and 45 are conjugated to CRM_{197},

wherein the pneumococcal vaccine composition is about a 0.5 mL dose formulated as a sterile liquid comprising:

about 2.2 µg to about 4.4 µg of each pneumococcal polysaccharide,

about 5 µg to about 20 µg of PsaA,

about 20 µg to about 50 µg of CRM_{197},

about 0.125 mg of elemental aluminum as about 0.5 mg aluminum phosphate,

sodium chloride, and

a L-histidine buffer.

36. The pneumococcal vaccine composition of any one of the preceding claims wherein the pneumococcal vaccine composition is a 22 valent pneumococcal vaccine composition comprising:

pneumococcal polysaccharides selected from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 10A, 12F, 14, 15A, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38 wherein at least serotypes 3, 6A and 6B are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 9V, 10A, , 12F, 14, 15A, 15B, 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38 are conjugated to CRM_{197},

wherein the pneumococcal vaccine composition is about a 0.5 mL dose formulated as a sterile liquid comprising:

about 2.2 µg to about 4.4 µg of each pneumococcal polysaccharide,

about 5 µg to about 20 µg of PsaA,

about 20 µg to about 50 µg of CRM_{197},

Petitioner Merck Ex-1015, 1794

about 0.125 mg of elemental aluminum as about 0.5 mg aluminum phosphate,
sodium chloride, and
a L-histidine buffer.

37. The pneumococcal vaccine composition of any one of the preceding claims wherein the pneumococcal vaccine composition is a 24 valent pneumococcal vaccine composition comprising:

pneumococcal polysaccharides selected from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 12F, 14, 15A, 15B, 16F, 18C, 19A, 19F, 22F, 23F, 33F, 34, 35B and 38 wherein at least serotypes 3, 6A and 6B are conjugated to PsaA and one or more serotypes 1, 4, 5, 7F, 8, 9V, 10A, 12F, 14, 15A, 15B, 16F, 18C, 19A, 19F, 22F, 23F, 33F and 35B are conjugated to CRM_{197},

wherein the pneumococcal vaccine composition is about a 0.5 mL dose formulated as a sterile liquid comprising:

about 2.2 µg to about 4.4 µg of each pneumococcal polysaccharide,
about 5 µg to about 20 µg of PsaA,
about 20 µg to about 50 µg of CRM_{197},
about 0.125 mg of elemental aluminum as about 0.5 mg aluminum phosphate,
sodium chloride, and
a L-histidine buffer.

38. A method of treating a subject in need thereof comprising, administering the pneumococcal vaccine composition of any one of the preceding claims to the subject in need thereof.

39. The method of claim 38 wherein the subject has a disease mediated by *streptococcus pneumoniae.*

Petitioner Merck Ex-1015, 1795

40. The method of claim 39 wherein the disease mediated by *streptococcus pneumoniae* is invasive pneumococcal disease (IPD).

41. The method of any one of claims 38-40 wherein the subject is a human.

42. The method of claim 41 wherein the human is an infant (less than about 1 year of age), a toddler (about 12 months to about 24 months of age), a young child (about 2 years to about 5 years of age), an older child (about 5 years to about 13 years of age), an adolescent (about 13 years to about 18 years of age), an adult (about 18 years to about 65 years of age), or an elder (more than about 65 years of age).

43. A method of inducing an immune response to a *S. pneumoniae* capsular polysaccharide conjugate, comprising administering an immunologically effective amount of the pneumococcal vaccine composition of any one of claims 1-37 to a subject in need thereof.

44. The method of claim 43 wherein the method further comprises formulating the polysaccharide-protein conjugate into the pneumococcal vaccine composition including an adjuvant, an excipient, and a buffer.

45. The method of claim 44 wherein the adjuvant is aluminum phosphate.

Petitioner Merck Ex-1015, 1796

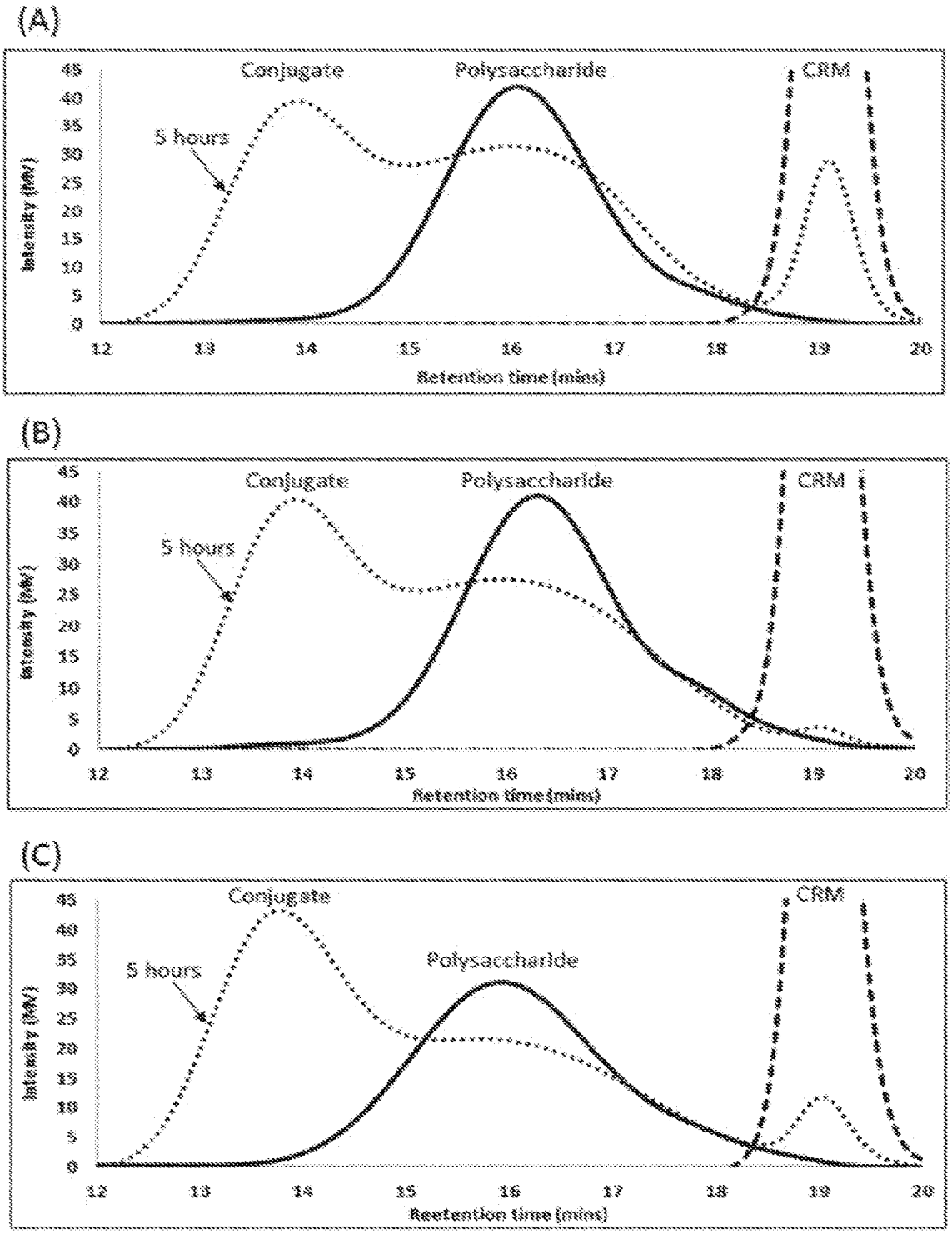

(A)
Conjugate
Polysaccharide
CRM
5 hours
Intensity (MV)
Retention time (mins)
(B)
Conjugate
Polysaccharide
CRM
5 hours
Intensity (MV)
Retention time (mins)
(C)
Conjugate
CRM
5 hours
Polysaccharide
Intensity (MV)
Reetention time (mins)

FIG. 1

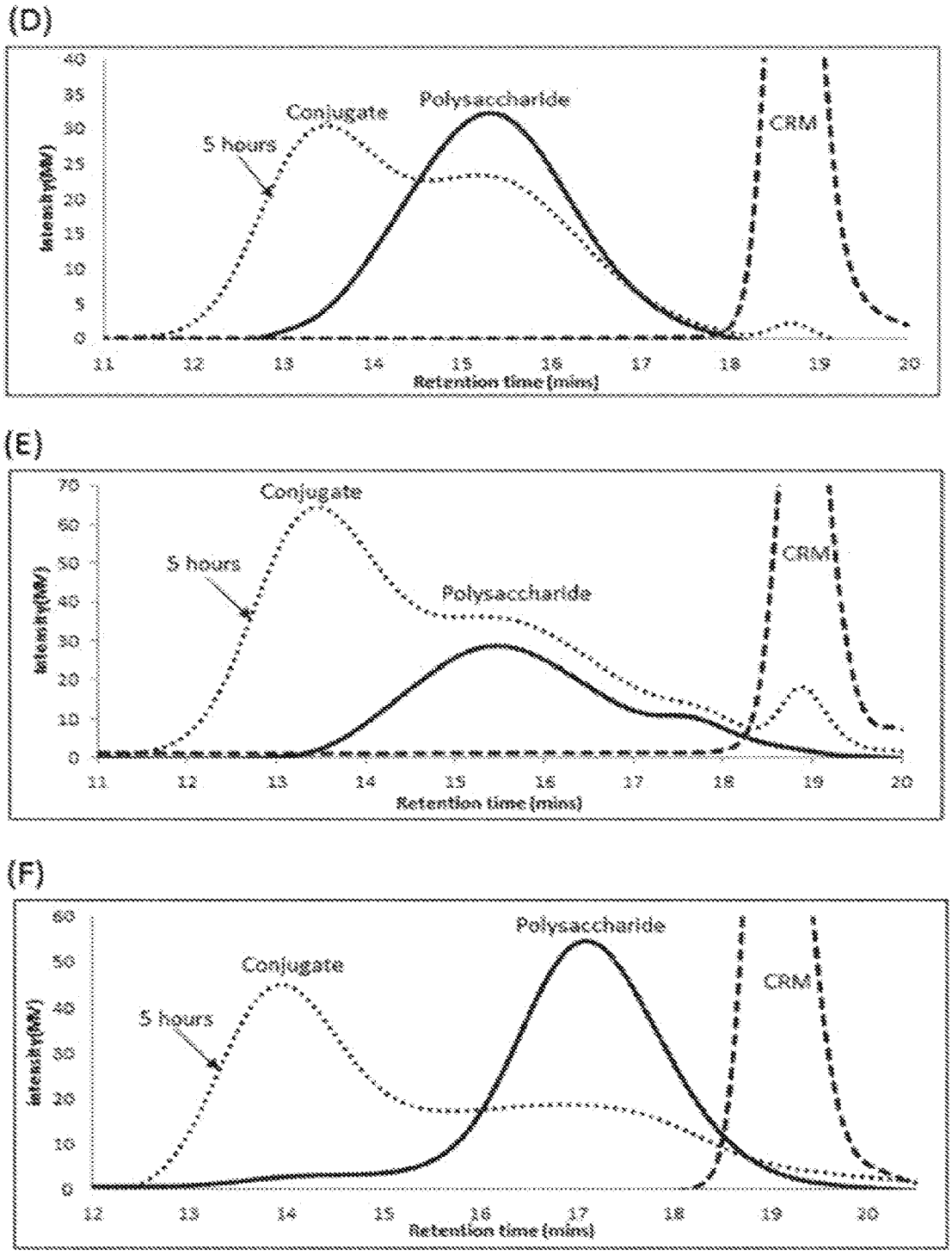

(D)
Conjugate
Polysaccharide
CRM
5 hours
Retention time (mins)
(E)
Conjugate
5 hours
Polysaccharide
CRM
Retention time (mins)
(F)
Polysaccharide
Conjugate
CRM
5 hours
Retention time (mins)

FIG. 1 (contd.)

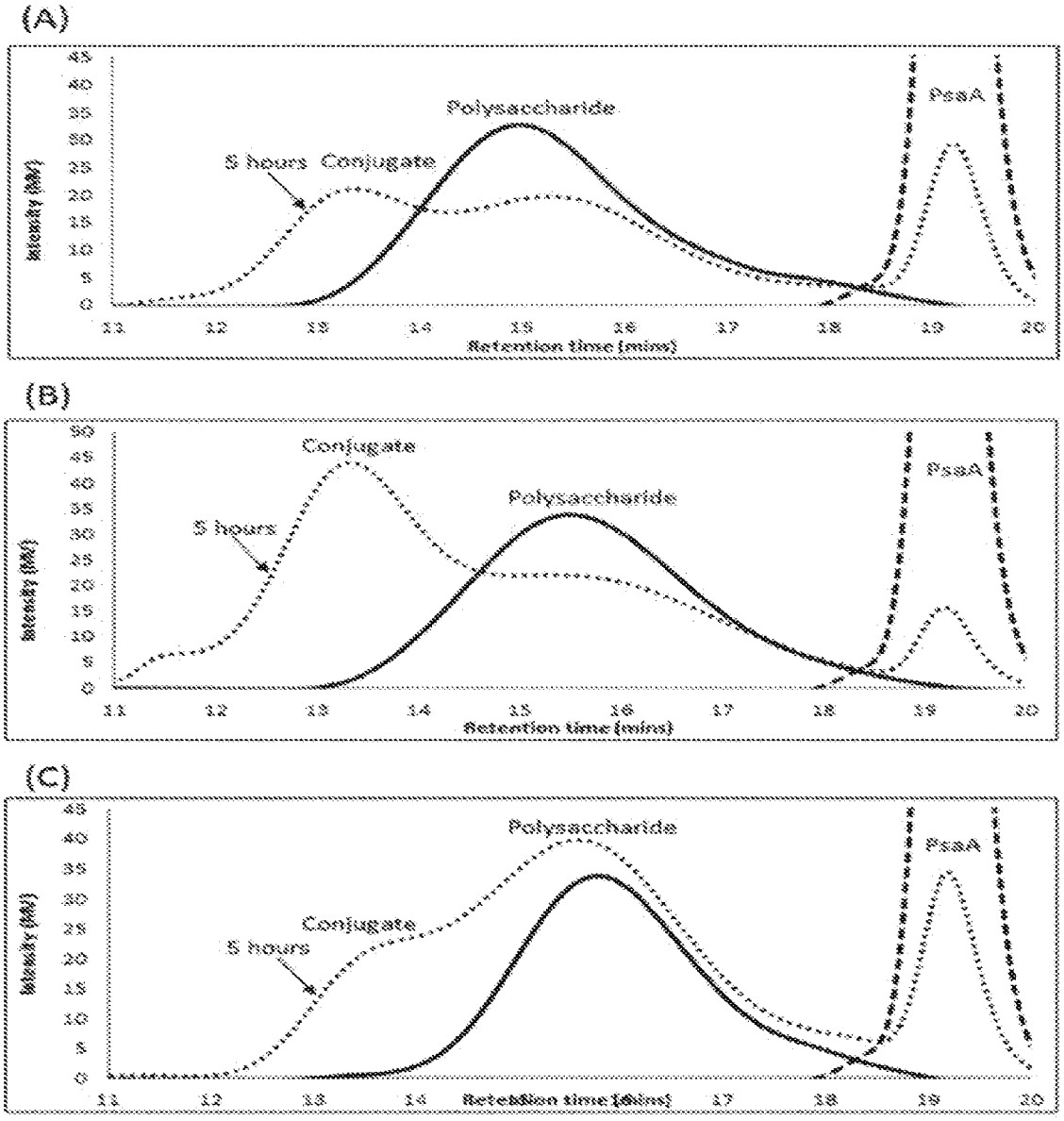

(A)
Intensity (MV)
Polysaccharide
PsaA
5 hours Conjugate
Retention time (mins)
(B)
Intensity (MV)
Conjugate
PsaA
Polysaccharide
5 hours
Retention time (mins)
(C)
Intensity (MV)
Polysaccharide
PsaA
Conjugate
5 hours
Retention time (mins)

FIG. 2

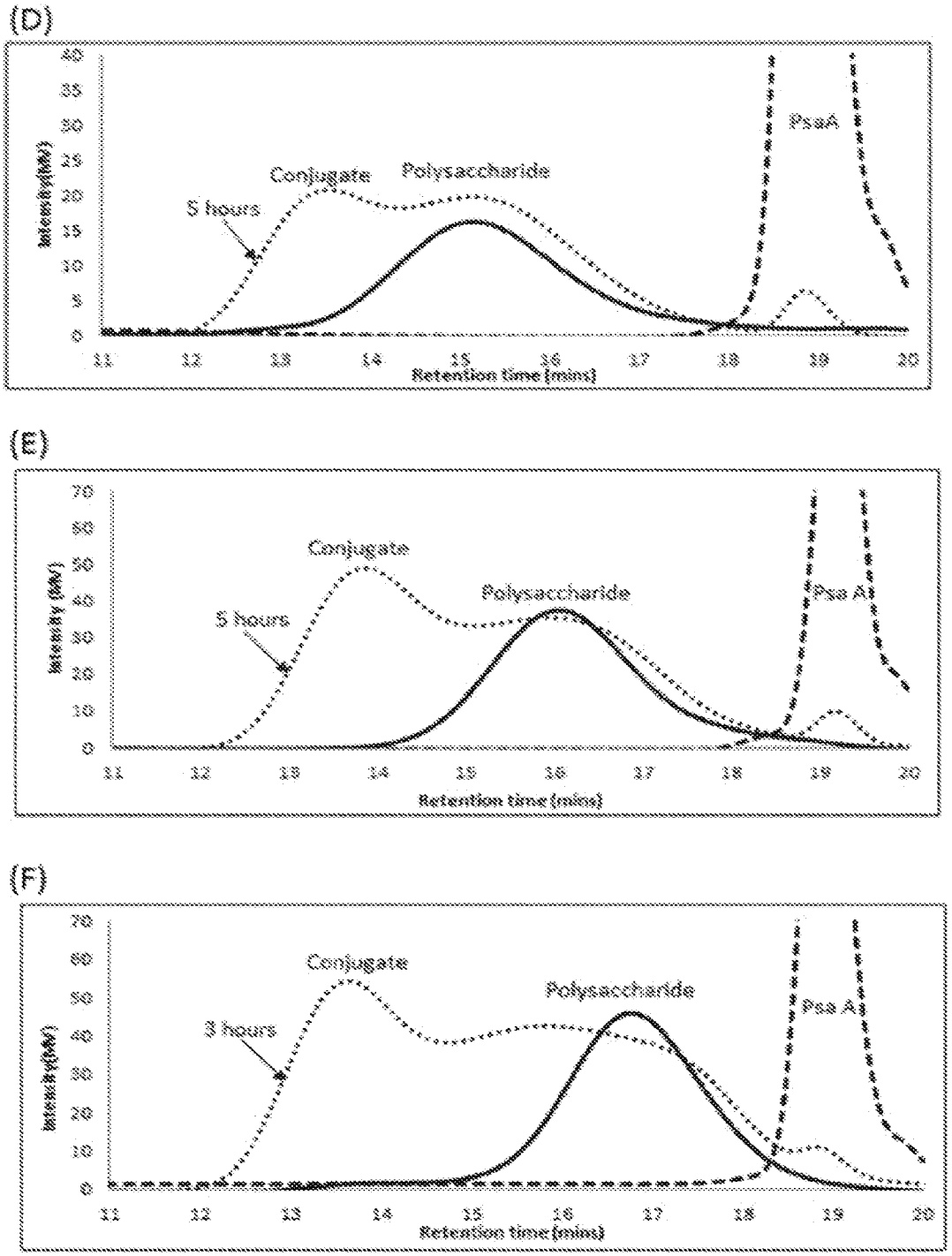

(D)
Conjugate
Polysaccharide
5 hours
PsaA
Retention time (mins)
(E)
Conjugate
Polysaccharide
5 hours
Psa A
Retention time (mins)
(F)
Conjugate
Polysaccharide
3 hours
Psa A
Retention time (mins)

FIG. 2 (contd.)

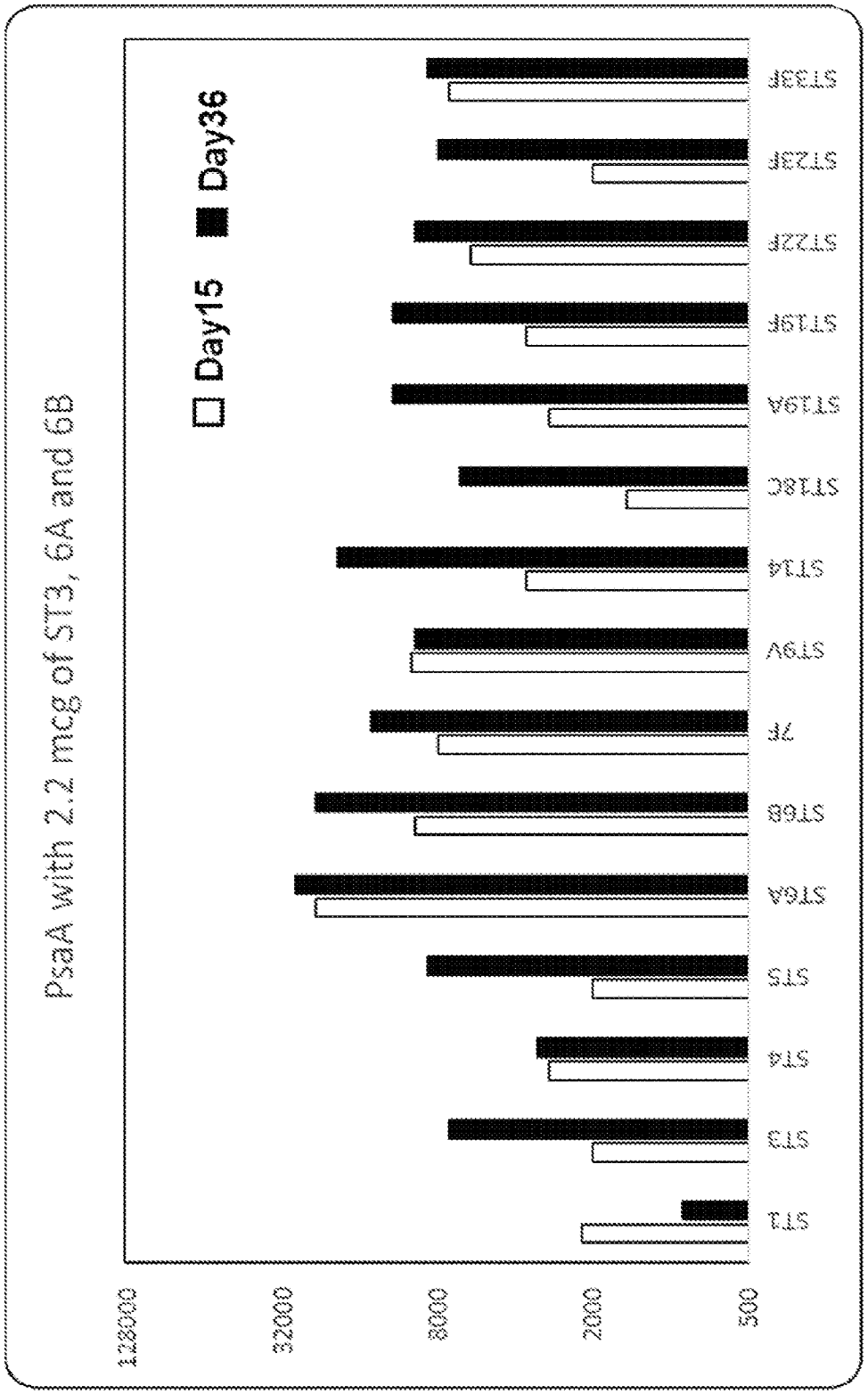

PsaA with 2.2 mcg of ST3, 6A and 6B
Day15
Day36
128000
32000
8000
2000
500
ST1
ST3
ST4
ST5
ST6A
ST6B
7F
ST9V
ST14
ST18C
ST19A
ST19F
ST22F
ST23F
ST33F

FIG. 3

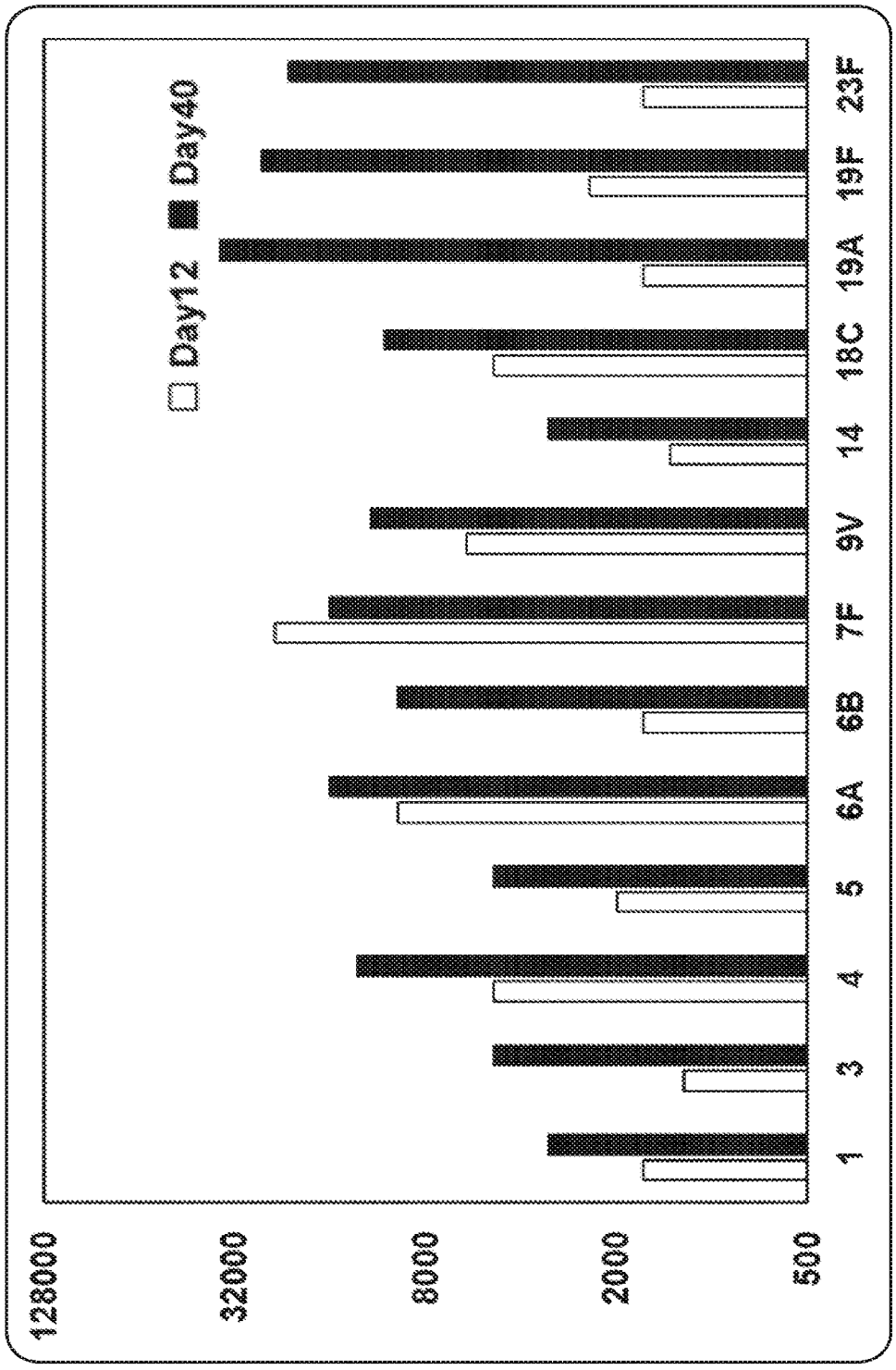

Day12
Day40
128000
32000
8000
2000
500
1
3
4
5
6A
6B
7F
9V
14
18C
19A
19F
23F

FIG. 4

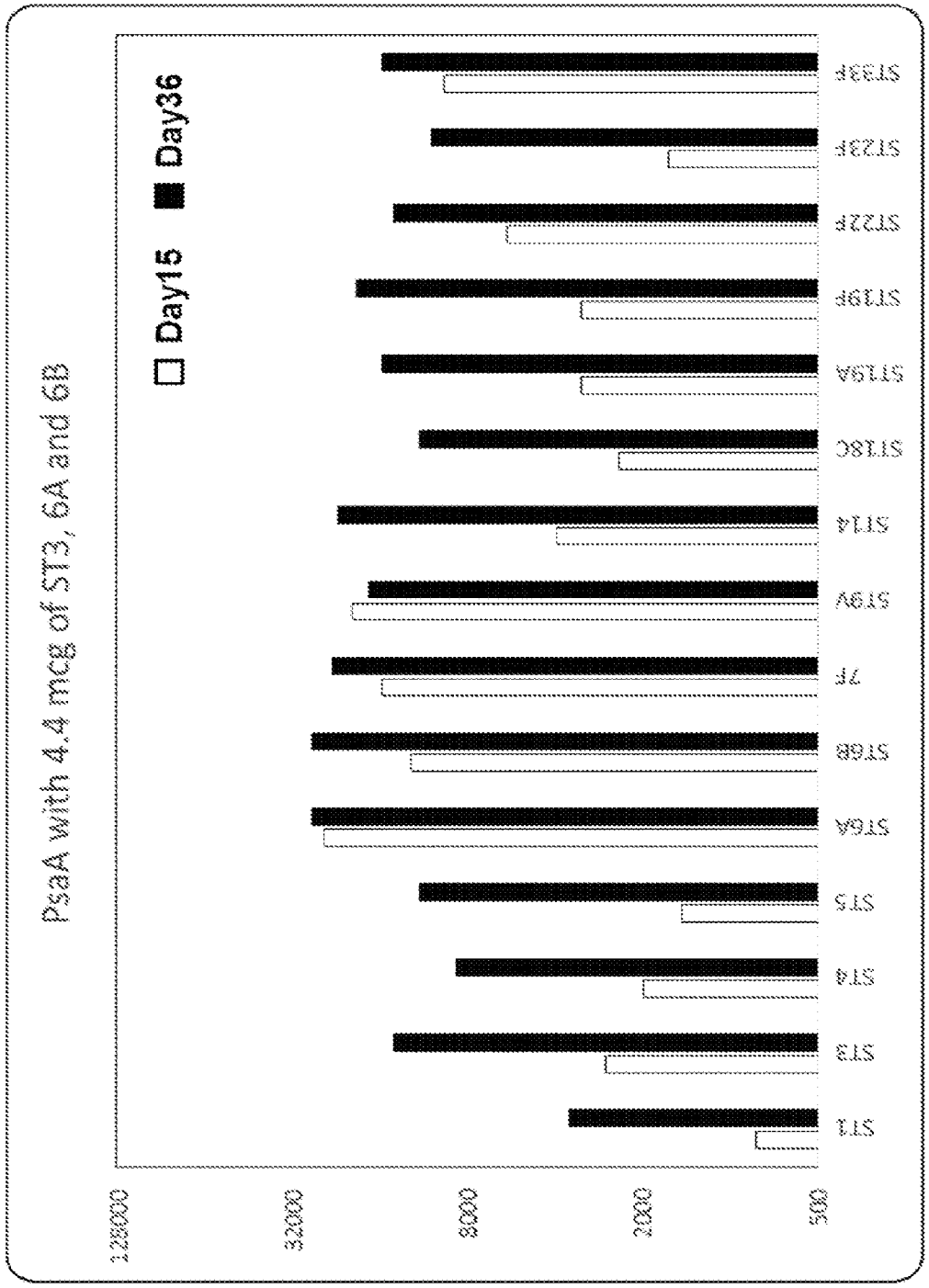

PsaA with 4.4 mcg of ST3, 6A and 6B
Day15
Day36
128000
32000
8000
2000
500
ST1
ST3
ST4
ST5
ST6A
ST6B
7F
ST9V
ST14
ST18C
ST19A
ST19F
ST22F
ST23F
ST33F

FIG. 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/054237

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/09 A61K39/385 A61K39/39 A61P31/04 A61K39/00
ADD.

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, SCISEARCH, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LIN H ET AL: "Preparation and immunogenicity of capsular polysaccharide-surface adhesin A (PsaA) conjugate of Streptococcuspneumoniae", IMMUNOBIOLOGY, URBAN UND FISCHER VERLAG, DE, vol. 215, no. 7, 1 July 2010 (2010-07-01), pages 545-550, XP027066167, ISSN: 0171-2985, DOI: 10.1016/J.IMBIO.2009.08.008 [retrieved on 2009-10-31] table 1 page 548, paragraph bridging - page 549 -----	1-45
Y	EP 2 425 856 A1 (WYETH LLC [US]) 7 March 2012 (2012-03-07) examples 15,16 ----- -/--	1-45

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 November 2017	28/11/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Domingues, Helena

1

Form PCT/ISA/210 (second sheet) (April 2005)

Petitioner Merck Ex-1015, 1804

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/054237

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ALLANA J SUCHER ET AL.: "Prevnar 13, the New 13-Valent Pneumococcal Conjugate Vaccine", THE ANNALS OF PHARMACOTHERAPY, vol. 45, no. 12, 1 December 2011 (2011-12-01), pages 1516-1524, XP055411056, the whole document	1-45
Y	WO 2010/120921 A1 (UNIV HOWARD [US]; US OF AMERICA DEPT OF HEALTH A [US]; TAI STANLEY SHI) 21 October 2010 (2010-10-21) page 16 - page 19	1-45
Y,P	WO 2016/207905 A2 (BIOLOGICAL E LTD [IN]) 29 December 2016 (2016-12-29) page 7 - page 8 claims 1,2	1-45

1

Petitioner Merck Ex-1015, 1805

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2017/054237

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 2425856 A1	07-03-2012	AR 053354 A1	02-05-2007
		AT 548051 T	15-03-2012
		AU 2006235013 A1	19-10-2006
		BR PI0607025 A2	28-07-2009
		CA 2604363 A1	19-10-2006
		CN 101180079 A	14-05-2008
		CN 102716480 A	10-10-2012
		CN 104815327 A	05-08-2015
		CY 1112777 T1	10-02-2016
		DK 1868645 T3	10-04-2012
		EP 1868645 A1	26-12-2007
		EP 2425851 A1	07-03-2012
		EP 2425852 A1	07-03-2012
		EP 2425853 A1	07-03-2012
		EP 2425854 A1	07-03-2012
		EP 2425855 A1	07-03-2012
		EP 2425856 A1	07-03-2012
		ES 2382048 T3	04-06-2012
		HK 1120416 A1	23-11-2012
		HK 1213184 A1	30-06-2016
		IL 186367 A	30-09-2013
		JP 4472770 B2	02-06-2010
		JP 5173920 B2	03-04-2013
		JP 5730261 B2	03-06-2015
		JP 2008535838 A	04-09-2008
		JP 2009161567 A	23-07-2009
		JP 2013006881 A	10-01-2013
		KR 20070118700 A	17-12-2007
		KR 20130048262 A	09-05-2013
		KR 20150061018 A	03-06-2015
		KR 20150061019 A	03-06-2015
		KR 20150061020 A	03-06-2015
		KR 20150061021 A	03-06-2015
		KR 20170086139 A	25-07-2017
		MY 145150 A	30-12-2011
		NZ 562406 A	25-09-2009
		PL 1868645 T3	31-07-2012
		PT 1868645 E	17-05-2012
		RS 52249 B	31-10-2012
		SI 1868645 T1	30-04-2012
		TW I386222 B	21-02-2013
		TW 201212937 A	01-04-2012
		TW 201438734 A	16-10-2014
		US 2006228380 A1	12-10-2006
		US 2009130137 A1	21-05-2009
		US 2012237542 A1	20-09-2012
		US 2014314805 A1	23-10-2014
		US 2016158345 A1	09-06-2016
		WO 2006110381 A1	19-10-2006
		ZA 200709483 B	25-03-2009
WO 2010120921 A1	21-10-2010	CA 2758921 A1	21-10-2010
		EP 2419130 A1	22-02-2012
		JP 5744842 B2	08-07-2015
		JP 2012524099 A	11-10-2012
		US 2010266625 A1	21-10-2010
		US 2012009213 A1	12-01-2012
		US 2015182613 A1	02-07-2015

Petitioner Merck Ex-1015, 1806

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2017/054237

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		WO 2010120921 A1	21-10-2010
WO 2016207905 A2	29-12-2016	NONE	

Petitioner Merck Ex-1015, 1807

DOCKET NO.: P1143.70000US05

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Bruce D. Forrest
Application No.:	17/347,435
Confirmation No.:	4020
Filed:	June 14, 2021
For:	SACCHARIDE-POLYPEPTIDE CONJUGATE COMPOSITIONS AND METHODS OF USE THEREOF
Examiner:	Khatol S. Shahnan Shah
Art Unit:	1645

Certificate of Electronic Filing under 37 C.F.R. § 1.8

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: April 22, 2025 Electronic Signature for Abigail S. Feldman: /Abigail S. Feldman/

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT FILED PURSUANT TO THE DUTY OF DISCLOSURE UNDER 37 C.F.R. §§ 1.56, 1.97 AND 1.98

Commissioner:

Pursuant to the duty of disclosure under 37 C.F.R. §§ 1.56, 1.97 and 1.98, the undersigned requests consideration of this Information Disclosure Statement.

PART I: Compliance with 37 C.F.R. § 1.97 and 37 C.F.R. § 1.98

This Information Disclosure Statement has been filed after the mailing date of either a Final Action under 37 C.F.R. § 1.113 or a Notice of Allowance under 37 C.F.R. § 1.311 and is being filed on or before payment of an Issue Fee.

The undersigned hereby states, as specified in 37 C.F.R. § 1.97(e), that each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart for the present Application not more than three months prior to the filing of this Statement.

Please charge our Credit Card in the amount of $112.00 covering the fee set forth in 37 C.F.R. § 1.17(p).

The undersigned hereby states, as specified in 37 C.F.R. §§ 1.97(a) and 1.98(a)(4), that this Information Disclosure Statement does not cause the cumulative number of items of information cited in the above-identified application to exceed any item threshold specified in 37 C.F.R. § 1.17. No fee is required.

PART II: Information Cited

The undersigned hereby makes of record in the present Application the information listed on the attached Form PTO-1449 (modified PTO/SB/08). The order of presentation of the references should not be construed as an indication of the importance of the references.

The undersigned would also like to bring to the Examiner's attention the enclosed search report from a corresponding foreign patent application:

Serial No.	**Date of Mailing**	**Type of Communication**	**Docket No.**
EP 24193141.9	03-05-2025	Extended European Search Report	P1143.70000EP01

PART III: Remarks

Documents cited anywhere in the Information Disclosure Statement are enclosed unless otherwise indicated. It is respectfully requested that:

1. The Examiner consider completely the cited information, along with any other information, in reaching a determination concerning the patentability of the present claims;

2. The enclosed Form PTO-1449 (modified PTO/SB/08) be signed by the Examiner to evidence that the cited information has been fully considered by the United States Patent and Trademark Office during the examination of the present Application; and

3. The citations for the information be printed on any patent which issues from the present Application.

By submitting this Information Disclosure Statement, the undersigned makes no representation that a search has been performed, of the extent of any search performed, or that more relevant information does not exist.

By submitting this Information Disclosure Statement, the undersigned makes no representation that the information cited in the Statement is, or is considered to be, material to patentability as defined in 37 C.F.R. § 1.56(b).

By submitting this Information Disclosure Statement, the undersigned makes no representation that the information cited in the Statement is, or is considered to be, in fact, prior art as defined by 35 U.S.C. § 102.

Notwithstanding any statements by the undersigned, the Examiner is urged to form his or her own conclusion regarding the relevance of the cited information.

An early and favorable action is hereby requested.

The Director is hereby authorized to charge any deficiency in the fees due, or credit any overpayment, by the filing of this Information Disclosure Statement to our Deposit Account No. 23/2825, under Docket No. P1143.70000US05, from which the undersigned is authorized to draw.

Respectfully submitted,

Electronic signature: /Jessica A. von Reyn/
Jessica A. von Reyn
Registration No.: 76,839
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

Docket No.: P1143.70000US05
Date: April 22, 2025

Docket No.: P1143.70000US05
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Bruce D. Forrest
Application No.:	17/347,435
Confirmation No.:	4020
Filed:	June 14, 2021
For:	SACCHARIDE-POLYPEPTIDE CONJUGATE COMPOSITIONS AND METHODS OF USE THEREOF
Examiner:	Khatol S. Shahnan Shah
Art Unit:	1645

Certificate of Electronic Filing under 37 C.F.R. § 1.8
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: April 22, 2025 Signature: /Emma Dereberry/ (Emma Dereberry)

RESPONSE UNDER 37 C.F.R. § 1.116

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

In response to the final Office Action, dated January 31, 2025, Applicant respectfully requests entrance of the following Amendment and consideration of the following Remarks. The deadline for responding to the Office Action is April 30, 2025. Applicant thus submits that the present Response is timely submitted on Tuesday, April 22, 2025.

Please amend the above-identified Application as follows:

Amendments to the Claims are reflected in the Listing of Claims, which begins on page 2 of this paper.

Remarks begin on page 7 of this paper.

AMENDMENTS TO THE CLAIMS

This Listing of Claims will replace all prior versions, and listings, of claims in the Application:

Listing of Claims

1-295. (Canceled)

296. (Previously Presented) A pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31, and at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38, wherein the at least one additional serotype is not the first serotype; and wherein the fragment of the capsular polysaccharide is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, a hexasaccharide, or an oligosaccharide.

297. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 31.

298. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 24F.

299. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 20A.

Petitioner Merck Ex-1015, 1812

300. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 16F.

301. (Currently Amended) The pharmaceutical composition of claim 296, wherein ~~at least one~~ the polypeptide comprises a mixture of polypeptides.

302. (Currently Amended) The pharmaceutical composition of claim 296, wherein ~~at least one~~ the polypeptide comprises cross-reacting material 197 (CRM_{197}), tetanus toxoid, a diphtheria toxoid, cholera toxoid, pertussis toxoid, inactivated or mutant pneumococcal pneumolysin, pneumococcal surface protein A, pneumococcal adhesion protein A, pneumococcal lipoprotein PsaA, C5a peptidase group A or group B *Streptococcus*, a non-typable *H. influenzae* P4 protein, a non-typable *H. influenzae* P6 protein, *M. catarrhalis* uspA, keyhole limpet haemocyanin (KLH), outer membrane protein complex (OMPC) from *N. meningitidis*, a purified protein derivative of tuberculin(PPD), protein D from *H. influenzae*, PspA, any fragment thereof, or any combination thereof.

303. (Previously Presented) The pharmaceutical composition of claim 296, further comprising an adjuvant; a chelating agent; a surfactant; an emulsifier; a buffering agent; a preservative; a salt; an anti-fungal compound; or a combination thereof.

304. (Previously Presented) The pharmaceutical composition of claim 296, wherein the pharmaceutical composition is in the form of an intramuscularly injectable composition, intradermally injectable composition, subcutaneously injectable composition, or an intranasally administrable composition.

305. (Previously Presented) The pharmaceutical composition of claim 296, wherein at least one of the immunogenic saccharide-polypeptide conjugates elicits an opsonophagocytic response.

Petitioner Merck Ex-1015, 1813

306. (Previously Presented) The pharmaceutical composition of claim 296, wherein the immunogenic saccharide-polypeptide conjugates are collectively present in an amount of at least 0.001%, by weight, based on the weight of the pharmaceutical composition.

307. (Previously Presented) The pharmaceutical composition of claim 296, wherein the immunogenic saccharide-polypeptide conjugates comprise: (i) the capsular polysaccharide at least partially embedded in the polypeptide, (ii) the capsular polysaccharide chemically cross-linked to the polypeptide, and/or (iii) the capsular polysaccharide at least partially chemically cross-linked to the polypeptide.

308. (Currently Amended) The pharmaceutical composition of claim 296, wherein a toxin activity of ~~at least one of~~ the polypeptide[[s]] is at least partly mitigated.

309. (Previously Presented) The pharmaceutical composition of claim 296, wherein each of the immunogenic saccharide-polypeptide conjugates is present in an amount of at least 0.001%, by weight, based on the weight of the pharmaceutical composition.

310. (Withdrawn – Currently Amended) A method comprising administering to a subject ~~a first composition, wherein the first composition comprises~~ the pharmaceutical composition of claim 296.

311.-315. (Cancelled)

316. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 16F and the at least one additional serotype comprises 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, and 15A.

317. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 20A and the at least one additional serotype comprises 7F, 8, 9N, 15A, 15C, 16F, 19A, 22F, 23A, and 23B.

Petitioner Merck Ex-1015, 1814

318. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 23B and the at least one additional serotype comprises 16F, 20A, 22F, 23A, 24F, 31, 33F, and 35B.

319. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 24F and the at least one additional serotype comprises 3, 7F, 8, 9N, 10A, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, and 31.

320. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 16F and the at least one additional serotype comprises 3, 7F, 8, 9N, 10A, 12F, 15A, 15C, 17F, 20A, 22F, 23A, 23B, 31, 33F, and 35B.

321. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 24F and the at least one additional serotype comprises 3, 6A, 7F, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 19A, 20A, 22F, 23B, 31, and 35B.

322. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 31 and the at least one additional serotype comprises 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 22F, 33F, and 35B.

323. (New) The pharmaceutical composition of claim 296, wherein the first serotype is 20B.

324. (New) The pharmaceutical composition of claim 323, wherein the at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 16F, 17F, 18C, 19A, 19F, 22F, 23A, 23B, 23F, 31, 33F, and 35B.

Petitioner Merck Ex-1015, 1815

325. (New) The pharmaceutical composition of claim 298, wherein the at least one additional serotype comprises 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 23F, 31, 33F, and 35B.

326. (New) The pharmaceutical composition of claim 296, wherein the first serotype is 16F and the at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 17F, 18C, 19A, 19F, 20B, 22F, 23A, 23B, 23F, 31, 33F, and 35B.

327. (New) The pharmaceutical composition of claim 296, wherein the first serotype is 16F and the at least one additional serotype comprises 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 17F, 19A, 20A, 22F, 23A, 23B, 23F, 24F, 31, 33F, and 35B.

Petitioner Merck Ex-1015, 1816

REMARKS

Claims 296-322 are pending in the Application before entrance of the present Amendment, of which claims 310-315 are withdrawn from consideration by the Examiner at this time. By the present Amendment, claims 311-315 are canceled, claims 301, 302, 308, and 310 are amended, and new claims 323-327 are added. Applicant reserves the right to pursue the subject matter canceled from the claims in one or more future continuing applications claiming priority to the present Application. The amendments to claims 301, 302, 308, and 310 to improve readability and to ensure a proper antecedent basis. Support for new claims 323-327 can be found throughout the originally filed Application, *e.g.*, original claims 62, 67, and 73.

After entrance of the present Amendment, claims 296-323 will be pending in the Application, with claim 311 being withdrawn from consideration by the Examiner at this time. Applicant submits that no new matter is added to the Application by this Amendment.

Amendment or cancellation of the claims during prosecution of this Application is not to be construed as acquiescence to any of the objections or rejections set forth in the Office Action and was done solely to expedite prosecution of the Application. Applicant reserves the right to pursue the claims as originally filed or similar claims in this Application or one or more continuing patent applications claiming priority to this Application.

Each of the rejections levied by the Examiner is addressed in turn below.

Claim Rejections under 35 U.S.C. § 102

The Examiner rejected claims 296, 298, 299, and 301-309 under 35 U.S.C. § 102 as allegedly being anticipated by Porro *et al.* (WO 2014/118201; hereinafter "Porro"). Applicant respectfully disagrees.

The claims are directed to a pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31, and at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A,

Petitioner Merck Ex-1015, 1817

15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38, wherein the at least one additional serotype is not the first serotype; and wherein the fragment of the capsular polysaccharide is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, a hexasaccharide, or an oligosaccharide.

According to MPEP 2131, not only does an anticipatory reference have to teach each and every element as set forth in the claim, but it also has to teach the arrangement or combination of the elements as required by the claim. Porro does not do teach or suggest the immune saccharide-polypeptide conjugates of the claims. In particular, Porro does not disclose immunogenic saccharide-polypeptide conjugates, **each** comprising a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide. Instead, Porro relates to **multivalent** molecular constructs comprising **at least three** carbohydrate structures (*e.g.*, capsular polysaccharides) all bound to a helper-T dependent carrier protein (*see, e.g.*, Abstract and claim 1 of Porro). Porro specifically explains that the **multivalent** construct structure is beneficial to address carrier protein-dependent immune-suppression and immune interference, noting that the "vaccine formulation encompassing as many as eighteen type-specific conjugate antigens, as an example, will be synthesized by only using one third (or 33%) of the amount of carrier protein needed in the nowadays available single-antigen-associated formulation, so that the immunogenic burden on the immune-system of the host will be significantly lower and, consequently, safer" (Porro, p. 4). Porro also indicates that the "new generation of conjugate antigens expressing **multiple specificities** or obtaining vaccines with an always broader spectrum of **protection against a variety of bacterial pathogens** while drastically reducing the amount of carrier protein" will improve "the cost of production of the vaccines, … production efficiency, … production accuracy, … safety, … [and] the public utility of such conjugate vaccines" (Porro, pages 9-10; emphasis added).

Therefore, as Porro does not anticipate the claims, Applicant respectfully requests that this rejection be withdrawn.

Claim Rejections under 35 U.S.C. § 103

The Examiner rejected claims 296-309 and 316-322 under 35 U.S.C. § 103 as allegedly being obvious over Porro in view of Mekalanos (US 9,533,032) and further in view of del Amo *et*

Petitioner Merck Ex-1015, 1818

al., "High invasiveness of pneumococcal serotypes included in the new generation of conjugate vaccines." *Clin. Microbiol. Infect.* 2013, 20(7):684-9 (hereinafter "del Amo"). Applicant respectfully disagrees.

The deficiencies of Porro and discussed above. Namely, Porro does not teach or suggest immunogenic saccharide-polypeptide conjugates, **each** comprising a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide. Mekalanos, cited for its purported disclosure of serotypes 16F, 19A, 23B, 24F, and 31, describes vaccine compositions comprising an antigen entrapped within a cross-linked carrier protein matrix, and does not remedy the deficiencies of Porro. Similarly, the Examiner cited del Amo for its purported disclosure of numerous serotypes (*e.g.*, 1, 2, 3, 4, 5, 6A/6B, 6C, 7C/(7B/40), 7F/7A, 8, 9N/9L, 9V/9A, 10A, 10F/(10C/33C), 11A/11D, 12F/(12A/44/46), 13, 14, 15A/15F, 15B/15C, 16F, 17F, 18/(18A/18B/18C/18F), 19A, 19F, 20, 21, 22F/22A, 23A, 23B, 23F, 24/(24A/24B/24F), 31, 33F/(33A/37), 34, 35A/(35C/42), 35B, 35F/47F, 38/25F, and 39); however, the list of serotypes in del Amo includes those that may be detected using an *in vitro* assay, not for conjugation, let alone for inclusion in an immunogenic saccharide-polypeptide conjugate as claimed.

Therefore, as none of the cited references, alone or in combination, teaches or suggests the immunogenic saccharide-polypeptide conjugates of the claims, withdrawal of the rejection is respectfully requested.

General Comments on Dependent Claims

Each of the dependent claims depends from a base claim that is believed to be in condition for allowance, and Applicant therefore believes that it is unnecessary at this time to argue the allowability of each of the dependent claims individually. Applicant does not, however, necessarily concur with the interpretation of the dependent claims as set forth in the Office Action, nor does Applicant concur that the basis for the rejection of any of the dependent claims is proper. Therefore, Applicant reserves the right to specifically address the patentability of the dependent claims in the future.

Petitioner Merck Ex-1015, 1819

In view of the foregoing, this Application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this response, the Application is not in condition for allowance, the Examiner is requested to call the undersigned at the telephone number indicated below to discuss any outstanding issues.

If this Response is not considered timely filed, and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time.

Applicant believes no fee is due with this Response. However, if a fee is due with this Amendment, please charge our Deposit Account No. 23/2825, under Docket No. P1143.70000US05, from which the undersigned is authorized to draw.

Dated: April 22, 2025

Respectfully submitted,

Electronic signature: /Jessica A. von Reyn/
Jessica A. von Reyn
Registration Number: 76,839
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

Petitioner Merck Ex-1015, 1820

Doc Code: TRAN.LET
Document Description: Transmittal Letter

USED IN LIEU OF PTO/SB/21 (07-09)

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	

Application Number	17/347,435-Conf. #4020
Filing Date	June 14, 2021
First Named Inventor	Bruce D. Forrest
Art Unit	1645
Examiner Name	Khatol S. Shahnan Shah
Attorney Docket Number	P1143.70000US05

ENCLOSURES (*Check all that apply*)

- [ ] Fee Transmittal Form
  - [ ] Fee Attached
- [x] Amendment/Reply
  - [x] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) (please Identify below):

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	WOLF, GREENFIELD & SACKS, P.C.		
Signature	/Jessica A. von Reyn/		
Printed name	Jessica A. von Reyn		
Date	April 22, 2025	Reg. No.	76,839

Certificate of Electronic Filing under 37 C.F.R. § 1.8

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: April 22, 2025 Signature: /Emma Dereberry/ (Emma Dereberry)

13877066

Docket No.: P1143.70000US05
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Bruce D. Forrest
Application No.:	17/347,435
Confirmation No.:	4020
Filed:	June 14, 2021
For:	SACCHARIDE-POLYPEPTIDE CONJUGATE COMPOSITIONS AND METHODS OF USE THEREOF
Examiner:	Khatol S. Shahnan Shah
Art Unit:	1645

Certificate of Electronic Filing under 37 C.F.R. § 1.8
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: April 22, 2025 Signature: /Emma Dereberry/ (Emma Dereberry)

RESPONSE UNDER 37 C.F.R. § 1.116

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

In response to the final Office Action, dated January 31, 2025, Applicant respectfully requests entrance of the following Amendment and consideration of the following Remarks. The deadline for responding to the Office Action is April 30, 2025. Applicant thus submits that the present Response is timely submitted on Tuesday, April 22, 2025.

Please amend the above-identified Application as follows:

Amendments to the Claims are reflected in the Listing of Claims, which begins on page 2 of this paper.

Remarks begin on page 7 of this paper.

AMENDMENTS TO THE CLAIMS

This Listing of Claims will replace all prior versions, and listings, of claims in the Application:

Listing of Claims

1-295. (Canceled)

296. (Previously Presented) A pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31, and at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38, wherein the at least one additional serotype is not the first serotype; and wherein the fragment of the capsular polysaccharide is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, a hexasaccharide, or an oligosaccharide.

297. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 31.

298. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 24F.

299. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 20A.

Petitioner Merck Ex-1015, 1823

300. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 16F.

301. (Currently Amended) The pharmaceutical composition of claim 296, wherein ~~at least one~~ the polypeptide comprises a mixture of polypeptides.

302. (Currently Amended) The pharmaceutical composition of claim 296, wherein ~~at least one~~ the polypeptide comprises cross-reacting material 197 (CRM_{197}), tetanus toxoid, a diphtheria toxoid, cholera toxoid, pertussis toxoid, inactivated or mutant pneumococcal pneumolysin, pneumococcal surface protein A, pneumococcal adhesion protein A, pneumococcal lipoprotein PsaA, C5a peptidase group A or group B *Streptococcus*, a non-typable *H. influenzae* P4 protein, a non-typable *H. influenzae* P6 protein, *M. catarrhalis* uspA, keyhole limpet haemocyanin (KLH), outer membrane protein complex (OMPC) from *N. meningitidis*, a purified protein derivative of tuberculin(PPD), protein D from *H. influenzae*, PspA, any fragment thereof, or any combination thereof.

303. (Previously Presented) The pharmaceutical composition of claim 296, further comprising an adjuvant; a chelating agent; a surfactant; an emulsifier; a buffering agent; a preservative; a salt; an anti-fungal compound; or a combination thereof.

304. (Previously Presented) The pharmaceutical composition of claim 296, wherein the pharmaceutical composition is in the form of an intramuscularly injectable composition, intradermally injectable composition, subcutaneously injectable composition, or an intranasally administrable composition.

305. (Previously Presented) The pharmaceutical composition of claim 296, wherein at least one of the immunogenic saccharide-polypeptide conjugates elicits an opsonophagocytic response.

Petitioner Merck Ex-1015, 1824

306. (Previously Presented) The pharmaceutical composition of claim 296, wherein the immunogenic saccharide-polypeptide conjugates are collectively present in an amount of at least 0.001%, by weight, based on the weight of the pharmaceutical composition.

307. (Previously Presented) The pharmaceutical composition of claim 296, wherein the immunogenic saccharide-polypeptide conjugates comprise: (i) the capsular polysaccharide at least partially embedded in the polypeptide, (ii) the capsular polysaccharide chemically cross-linked to the polypeptide, and/or (iii) the capsular polysaccharide at least partially chemically cross-linked to the polypeptide.

308. (Currently Amended) The pharmaceutical composition of claim 296, wherein a toxin activity of ~~at least one of~~ the polypeptide[[s]] is at least partly mitigated.

309. (Previously Presented) The pharmaceutical composition of claim 296, wherein each of the immunogenic saccharide-polypeptide conjugates is present in an amount of at least 0.001%, by weight, based on the weight of the pharmaceutical composition.

310. (Withdrawn – Currently Amended) A method comprising administering to a subject ~~a first composition, wherein the first composition comprises~~ the pharmaceutical composition of claim 296.

311.-315. (Cancelled)

316. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 16F and the at least one additional serotype comprises 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, and 15A.

317. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 20A and the at least one additional serotype comprises 7F, 8, 9N, 15A, 15C, 16F, 19A, 22F, 23A, and 23B.

Petitioner Merck Ex-1015, 1825

318. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 23B and the at least one additional serotype comprises 16F, 20A, 22F, 23A, 24F, 31, 33F, and 35B.

319. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 24F and the at least one additional serotype comprises 3, 7F, 8, 9N, 10A, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, and 31.

320. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 16F and the at least one additional serotype comprises 3, 7F, 8, 9N, 10A, 12F, 15A, 15C, 17F, 20A, 22F, 23A, 23B, 31, 33F, and 35B.

321. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 24F and the at least one additional serotype comprises 3, 6A, 7F, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 19A, 20A, 22F, 23B, 31, and 35B.

322. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 31 and the at least one additional serotype comprises 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 22F, 33F, and 35B.

323. (New) The pharmaceutical composition of claim 296, wherein the first serotype is 20B.

324. (New) The pharmaceutical composition of claim 323, wherein the at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 16F, 17F, 18C, 19A, 19F, 22F, 23A, 23B, 23F, 31, 33F, and 35B.

Petitioner Merck Ex-1015, 1826

325. (New) The pharmaceutical composition of claim 298, wherein the at least one additional serotype comprises 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 23F, 31, 33F, and 35B.

326. (New) The pharmaceutical composition of claim 296, wherein the first serotype is 16F and the at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 17F, 18C, 19A, 19F, 20B, 22F, 23A, 23B, 23F, 31, 33F, and 35B.

327. (New) The pharmaceutical composition of claim 296, wherein the first serotype is 16F and the at least one additional serotype comprises 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 17F, 19A, 20A, 22F, 23A, 23B, 23F, 24F, 31, 33F, and 35B.

Petitioner Merck Ex-1015, 1827

REMARKS

Claims 296-322 are pending in the Application before entrance of the present Amendment, of which claims 310-315 are withdrawn from consideration by the Examiner at this time. By the present Amendment, claims 311-315 are canceled, claims 301, 302, 308, and 310 are amended, and new claims 323-327 are added. Applicant reserves the right to pursue the subject matter canceled from the claims in one or more future continuing applications claiming priority to the present Application. The amendments to claims 301, 302, 308, and 310 to improve readability and to ensure a proper antecedent basis. Support for new claims 323-327 can be found throughout the originally filed Application, *e.g.*, original claims 62, 67, and 73.

After entrance of the present Amendment, claims 296-323 will be pending in the Application, with claim 311 being withdrawn from consideration by the Examiner at this time. Applicant submits that no new matter is added to the Application by this Amendment.

Amendment or cancellation of the claims during prosecution of this Application is not to be construed as acquiescence to any of the objections or rejections set forth in the Office Action and was done solely to expedite prosecution of the Application. Applicant reserves the right to pursue the claims as originally filed or similar claims in this Application or one or more continuing patent applications claiming priority to this Application.

Each of the rejections levied by the Examiner is addressed in turn below.

Claim Rejections under 35 U.S.C. § 102

The Examiner rejected claims 296, 298, 299, and 301-309 under 35 U.S.C. § 102 as allegedly being anticipated by Porro *et al.* (WO 2014/118201; hereinafter "Porro"). Applicant respectfully disagrees.

The claims are directed to a pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31, and at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A,

Petitioner Merck Ex-1015, 1828

15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38, wherein the at least one additional serotype is not the first serotype; and wherein the fragment of the capsular polysaccharide is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, a hexasaccharide, or an oligosaccharide.

According to MPEP 2131, not only does an anticipatory reference have to teach each and every element as set forth in the claim, but it also has to teach the arrangement or combination of the elements as required by the claim. Porro does not do teach or suggest the immune saccharide-polypeptide conjugates of the claims. In particular, Porro does not disclose immunogenic saccharide-polypeptide conjugates, **each** comprising a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide. Instead, Porro relates to **multivalent** molecular constructs comprising **at least three** carbohydrate structures (*e.g.*, capsular polysaccharides) all bound to a helper-T dependent carrier protein (*see, e.g.*, Abstract and claim 1 of Porro). Porro specifically explains that the **multivalent** construct structure is beneficial to address carrier protein-dependent immune-suppression and immune interference, noting that the "vaccine formulation encompassing as many as eighteen type-specific conjugate antigens, as an example, will be synthesized by only using one third (or 33%) of the amount of carrier protein needed in the nowadays available single-antigen-associated formulation, so that the immunogenic burden on the immune-system of the host will be significantly lower and, consequently, safer" (Porro, p. 4). Porro also indicates that the "new generation of conjugate antigens expressing **multiple specificities** or obtaining vaccines with an always broader spectrum of **protection against a variety of bacterial pathogens** while drastically reducing the amount of carrier protein" will improve "the cost of production of the vaccines, … production efficiency, … production accuracy, … safety, … [and] the public utility of such conjugate vaccines" (Porro, pages 9-10; emphasis added).

Therefore, as Porro does not anticipate the claims, Applicant respectfully requests that this rejection be withdrawn.

Claim Rejections under 35 U.S.C. § 103

The Examiner rejected claims 296-309 and 316-322 under 35 U.S.C. § 103 as allegedly being obvious over Porro in view of Mekalanos (US 9,533,032) and further in view of del Amo *et*

Petitioner Merck Ex-1015, 1829

al., "High invasiveness of pneumococcal serotypes included in the new generation of conjugate vaccines." *Clin. Microbiol. Infect.* 2013, 20(7):684-9 (hereinafter "del Amo"). Applicant respectfully disagrees.

The deficiencies of Porro and discussed above. Namely, Porro does not teach or suggest immunogenic saccharide-polypeptide conjugates, **each** comprising a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide. Mekalanos, cited for its purported disclosure of serotypes 16F, 19A, 23B, 24F, and 31, describes vaccine compositions comprising an antigen entrapped within a cross-linked carrier protein matrix, and does not remedy the deficiencies of Porro. Similarly, the Examiner cited del Amo for its purported disclosure of numerous serotypes (*e.g.*, 1, 2, 3, 4, 5, 6A/6B, 6C, 7C/(7B/40), 7F/7A, 8, 9N/9L, 9V/9A, 10A, 10F/(10C/33C), 11A/11D, 12F/(12A/44/46), 13, 14, 15A/15F, 15B/15C, 16F, 17F, 18/(18A/18B/18C/18F), 19A, 19F, 20, 21, 22F/22A, 23A, 23B, 23F, 24/(24A/24B/24F), 31, 33F/(33A/37), 34, 35A/(35C/42), 35B, 35F/47F, 38/25F, and 39); however, the list of serotypes in del Amo includes those that may be detected using an *in vitro* assay, not for conjugation, let alone for inclusion in an immunogenic saccharide-polypeptide conjugate as claimed.

Therefore, as none of the cited references, alone or in combination, teaches or suggests the immunogenic saccharide-polypeptide conjugates of the claims, withdrawal of the rejection is respectfully requested.

General Comments on Dependent Claims

Each of the dependent claims depends from a base claim that is believed to be in condition for allowance, and Applicant therefore believes that it is unnecessary at this time to argue the allowability of each of the dependent claims individually. Applicant does not, however, necessarily concur with the interpretation of the dependent claims as set forth in the Office Action, nor does Applicant concur that the basis for the rejection of any of the dependent claims is proper. Therefore, Applicant reserves the right to specifically address the patentability of the dependent claims in the future.

Petitioner Merck Ex-1015, 1830

In view of the foregoing, this Application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this response, the Application is not in condition for allowance, the Examiner is requested to call the undersigned at the telephone number indicated below to discuss any outstanding issues.

If this Response is not considered timely filed, and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time.

Applicant believes no fee is due with this Response. However, if a fee is due with this Amendment, please charge our Deposit Account No. 23/2825, under Docket No. P1143.70000US05, from which the undersigned is authorized to draw.

Dated: April 22, 2025

Respectfully submitted,

Electronic signature: /Jessica A. von Reyn/
Jessica A. von Reyn
Registration Number: 76,839
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

Petitioner Merck Ex-1015, 1831

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/347,435	**04/22/2025 10:13:39 AM Z ET**	**P1143.70000US05**

Title of Invention

SACCHARIDE-POLYPEPTIDE CONJUGATE COMPOSITIONS AND METHODS OF USE THEREOF

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	4020	FILED BY	Emma Dereberry
PATENT CENTER #	70102513	FILING DATE	06/14/2021
CUSTOMER #	23628	FIRST NAMED INVENTOR	Bruce D. Forrest
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jessica von Reyn

Documents

TOTAL DOCUMENTS: 4

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
P114370000US05-TRN-JXV.pdf		1	Miscellaneous Incoming Letter	25 KB
P114370000US05-116AMN-JXV.pdf		10	-	63 KB
P114370000US05-116AMN-JXV-A.NE.pdf	(1-1)	1	Response After Final Action	26 KB
P114370000US05-116AMN-JXV-CLM.pdf	(2-6)	5	Claims	38 KB
P114370000US05-116AMN-JXV-REM.pdf	(7-10)	4	Applicant Arguments/Remarks Made in an Amendment	41 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
P114370000US05-TRN-JXV.pdf	E3EA51796DC0CDFF419106DE6EB070B55D7C6A0623DC96F64F5B8FE013C5DB5F529B1BBF727A7FAC293CCB0CC3FC08EEB4484A078BFD3E7A6702506B332A3263
P114370000US05-116AMN-JXV.pdf	AD865DF14C5C533E9E7FE7B0E632B332B53CBBB33B612514D11127E7CFAE8C0509979684133858 7EF821712D8CA36C4800131E9CA47937A99E795FEBE1055F1E
P114370000US05-116AMN-JXV-A.NE.pdf	8568B6A81648ACC81AD703D645F65650D880DC30D8E6BB80902BA0B039ED87CF26343D78A7F7C12C16245349A749B2AC9C852FEC879DC1C6298CCE205DC4B1E6
P114370000US05-116AMN-JXV-CLM.pdf	7E9F8312650A91F535958ADF8AC3A8D4D1071ED8EE0435AEDF6198E49AF9745A0D4144812AB4F8D368F75FD8A100C66B1AB36ABCBF9F86BA332FA6C67F7F3495
P114370000US05-116AMN-JXV-REM.pdf	7AF9F399CE969C489F6B9165C0B5C81DA451C722B177A53668EC1C900406518CD4C845555008ABB842B3E1574F0A6E6C20D088CF2BF197A9DD4C3B7AF6A1CA7F

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 17/347,435	Filing Date 06/14/2021	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $240 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	04/22/2025	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 27	Minus	** 27	= 0		x $80 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $240 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	ADMIN
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/ERNEST D DAVIS/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/347,435	06/14/2021	Bruce D. Forrest	P1143.70000US05	4020

23628 7590 05/08/2025
WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER	
SHAHNAN SHAH, KHATOL S	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
05/08/2025	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents_eOfficeAction@WolfGreenfield.com
WGS_eOfficeAction@WolfGreenfield.com

Petitioner Merck Ex-1015, 1835

Attachment to Advisory Action

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

2. Applicants after final amendment and response of 4/22/2025 are acknowledged. Claims 301, 302, 308 and 310 have been amended. Withdrawn claims 311-315 have been canceled. New claims 323-327 have been added. The amendment has NOT been entered for the reasons mentioned in note below:

Amended claims 301, 302, 308 and 310 and new claims 323-327 were added. Some amendments raise new issues that would require further consideration and search. The new issues include deleted limitations such as changing the number of polypeptides in the composition, and adding one or more first and additional serotypes in the pharmaceutical composition.

The proposed after final amendments do not place the application in better form for appeal and do not materially reduce or simplify the issues for appeal.

The present adding new claims 323-327 without canceling corresponding number of finally rejected claim. Canceling claims 311-315 does solve this issue because claims 311-315 were not finally rejected. Claims 311-315 were withdrawn. Therefore, the proposed after final amendment will not be entered and the rejections recited below are maintained.

Status of Claims

3. Claims 296-322 are pending. Claims 1-295 have canceled by previous amendments. Claims 310-315 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on May 20, 2024. Claims 296-309 and 316-322 had been under examination.

Claim Rejections - 35 USC § 102 Maintained

4. Rejection of claims **296**, 298, 299, 301, 302, 303, 304, 305, 306, 307, 308 and 309 are rejected under 35 U.S.C. 102(a)(1)/102(a)(2) as being anticipated by Porro et al.,

(WO 2014/118201 A1), priority to 1/31/2013, is maintained for reasons of record and Applicants comments are not being further considered because prosecution on the merits in closed in view of the finality of the previous office action.

Claim Rejections - 35 USC § 103 Maintained

5. Claims 296-309 and new claims 316-322 are rejected under 35 U.S.C. 103 as being unpatentable over Porro et al., (WO 2014/118201 A1), priority to 1/31/2013, in view of John J. Mekalanos US 9533032 B and further in view of del Amo et al. (Clinical Microbiology and Infection vol. 20, pp. 684-689, 8 November 2013), is maintained for reasons of record and Applicants comments are not being further considered because prosecution on the merits in closed in view of the finality of the previous office action.

Conclusion

6. No claims are allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KHATOL S SHAHNAN SHAH whose telephone number is (571)272-0863. The examiner can normally be reached on Mon-Tue, Thurs-Fri 12pm-8pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Khatol S Shahnan-Shah/
Examiner, Art Unit 1645

April 29, 2025

/JANA A HINES/

Primary Examiner, Art Unit 1645

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 17/347,435	**Applicant(s)** Forrest et al.	
	Examiner KHATOL S SHAHNAN SHAH	**Art Unit** 1645	**AIA (First Inventor to File) Status** Yes

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 22 April 2025 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

NO NOTICE OF APPEAL FILED

1. ☑ The reply was filed after a final rejection. No Notice of Appeal has been filed. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114 if this is a utility or plant application. Note that RCEs are not permitted in design applications. The reply must be filed within one of the following time periods:
   a) ☑ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action; or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
   c) ☐ A prior Advisory Action was mailed more than 3 months after the mailing date of the final rejection in response to a first after-final reply filed within 2 months of the mailing date of the final rejection.The current period for reply expires ____ months from the mailing date of *the prior Advisory Action* or SIX MONTHS from the mailing date of the final rejection, whichever is earlier.
   Examiner Note: If box 1 is checked, check either box (a), (b) or (c). ONLY CHECK BOX (b) WHEN THIS ADVISORY ACTION IS THE FIRST RESPONSE TO APPLICANTS FIRST AFTER-FINAL REPLY WHICH WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. ONLY CHECK BOX (c) IN THE LIMITED SITUATION SET FORTH UNDER BOX (c). See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) or (c) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37CFR 41.37(a).

AMENDMENTS

3. ☑ The proposed amendments filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   a) ☑ They raise new issues that would require further consideration and/or search (see NOTE below);
   b) ☐ They raise the issue of new matter (see NOTE below);
   c) ☑ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   d) ☑ They present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: See attached (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☑ For purposes of appeal, the proposed amendment(s):(a) ☑ will not be entered; or (b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____
9. ☐ The affidavit or other evidence filed after final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
10. ☐ The affidavit or other evidence filed after the date of filing the Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
11. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

12. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
13. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
14. ☐ Other: _____.

STATUS OF CLAIMS

15. The status of the claim(s) is (or will be) as follows:
    Claim(s) allowed:None.
    Claim(s) objected to:None.
    Claim(s) rejected:206-309 and 316-322.
    Claim(s) withdrawn from consideration:31-315.

/KHATOL S SHAHNAN SHAH/ Examiner, Art Unit 1645	/JANA A HINES/ Primary Examiner, Art Unit 1645

Petitioner Merck Ex-1015, 1839

DO NOT ENTER: /K.S.S/

04/29/2025

Docket No.: P1143.70000US05
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Bruce D. Forrest
Application No.:	17/347,435
Confirmation No.:	4020
Filed:	June 14, 2021
For:	SACCHARIDE-POLYPEPTIDE CONJUGATE COMPOSITIONS AND METHODS OF USE THEREOF
Examiner:	Khatol S. Shahnan Shah
Art Unit:	1645

Certificate of Electronic Filing under 37 C.F.R. § 1.8
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: April 22, 2025 Signature: /Emma Dereberry/ (Emma Dereberry)

RESPONSE UNDER 37 C.F.R. § 1.116

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

In response to the final Office Action, dated January 31, 2025, Applicant respectfully requests entrance of the following Amendment and consideration of the following Remarks. The deadline for responding to the Office Action is April 30, 2025. Applicant thus submits that the present Response is timely submitted on Tuesday, April 22, 2025.

Please amend the above-identified Application as follows:

Amendments to the Claims are reflected in the Listing of Claims, which begins on page 2 of this paper.

Remarks begin on page 7 of this paper.

REMARKS

Claims 296-322 are pending in the Application before entrance of the present Amendment, of which claims 310-315 are withdrawn from consideration by the Examiner at this time. By the present Amendment, claims 311-315 are canceled, claims 301, 302, 308, and 310 are amended, and new claims 323-327 are added. Applicant reserves the right to pursue the subject matter canceled from the claims in one or more future continuing applications claiming priority to the present Application. The amendments to claims 301, 302, 308, and 310 to improve readability and to ensure a proper antecedent basis. Support for new claims 323-327 can be found throughout the originally filed Application, *e.g.*, original claims 62, 67, and 73.

After entrance of the present Amendment, claims 296-323 will be pending in the Application, with claim 311 being withdrawn from consideration by the Examiner at this time. Applicant submits that no new matter is added to the Application by this Amendment.

Amendment or cancellation of the claims during prosecution of this Application is not to be construed as acquiescence to any of the objections or rejections set forth in the Office Action and was done solely to expedite prosecution of the Application. Applicant reserves the right to pursue the claims as originally filed or similar claims in this Application or one or more continuing patent applications claiming priority to this Application.

Each of the rejections levied by the Examiner is addressed in turn below.

Claim Rejections under 35 U.S.C. § 102

The Examiner rejected claims 296, 298, 299, and 301-309 under 35 U.S.C. § 102 as allegedly being anticipated by Porro *et al.* (WO 2014/118201; hereinafter "Porro"). Applicant respectfully disagrees.

The claims are directed to a pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31, and at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A,

Petitioner Merck Ex-1015, 1841

15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38, wherein the at least one additional serotype is not the first serotype; and wherein the fragment of the capsular polysaccharide is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, a hexasaccharide, or an oligosaccharide.

According to MPEP 2131, not only does an anticipatory reference have to teach each and every element as set forth in the claim, but it also has to teach the arrangement or combination of the elements as required by the claim. Porro does not do teach or suggest the immune saccharide-polypeptide conjugates of the claims. In particular, Porro does not disclose immunogenic saccharide-polypeptide conjugates, **each** comprising a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide. Instead, Porro relates to **multivalent** molecular constructs comprising **at least three** carbohydrate structures (*e.g.*, capsular polysaccharides) all bound to a helper-T dependent carrier protein (*see, e.g.*, Abstract and claim 1 of Porro). Porro specifically explains that the **multivalent** construct structure is beneficial to address carrier protein-dependent immune-suppression and immune interference, noting that the "vaccine formulation encompassing as many as eighteen type-specific conjugate antigens, as an example, will be synthesized by only using one third (or 33%) of the amount of carrier protein needed in the nowadays available single-antigen-associated formulation, so that the immunogenic burden on the immune-system of the host will be significantly lower and, consequently, safer" (Porro, p. 4). Porro also indicates that the "new generation of conjugate antigens expressing **multiple specificities** or obtaining vaccines with an always broader spectrum of **protection against a variety of bacterial pathogens** while drastically reducing the amount of carrier protein" will improve "the cost of production of the vaccines, … production efficiency, … production accuracy, … safety, … [and] the public utility of such conjugate vaccines" (Porro, pages 9-10; emphasis added).

Therefore, as Porro does not anticipate the claims, Applicant respectfully requests that this rejection be withdrawn.

Claim Rejections under 35 U.S.C. § 103

The Examiner rejected claims 296-309 and 316-322 under 35 U.S.C. § 103 as allegedly being obvious over Porro in view of Mekalanos (US 9,533,032) and further in view of del Amo *et*

Petitioner Merck Ex-1015, 1842

al., "High invasiveness of pneumococcal serotypes included in the new generation of conjugate vaccines." *Clin. Microbiol. Infect.* 2013, 20(7):684-9 (hereinafter "del Amo"). Applicant respectfully disagrees.

The deficiencies of Porro and discussed above. Namely, Porro does not teach or suggest immunogenic saccharide-polypeptide conjugates, **each** comprising a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide. Mekalanos, cited for its purported disclosure of serotypes 16F, 19A, 23B, 24F, and 31, describes vaccine compositions comprising an antigen entrapped within a cross-linked carrier protein matrix, and does not remedy the deficiencies of Porro. Similarly, the Examiner cited del Amo for its purported disclosure of numerous serotypes (*e.g.*, 1, 2, 3, 4, 5, 6A/6B, 6C, 7C/(7B/40), 7F/7A, 8, 9N/9L, 9V/9A, 10A, 10F/(10C/33C), 11A/11D, 12F/(12A/44/46), 13, 14, 15A/15F, 15B/15C, 16F, 17F, 18/(18A/18B/18C/18F), 19A, 19F, 20, 21, 22F/22A, 23A, 23B, 23F, 24/(24A/24B/24F), 31, 33F/(33A/37), 34, 35A/(35C/42), 35B, 35F/47F, 38/25F, and 39); however, the list of serotypes in del Amo includes those that may be detected using an *in vitro* assay, not for conjugation, let alone for inclusion in an immunogenic saccharide-polypeptide conjugate as claimed.

Therefore, as none of the cited references, alone or in combination, teaches or suggests the immunogenic saccharide-polypeptide conjugates of the claims, withdrawal of the rejection is respectfully requested.

General Comments on Dependent Claims

Each of the dependent claims depends from a base claim that is believed to be in condition for allowance, and Applicant therefore believes that it is unnecessary at this time to argue the allowability of each of the dependent claims individually. Applicant does not, however, necessarily concur with the interpretation of the dependent claims as set forth in the Office Action, nor does Applicant concur that the basis for the rejection of any of the dependent claims is proper. Therefore, Applicant reserves the right to specifically address the patentability of the dependent claims in the future.

Petitioner Merck Ex-1015, 1843

In view of the foregoing, this Application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this response, the Application is not in condition for allowance, the Examiner is requested to call the undersigned at the telephone number indicated below to discuss any outstanding issues.

If this Response is not considered timely filed, and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time.

Applicant believes no fee is due with this Response. However, if a fee is due with this Amendment, please charge our Deposit Account No. 23/2825, under Docket No. P1143.70000US05, from which the undersigned is authorized to draw.

Dated: April 22, 2025

Respectfully submitted,

Electronic signature: /Jessica A. von Reyn/
Jessica A. von Reyn
Registration Number: 76,839
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

Petitioner Merck Ex-1015, 1844

Docket No.: P1143.70000US05
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Bruce D. Forrest
Application No.:	17/347,435
Confirmation No.:	4020
Filed:	June 14, 2021
For:	SACCHARIDE-POLYPEPTIDE CONJUGATE COMPOSITIONS AND METHODS OF USE THEREOF
Examiner:	Khatol S. Shahnan Shah
Art Unit:	1645

Certificate of Electronic Filing under 37 C.F.R. § 1.8
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: May 16, 2025 Signature: /Emma Dereberry/ (Emma Dereberry)

SUPPLEMENTAL RESPONSE UNDER 37 C.F.R. § 1.114

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

In response to the Office Action dated January 31, 2025, Applicant filed a Response under 37 C.F.R. § 1.116 on April 22, 2025. An Advisory Action was issued by the Office on May 8, 2025, indicating that the case was not in condition for allowance. In response to the final Office Action and subsequent Advisory Action, Applicant respectfully requests entrance of the following Amendment and consideration of the following Remarks which are being filed with a Request for Continued Examination. The deadline for responding to the final Office Action was April 30, 2025. A one-month extension of time from April 30, 2025, up to and including May 31, 2025, is hereby respectfully requested to file this Supplemental Response and Request for Continued Examination, and the required extension fee is being paid by the USPTO Electronic Filing System's credit card

payment option. Applicant thus submits that the filing of this Supplemental Response is timely submitted on Friday, May 16, 2025.

Please amend the above-identified Application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this response.

Remarks begin on page 8 of this response.

Petitioner Merck Ex-1015, 1846

AMENDMENTS TO THE CLAIMS

This Listing of Claims will replace all prior versions, and listings, of claims in the Application:

Listing of Claims

1-295. (Canceled)

296. (Previously Presented) A pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31, and at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38, wherein the at least one additional serotype is not the first serotype; and wherein the fragment of the capsular polysaccharide is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, a hexasaccharide, or an oligosaccharide.

297. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 31.

298. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 24F.

299. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 20A.

Petitioner Merck Ex-1015, 1847

300. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 16F.

301. (Currently Amended) The pharmaceutical composition of claim 296, wherein ~~at least one~~ the polypeptide comprises a mixture of polypeptides.

302. (Currently Amended) The pharmaceutical composition of claim 296, wherein ~~at least one~~ the polypeptide comprises cross-reacting material 197 (CRM_{197}), tetanus toxoid, a diphtheria toxoid, cholera toxoid, pertussis toxoid, inactivated or mutant pneumococcal pneumolysin, pneumococcal surface protein A, pneumococcal adhesion protein A, pneumococcal lipoprotein PsaA, C5a peptidase group A or group B *Streptococcus*, a non-typable *H. influenzae* P4 protein, a non-typable *H. influenzae* P6 protein, *M. catarrhalis* uspA, keyhole limpet haemocyanin (KLH), outer membrane protein complex (OMPC) from *N. meningitidis*, a purified protein derivative of tuberculin(PPD), protein D from *H. influenzae*, PspA, any fragment thereof, or any combination thereof.

303. (Previously Presented) The pharmaceutical composition of claim 296, further comprising an adjuvant; a chelating agent; a surfactant; an emulsifier; a buffering agent; a preservative; a salt; an anti-fungal compound; or a combination thereof.

304. (Previously Presented) The pharmaceutical composition of claim 296, wherein the pharmaceutical composition is in the form of an intramuscularly injectable composition, intradermally injectable composition, subcutaneously injectable composition, or an intranasally administrable composition.

305. (Previously Presented) The pharmaceutical composition of claim 296, wherein at least one of the immunogenic saccharide-polypeptide conjugates elicits an opsonophagocytic response.

Petitioner Merck Ex-1015, 1848

306. (Previously Presented) The pharmaceutical composition of claim 296, wherein the immunogenic saccharide-polypeptide conjugates are collectively present in an amount of at least 0.001%, by weight, based on the weight of the pharmaceutical composition.

307. (Previously Presented) The pharmaceutical composition of claim 296, wherein the immunogenic saccharide-polypeptide conjugates comprise: (i) the capsular polysaccharide at least partially embedded in the polypeptide, (ii) the capsular polysaccharide chemically cross-linked to the polypeptide, and/or (iii) the capsular polysaccharide at least partially chemically cross-linked to the polypeptide.

308. (Currently Amended) The pharmaceutical composition of claim 296, wherein a toxin activity of ~~at least one of~~ the polypeptide[[s]] is at least partly mitigated.

309. (Previously Presented) The pharmaceutical composition of claim 296, wherein each of the immunogenic saccharide-polypeptide conjugates is present in an amount of at least 0.001%, by weight, based on the weight of the pharmaceutical composition.

310. (Withdrawn – Currently Amended) A method comprising administering to a subject ~~a first composition, wherein the first composition comprises~~ the pharmaceutical composition of claim 296.

311.-315. (Cancelled)

316. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 16F and the at least one additional serotype comprises 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, and 15A.

317. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 20A and the at least one additional serotype comprises 7F, 8, 9N, 15A, 15C, 16F, 19A, 22F, 23A, and 23B.

Petitioner Merck Ex-1015, 1849

318. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 23B and the at least one additional serotype comprises 16F, 20A, 22F, 23A, 24F, 31, 33F, and 35B.

319. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 24F and the at least one additional serotype comprises 3, 7F, 8, 9N, 10A, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, and 31.

320. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 16F and the at least one additional serotype comprises 3, 7F, 8, 9N, 10A, 12F, 15A, 15C, 17F, 20A, 22F, 23A, 23B, 31, 33F, and 35B.

321. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 24F and the at least one additional serotype comprises 3, 6A, 7F, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 19A, 20A, 22F, 23B, 31, and 35B.

322. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 31 and the at least one additional serotype comprises 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 22F, 33F, and 35B.

323. (New) The pharmaceutical composition of claim 296, wherein the first serotype is 20B.

324. (New) The pharmaceutical composition of claim 323, wherein the at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 16F, 17F, 18C, 19A, 19F, 22F, 23A, 23B, 23F, 31, 33F, and 35B.

Petitioner Merck Ex-1015, 1850

325. (New) The pharmaceutical composition of claim 298, wherein the at least one additional serotype comprises 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 23F, 31, 33F, and 35B.

326. (New) The pharmaceutical composition of claim 296, wherein the first serotype is 16F and the at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 17F, 18C, 19A, 19F, 20B, 22F, 23A, 23B, 23F, 31, 33F, and 35B.

327. (New) The pharmaceutical composition of claim 296, wherein the first serotype is 16F and the at least one additional serotype comprises 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 17F, 19A, 20A, 22F, 23A, 23B, 23F, 24F, 31, 33F, and 35B.

Petitioner Merck Ex-1015, 1851

REMARKS

Claims 296-322 are pending in the Application before entrance of the present Amendment, of which claims 310-315 are withdrawn from consideration by the Examiner at this time. By the present Amendment, claims 311-315 are canceled, claims 301, 302, 308, and 310 are amended, and new claims 323-327 are added. Applicant reserves the right to pursue the subject matter canceled from the claims in one or more future continuing applications claiming priority to the present Application. The amendments to claims 301, 302, 308, and 310 to improve readability and to ensure a proper antecedent basis. Support for new claims 323-327 can be found throughout the originally filed Application, *e.g.*, original claims 62, 67, and 73.

After entrance of the present Amendment, claims 296-323 will be pending in the Application, with claim 311 being withdrawn from consideration by the Examiner at this time. Applicant submits that no new matter is added to the Application by this Amendment.

Amendment or cancellation of the claims during prosecution of this Application is not to be construed as acquiescence to any of the objections or rejections set forth in the Office Action and was done solely to expedite prosecution of the Application. Applicant reserves the right to pursue the claims as originally filed or similar claims in this Application or one or more continuing patent applications claiming priority to this Application.

Each of the rejections levied by the Examiner is addressed in turn below.

Claim Rejections under 35 U.S.C. § 102

The Examiner rejected claims 296, 298, 299, and 301-309 under 35 U.S.C. § 102 as allegedly being anticipated by Porro *et al.* (WO 2014/118201; hereinafter "Porro"). Applicant respectfully disagrees.

The claims are directed to a pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31, and at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A,

Petitioner Merck Ex-1015, 1852

15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38, wherein the at least one additional serotype is not the first serotype; and wherein the fragment of the capsular polysaccharide is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, a hexasaccharide, or an oligosaccharide.

According to MPEP 2131, not only does an anticipatory reference have to teach each and every element as set forth in the claim, but it also has to teach the arrangement or combination of the elements as required by the claim. Porro does not do teach or suggest the immune saccharide-polypeptide conjugates of the claims. In particular, Porro does not disclose immunogenic saccharide-polypeptide conjugates, **each** comprising a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide. Instead, Porro relates to **multivalent** molecular constructs comprising **at least three** carbohydrate structures (*e.g.*, capsular polysaccharides) all bound to a helper-T dependent carrier protein (*see, e.g.*, Abstract and claim 1 of Porro). Porro specifically explains that the **multivalent** construct structure is beneficial to address carrier protein-dependent immune-suppression and immune interference, noting that the "vaccine formulation encompassing as many as eighteen type-specific conjugate antigens, as an example, will be synthesized by only using one third (or 33%) of the amount of carrier protein needed in the nowadays available single-antigen-associated formulation, so that the immunogenic burden on the immune-system of the host will be significantly lower and, consequently, safer" (Porro, p. 4). Porro also indicates that the "new generation of conjugate antigens expressing **multiple specificities** or obtaining vaccines with an always broader spectrum of **protection against a variety of bacterial pathogens** while drastically reducing the amount of carrier protein" will improve "the cost of production of the vaccines, … production efficiency, … production accuracy, … safety, … [and] the public utility of such conjugate vaccines" (Porro, pages 9-10; emphasis added).

Therefore, as Porro does not anticipate the claims, Applicant respectfully requests that this rejection be withdrawn.

Claim Rejections under 35 U.S.C. § 103

The Examiner rejected claims 296-309 and 316-322 under 35 U.S.C. § 103 as allegedly being obvious over Porro in view of Mekalanos (US 9,533,032) and further in view of del Amo *et*

Petitioner Merck Ex-1015, 1853

al., "High invasiveness of pneumococcal serotypes included in the new generation of conjugate vaccines." *Clin. Microbiol. Infect.* 2013, 20(7):684-9 (hereinafter "del Amo"). Applicant respectfully disagrees.

The deficiencies of Porro and discussed above. Namely, Porro does not teach or suggest immunogenic saccharide-polypeptide conjugates, **each** comprising a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide. Mekalanos, cited for its purported disclosure of serotypes 16F, 19A, 23B, 24F, and 31, describes vaccine compositions comprising an antigen entrapped within a cross-linked carrier protein matrix, and does not remedy the deficiencies of Porro. Similarly, the Examiner cited del Amo for its purported disclosure of numerous serotypes (*e.g.*, 1, 2, 3, 4, 5, 6A/6B, 6C, 7C/(7B/40), 7F/7A, 8, 9N/9L, 9V/9A, 10A, 10F/(10C/33C), 11A/11D, 12F/(12A/44/46), 13, 14, 15A/15F, 15B/15C, 16F, 17F, 18/(18A/18B/18C/18F), 19A, 19F, 20, 21, 22F/22A, 23A, 23B, 23F, 24/(24A/24B/24F), 31, 33F/(33A/37), 34, 35A/(35C/42), 35B, 35F/47F, 38/25F, and 39); however, the list of serotypes in del Amo includes those that may be detected using an *in vitro* assay, not for conjugation, let alone for inclusion in an immunogenic saccharide-polypeptide conjugate as claimed.

Therefore, as none of the cited references, alone or in combination, teaches or suggests the immunogenic saccharide-polypeptide conjugates of the claims, withdrawal of the rejection is respectfully requested.

General Comments on Dependent Claims

Each of the dependent claims depends from a base claim that is believed to be in condition for allowance, and Applicant therefore believes that it is unnecessary at this time to argue the allowability of each of the dependent claims individually. Applicant does not, however, necessarily concur with the interpretation of the dependent claims as set forth in the Office Action, nor does Applicant concur that the basis for the rejection of any of the dependent claims is proper. Therefore, Applicant reserves the right to specifically address the patentability of the dependent claims in the future.

Petitioner Merck Ex-1015, 1854

In view of the foregoing, this Application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this response, the Application is not in condition for allowance, the Examiner is requested to call the undersigned at the telephone number indicated below to discuss any outstanding issues.

If this Response is not considered timely filed, and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time.

Applicant believes all fees due are being paid by credit card. However, if any additional fees are due, please charge them, or credit any overpayment, to our Deposit Account No. 23/2825, under Docket No. P1143.70000US05, from which the undersigned is authorized to draw.

Dated: May 16, 2025

Respectfully submitted,

Electronic signature: /Jessica A. von Reyn/
Jessica A. von Reyn
Registration Number: 76,839
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

Petitioner Merck Ex-1015, 1855

FEE TRANSMITTAL

(page 1 of 2)

Complete if known	
Application Number	17/347,435-Conf. #4020
Filing Date	June 14, 2021
First Named Inventor	Bruce D. Forrest
Examiner Name	K. S. Shahnan Shah
Art Unit	1645
Practitioner Docket No.	P1143.70000US05

[X] Applicant asserts small entity status. See 37 CFR 1.27.

[ ] Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

TOTAL AMOUNT OF PAYMENT ($) 694.00

METHOD OF PAYMENT (check all that apply)

[ ] Check [X] Credit Card [ ] Money Order [ ] None [ ] Other (please identify): _____

[X] Deposit Account Deposit Account Number: 23/2825 Deposit Account Name: Wolf, Greenfield & Sacks, P.C.

For the above-identified deposit account, the Director is hereby authorized to (check all that apply):

[ ] Charge fee(s) indicated below

[ ] Charge fee(s) indicated below, **except for the filing fee**

[X] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17, **except for any excess claims fees or multiple dependent claims fees**

[ ] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17

[X] Credit any overpayment of fee(s)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES (U = undiscounted fee; S = small entity fee; M = micro entity fee)

	FILING FEES			SEARCH FEES			EXAMINATION FEES			
Application Type	**U ($)**	**S ($)**	**M ($)**	**U ($)**	**S ($)**	**M ($)**	**U ($)**	**S ($)**	**M ($)**	**Fees Paid ($)**
Utility	350	140*	70	770	308	154	880	352	176	
Design	300	120	60	300	120	60	700	280	140	
Plant	240	96	48	485	194	97	725	290	145	
Reissue	350	140	70	770	308	154	2,550	1,020	510	
Provisional	325	130	65	0	0	0	0	0	0	

* The $140 small entity filing fee for a utility application is further reduced to $70 for a small entity applicant who files the application via Patent Center.

2. EXCESS CLAIM FEES

Fee Description	**Undiscounted Fee ($)**	**Small Entity Fee ($)**	**Micro Entity Fee ($)**
Each claim over 20 (including Reissues)	200	80	40
Each independent claim over 3 (including Reissues)	600	240	120
Multiple dependent claims	925	370	185

Total Claims		**Extra Claims**		**Fee ($)**		**Fee Paid ($)**
27	- 27 or HP =	_____	x	_____	=	_____

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims		**Extra Claims**		**Fee ($)**		**Fee Paid ($)**
1	- 3 or HP =	_____	x	_____	=	_____

paid for, if greater than 3.

Multiple Dependent Claims	
Fee ($)	**Fee Paid ($)**
_____	_____

HP = highest number of independent claims

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $450 ($180 for small entity) ($90 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets		**Extra Sheets**		**Number of each additional 50 or fraction thereof**		**Fee ($)**		**Fee Paid ($)**
_____	- 100 =	_____	/50 =	_____	(round **up** to a whole number) x	_____	=	_____

Certificate of Electronic Filing under 37 C.F.R. § 1.8

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: May 16, 2025 Signature: /Emma Dereberry/ (Emma Dereberry)

13959234

FEE TRANSMITTAL

(page 2 of 2)

4. CONTINUING APPLICATION FEE

If the actual filing date of the application is more than six years after the earliest benefit date, a continuing application fee is due. The earliest benefit date is the earliest filing date for which benefit is claimed under 35 U.S.C. 120, 121, 365(c), or 386(c) and § 1.78(d).

Choose only one of the following:

If the actual filing date is more than six years, and is less than or equal to nine years, after the earliest benefit date, the continuing application fee is $2,700 ($1,080 for small entity or $540 for micro entity). See 37 CFR 1.17(w)(1).

or

If the actual filing date is more than nine years after the earliest benefit date, the continuing application fee is $4,000 ($1,600 for small entity or $800 for micro entity), less any amount previously paid under 37 CFR 1.17(w)(1). See 37 CFR 1.17(w)(2).

	Fees Paid ($)

5. OTHER FEE(S)

			Fees Paid ($)
Non-English specification, $150 fee ($60 for small entity) ($30 for micro entity)			
Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, $400 fee ($200 small or micro entity)			
	2251	Extension for response within first month	94.00
Other (e.g., late filing surcharge):	2801	Request for continued examination (RCE) - 1st ...	600.00

SUBMITTED BY

Signature	/Jessica A. von Reyn/	Registration No. (Attorney/Agent)	76,839	Telephone	617.646.8000
Name (Print/Type)	Jessica A. von Reyn			Date	May 16, 2025

13959234

Request for Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	17/347,435-Conf. #4020
Filing Date	June 14, 2021
First Named Inventor	Bruce D. Forrest
Art Unit	1645
Examiner Name	Khatol S. Shahnan Shah
Attorney Docket Number	P1143.70000US05

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.

Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8,1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. [ ] Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

      i. [ ] Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

      ii. [ ] Other _____

   b. [X] Enclosed

      i. [X] Amendment/Reply

      ii. [ ] Affidavit(s)/ Declaration(s)

      iii. [ ] Information Disclosure Statement (IDS)

      iv. [X] Other Fee Transmittal, Extension of Time

2. Miscellaneous

   a. [ ] Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

   b. [ ] Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

   a. [X] The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 23/2825 .

      i. [X] RCE fee required under 37 CFR 1.17(e)

      ii. [X] Extension of time fee (37 CFR 1.136 and 1.17)

      iii. [ ] Other _____

   b. [ ] Check in the amount of $ _____ enclosed

   c. [X] Payment by credit card ~~(Form PTO-2038 enclosed)~~

   d. [ ] Payment by USPTO patent electronic filing system.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Jessica A. von Reyn/	Date	May 16, 2025
Name (Print/Type)	Jessica A. von Reyn	Registration No.	76,839

~~CERTIFICATE OF MAILING OR TRANSMISSION~~

~~I hereby certify that this correspondence is transmitted by the USPTO patent electronic filing system, or by facsimile to (571-273-8300, to the USPTO, or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.~~

~~Signature~~			
~~Name (Print/Type)~~		~~Date~~	

Certificate of Electronic Filing under 37 C.F.R. § 1.8

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: May 16, 2025 Signature: /Emma Dereberry/ (Emma Dereberry)

13959236

PTO/AIA/22 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) (NOT for Provisional Applications)

Docket Number (Optional): P1143.70000US05

Application Number	17/347,435-Conf. #4020	Filed	June 14, 2021

For: SACCHARIDE-POLYPEPTIDE CONJUGATE COMPOSITIONS AND METHODS OF USE THEREOF

Art Unit	1645	Examiner	K. S. Shahnan Shah

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	Micro Entity Fee	
[X]	One month (37 CFR 1.17(a)(1))	$235	$94	$47	$ 94.00
[ ]	Two months (37 CFR 1.17(a)(2))	$690	$276	$138	$
[ ]	Three months (37 CFR 1.17(a)(3))	$1,590	$636	$318	$
[ ]	Four months (37 CFR 1.17(a)(4))	$2,495	$998	$499	$
[ ]	Five months (37 CFR 1.17(a)(5))	$3,395	$1,358	$679	$

[X] Applicant asserts small entity status. See 37 CFR 1.27.

[ ] Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

[ ] A check in the amount of the fee is enclosed.

[X] Payment by credit card. ~~Form PTO-2038 is attached.~~

[ ] The Director has already been authorized to charge fees in this application to a Deposit Account.

[X] The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 23/2825 .

[X] Payment made via USPTO patent electronic filing system.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

[ ] applicant.

[X] attorney or agent of record. Registration number 76,839 .

[ ] attorney or agent acting under 37 CFR 1.34. Registration number _____ .

/Jessica A. von Reyn/ — Signature
May 16, 2025 — Date

Jessica A. von Reyn — Typed or printed name
617.646.8000 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

[ ] * Total of 1 forms are submitted.

Certificate of Electronic Filing under 37 C.F.R. § 1.8

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: May 16, 2025 Signature: /Emma Dereberry/ (Emma Dereberry)

13959239

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/347,435	**05/16/2025 11:13:45 AM Z ET**	**P1143.70000US05**

Title of Invention

SACCHARIDE-POLYPEPTIDE CONJUGATE COMPOSITIONS AND METHODS OF USE THEREOF

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	4020	FILED BY	Emma Dereberry
PATENT CENTER #	70458200	AUTHORIZED BY	Jessica von Reyn
CUSTOMER #	23628	FILING DATE	06/14/2021
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Bruce D. Forrest

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 8543	**E20255FB14488598**	**Emma Dereberry**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2251	EXTENSION FOR RESPONSE WITHIN FIRST MONTH, EXCEPT PROVISIONAL APPLICATIONS	94.00	1	94.00
2801	REQUEST FOR CONTINUED EXAMINATION (RCE) - 1ST REQUEST (SEE 37 CFR 1.114)	600.00	1	600.00
			TOTAL AMOUNT:	**$694.00**

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement

Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/347,435	**05/16/2025 11:13:45 AM Z ET**	**P1143.70000US05**

Title of Invention

SACCHARIDE-POLYPEPTIDE CONJUGATE COMPOSITIONS AND METHODS OF USE THEREOF

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	4020	FILED BY	Emma Dereberry
PATENT CENTER #	70458200	FILING DATE	06/14/2021
CUSTOMER #	23628	FIRST NAMED INVENTOR	Bruce D. Forrest
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jessica von Reyn

Documents

TOTAL DOCUMENTS: 6

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
P114370000US05-RCE-JXV.pdf		1	Request for Continued Examination (RCE)	28 KB
Warning: This is not a USPTO supplied RCE fillable form. Data in the form cannot be automatically loaded to other USPTO systems.				
P114370000US05-114AMN-JXV.pdf		11	-	65 KB
P114370000US05-114AMN-JXV-AMSB.pdf	(1-2)	2	Amendment Submitted/Entered with Filing of Continued Prosecution Application (CPA)/Request for Continued Examination(RCE)	28 KB
P114370000US05-114AMN-JXV-CLM.pdf	(3-7)	5	Claims	37 KB

P114370000US05-114AMN-JXV-REM.pdf	(8-11)	4	Applicant Arguments/Remarks Made in an Amendment	41 KB
P114370000US05-EXT-JXV.pdf		1	Extension of Time	33 KB
P114370000US05-FEE-JXV.pdf		2	Fee Worksheet (SB06)	83 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
P114370000US05-RCE-JXV.pdf	47A50A954021618FD3337D8EA78E348A9A58229FBFC0310543F80BD2C8D5B0824CD5C71195A487B76D778A9F7F1D4746C1F5C955C46FAD5B4762CD22079E1726
P114370000US05-114AMN-JXV.pdf	F90BEDC4B2A5E0025804A41C9AE68C85431E585688FE747F82A07111B13989CD676993F1A13AEA052745A91B3DFD4D8815DAC5083DE995AB4184346CF23AF17B
P114370000US05-114AMN-JXV-AMSB.pdf	3C46229BBC7A9FCCA3D9C210772BF5F731D8D1A48994D922B6F0B998D45773C753F122577B6E5A15A0F3378D086FA46EBA0CD4D63E0A557E78B14B84CC30E904
P114370000US05-114AMN-JXV-CLM.pdf	849A8F90A2A1B33F0571CC0A0FC97CE8550B53FA60D796EFB98E9EA50F378F4EFB257EE4AF9AB0D5E5EB3DE5B3AC1A7DD42316A9A3689CE0574FB97974A7DF90
P114370000US05-114AMN-JXV-REM.pdf	420906BDB8B0C002AFA4450745922F59A93DE6C109AF75AB7DDE0978D7677A6A6F8F2228D6AA75654253D94A6F3B60D07F00249E85D845A91E70766CDE6EE4C4
P114370000US05-EXT-JXV.pdf	65F987FFAC3A0E80496349DA0BA328C6C829B198926A7FB6F056347E97E53878E3299612D7BF07DE6DDD24BCB2B20DC644969AC8E1A535818582B72C593B2845
P114370000US05-FEE-JXV.pdf	937147FD851FD327137D14FBC7EA1361D262BB04B3A2F5C04CF47BA51132AFF6E8C5BA35B17681D6AAAAFFD4F7FA5DA697DB75242F5F79A6D283F28F95EA8B32

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C.

371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Docket No.: P1143.70000US05
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Bruce D. Forrest
Application No.:	17/347,435
Confirmation No.:	4020
Filed:	June 14, 2021
For:	SACCHARIDE-POLYPEPTIDE CONJUGATE COMPOSITIONS AND METHODS OF USE THEREOF
Examiner:	Khatol S. Shahnan Shah
Art Unit:	1645

Certificate of Electronic Filing under 37 C.F.R. § 1.8
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: May 16, 2025 Signature: /Emma Dereberry/ (Emma Dereberry)

SUPPLEMENTAL RESPONSE UNDER 37 C.F.R. § 1.114

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

In response to the Office Action dated January 31, 2025, Applicant filed a Response under 37 C.F.R. § 1.116 on April 22, 2025. An Advisory Action was issued by the Office on May 8, 2025, indicating that the case was not in condition for allowance. In response to the final Office Action and subsequent Advisory Action, Applicant respectfully requests entrance of the following Amendment and consideration of the following Remarks which are being filed with a Request for Continued Examination. The deadline for responding to the final Office Action was April 30, 2025. A one-month extension of time from April 30, 2025, up to and including May 31, 2025, is hereby respectfully requested to file this Supplemental Response and Request for Continued Examination, and the required extension fee is being paid by the USPTO Electronic Filing System's credit card

payment option. Applicant thus submits that the filing of this Supplemental Response is timely submitted on Friday, May 16, 2025.

Please amend the above-identified Application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this response.

Remarks begin on page 8 of this response.

Petitioner Merck Ex-1015, 1866

AMENDMENTS TO THE CLAIMS

This Listing of Claims will replace all prior versions, and listings, of claims in the Application:

Listing of Claims

1-295. (Canceled)

296. (Previously Presented) A pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31, and at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38, wherein the at least one additional serotype is not the first serotype; and wherein the fragment of the capsular polysaccharide is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, a hexasaccharide, or an oligosaccharide.

297. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 31.

298. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 24F.

299. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 20A.

Petitioner Merck Ex-1015, 1867

300. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 16F.

301. (Currently Amended) The pharmaceutical composition of claim 296, wherein ~~at least one~~ the polypeptide comprises a mixture of polypeptides.

302. (Currently Amended) The pharmaceutical composition of claim 296, wherein ~~at least one~~ the polypeptide comprises cross-reacting material 197 (CRM_{197}), tetanus toxoid, a diphtheria toxoid, cholera toxoid, pertussis toxoid, inactivated or mutant pneumococcal pneumolysin, pneumococcal surface protein A, pneumococcal adhesion protein A, pneumococcal lipoprotein PsaA, C5a peptidase group A or group B *Streptococcus*, a non-typable *H. influenzae* P4 protein, a non-typable *H. influenzae* P6 protein, *M. catarrhalis* uspA, keyhole limpet haemocyanin (KLH), outer membrane protein complex (OMPC) from *N. meningitidis*, a purified protein derivative of tuberculin(PPD), protein D from *H. influenzae*, PspA, any fragment thereof, or any combination thereof.

303. (Previously Presented) The pharmaceutical composition of claim 296, further comprising an adjuvant; a chelating agent; a surfactant; an emulsifier; a buffering agent; a preservative; a salt; an anti-fungal compound; or a combination thereof.

304. (Previously Presented) The pharmaceutical composition of claim 296, wherein the pharmaceutical composition is in the form of an intramuscularly injectable composition, intradermally injectable composition, subcutaneously injectable composition, or an intranasally administrable composition.

305. (Previously Presented) The pharmaceutical composition of claim 296, wherein at least one of the immunogenic saccharide-polypeptide conjugates elicits an opsonophagocytic response.

Petitioner Merck Ex-1015, 1868

306. (Previously Presented) The pharmaceutical composition of claim 296, wherein the immunogenic saccharide-polypeptide conjugates are collectively present in an amount of at least 0.001%, by weight, based on the weight of the pharmaceutical composition.

307. (Previously Presented) The pharmaceutical composition of claim 296, wherein the immunogenic saccharide-polypeptide conjugates comprise: (i) the capsular polysaccharide at least partially embedded in the polypeptide, (ii) the capsular polysaccharide chemically cross-linked to the polypeptide, and/or (iii) the capsular polysaccharide at least partially chemically cross-linked to the polypeptide.

308. (Currently Amended) The pharmaceutical composition of claim 296, wherein a toxin activity of ~~at least one of~~ the polypeptide[[s]] is at least partly mitigated.

309. (Previously Presented) The pharmaceutical composition of claim 296, wherein each of the immunogenic saccharide-polypeptide conjugates is present in an amount of at least 0.001%, by weight, based on the weight of the pharmaceutical composition.

310. (Withdrawn – Currently Amended) A method comprising administering to a subject ~~a first composition, wherein the first composition comprises~~ the pharmaceutical composition of claim 296.

311.-315. (Cancelled)

316. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 16F and the at least one additional serotype comprises 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, and 15A.

317. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 20A and the at least one additional serotype comprises 7F, 8, 9N, 15A, 15C, 16F, 19A, 22F, 23A, and 23B.

Petitioner Merck Ex-1015, 1869

318. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 23B and the at least one additional serotype comprises 16F, 20A, 22F, 23A, 24F, 31, 33F, and 35B.

319. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 24F and the at least one additional serotype comprises 3, 7F, 8, 9N, 10A, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, and 31.

320. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 16F and the at least one additional serotype comprises 3, 7F, 8, 9N, 10A, 12F, 15A, 15C, 17F, 20A, 22F, 23A, 23B, 31, 33F, and 35B.

321. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 24F and the at least one additional serotype comprises 3, 6A, 7F, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 19A, 20A, 22F, 23B, 31, and 35B.

322. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype comprises 31 and the at least one additional serotype comprises 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 22F, 33F, and 35B.

323. (New) The pharmaceutical composition of claim 296, wherein the first serotype is 20B.

324. (New) The pharmaceutical composition of claim 323, wherein the at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 16F, 17F, 18C, 19A, 19F, 22F, 23A, 23B, 23F, 31, 33F, and 35B.

Petitioner Merck Ex-1015, 1870

325. (New) The pharmaceutical composition of claim 298, wherein the at least one additional serotype comprises 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 23F, 31, 33F, and 35B.

326. (New) The pharmaceutical composition of claim 296, wherein the first serotype is 16F and the at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 17F, 18C, 19A, 19F, 20B, 22F, 23A, 23B, 23F, 31, 33F, and 35B.

327. (New) The pharmaceutical composition of claim 296, wherein the first serotype is 16F and the at least one additional serotype comprises 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 17F, 19A, 20A, 22F, 23A, 23B, 23F, 24F, 31, 33F, and 35B.

Petitioner Merck Ex-1015, 1871

REMARKS

Claims 296-322 are pending in the Application before entrance of the present Amendment, of which claims 310-315 are withdrawn from consideration by the Examiner at this time. By the present Amendment, claims 311-315 are canceled, claims 301, 302, 308, and 310 are amended, and new claims 323-327 are added. Applicant reserves the right to pursue the subject matter canceled from the claims in one or more future continuing applications claiming priority to the present Application. The amendments to claims 301, 302, 308, and 310 to improve readability and to ensure a proper antecedent basis. Support for new claims 323-327 can be found throughout the originally filed Application, *e.g.*, original claims 62, 67, and 73.

After entrance of the present Amendment, claims 296-323 will be pending in the Application, with claim 311 being withdrawn from consideration by the Examiner at this time. Applicant submits that no new matter is added to the Application by this Amendment.

Amendment or cancellation of the claims during prosecution of this Application is not to be construed as acquiescence to any of the objections or rejections set forth in the Office Action and was done solely to expedite prosecution of the Application. Applicant reserves the right to pursue the claims as originally filed or similar claims in this Application or one or more continuing patent applications claiming priority to this Application.

Each of the rejections levied by the Examiner is addressed in turn below.

Claim Rejections under 35 U.S.C. § 102

The Examiner rejected claims 296, 298, 299, and 301-309 under 35 U.S.C. § 102 as allegedly being anticipated by Porro *et al.* (WO 2014/118201; hereinafter "Porro"). Applicant respectfully disagrees.

The claims are directed to a pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31, and at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A,

Petitioner Merck Ex-1015, 1872

15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38, wherein the at least one additional serotype is not the first serotype; and wherein the fragment of the capsular polysaccharide is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, a hexasaccharide, or an oligosaccharide.

According to MPEP 2131, not only does an anticipatory reference have to teach each and every element as set forth in the claim, but it also has to teach the arrangement or combination of the elements as required by the claim. Porro does not do teach or suggest the immune saccharide-polypeptide conjugates of the claims. In particular, Porro does not disclose immunogenic saccharide-polypeptide conjugates, **each** comprising a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide. Instead, Porro relates to **multivalent** molecular constructs comprising **at least three** carbohydrate structures (*e.g.*, capsular polysaccharides) all bound to a helper-T dependent carrier protein (*see, e.g.*, Abstract and claim 1 of Porro). Porro specifically explains that the **multivalent** construct structure is beneficial to address carrier protein-dependent immune-suppression and immune interference, noting that the "vaccine formulation encompassing as many as eighteen type-specific conjugate antigens, as an example, will be synthesized by only using one third (or 33%) of the amount of carrier protein needed in the nowadays available single-antigen-associated formulation, so that the immunogenic burden on the immune-system of the host will be significantly lower and, consequently, safer" (Porro, p. 4). Porro also indicates that the "new generation of conjugate antigens expressing **multiple specificities** or obtaining vaccines with an always broader spectrum of **protection against a variety of bacterial pathogens** while drastically reducing the amount of carrier protein" will improve "the cost of production of the vaccines, … production efficiency, … production accuracy, … safety, … [and] the public utility of such conjugate vaccines" (Porro, pages 9-10; emphasis added).

Therefore, as Porro does not anticipate the claims, Applicant respectfully requests that this rejection be withdrawn.

Claim Rejections under 35 U.S.C. § 103

The Examiner rejected claims 296-309 and 316-322 under 35 U.S.C. § 103 as allegedly being obvious over Porro in view of Mekalanos (US 9,533,032) and further in view of del Amo *et*

Petitioner Merck Ex-1015, 1873

al., "High invasiveness of pneumococcal serotypes included in the new generation of conjugate vaccines." *Clin. Microbiol. Infect.* 2013, 20(7):684-9 (hereinafter "del Amo"). Applicant respectfully disagrees.

The deficiencies of Porro and discussed above. Namely, Porro does not teach or suggest immunogenic saccharide-polypeptide conjugates, **each** comprising a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide. Mekalanos, cited for its purported disclosure of serotypes 16F, 19A, 23B, 24F, and 31, describes vaccine compositions comprising an antigen entrapped within a cross-linked carrier protein matrix, and does not remedy the deficiencies of Porro. Similarly, the Examiner cited del Amo for its purported disclosure of numerous serotypes (*e.g.*, 1, 2, 3, 4, 5, 6A/6B, 6C, 7C/(7B/40), 7F/7A, 8, 9N/9L, 9V/9A, 10A, 10F/(10C/33C), 11A/11D, 12F/(12A/44/46), 13, 14, 15A/15F, 15B/15C, 16F, 17F, 18/(18A/18B/18C/18F), 19A, 19F, 20, 21, 22F/22A, 23A, 23B, 23F, 24/(24A/24B/24F), 31, 33F/(33A/37), 34, 35A/(35C/42), 35B, 35F/47F, 38/25F, and 39); however, the list of serotypes in del Amo includes those that may be detected using an *in vitro* assay, not for conjugation, let alone for inclusion in an immunogenic saccharide-polypeptide conjugate as claimed.

Therefore, as none of the cited references, alone or in combination, teaches or suggests the immunogenic saccharide-polypeptide conjugates of the claims, withdrawal of the rejection is respectfully requested.

General Comments on Dependent Claims

Each of the dependent claims depends from a base claim that is believed to be in condition for allowance, and Applicant therefore believes that it is unnecessary at this time to argue the allowability of each of the dependent claims individually. Applicant does not, however, necessarily concur with the interpretation of the dependent claims as set forth in the Office Action, nor does Applicant concur that the basis for the rejection of any of the dependent claims is proper. Therefore, Applicant reserves the right to specifically address the patentability of the dependent claims in the future.

Petitioner Merck Ex-1015, 1874

In view of the foregoing, this Application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this response, the Application is not in condition for allowance, the Examiner is requested to call the undersigned at the telephone number indicated below to discuss any outstanding issues.

If this Response is not considered timely filed, and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time.

Applicant believes all fees due are being paid by credit card. However, if any additional fees are due, please charge them, or credit any overpayment, to our Deposit Account No. 23/2825, under Docket No. P1143.70000US05, from which the undersigned is authorized to draw.

Dated: May 16, 2025

Respectfully submitted,

Electronic signature: /Jessica A. von Reyn/
Jessica A. von Reyn
Registration Number: 76,839
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

Petitioner Merck Ex-1015, 1875

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 17/347,435	Filing Date 06/14/2021	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $240 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	05/16/2025	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 27	Minus	** 27	= 0		x $80 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $240 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/LISA THOMAS/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/347,435	06/14/2021	Bruce D. Forrest	P1143.70000US05	4020

23628 7590 07/02/2025
WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER	
SHAHNAN SHAH, KHATOL S	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
07/02/2025	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents_eOfficeAction@WolfGreenfield.com
WGS_eOfficeAction@WolfGreenfield.com

Office Action Summary	Application No. 17/347,435	Applicant(s) Forrest et al.	
	Examiner KHATOL S SHAHNAN SHAH	Art Unit 1645	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 5/16/2025.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 296-310 and 316-327 is/are pending in the application.

5a) Of the above claim(s) 310 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 296-309 and 316-327 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 4/22/2025.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/16/2025 has been entered.

3. Applicants' amendment and response of 5/16/2025 are acknowledged. Claims 301, 302, 308 and 310 have been amended. New claims 323-327 have been added. Claims 311-315 have been canceled.

Status of Claims

4. Claims 296-310 and 316-327 are pending. Claims 301, 302, 308 and 310 have been amended. New claims 323-327 have been added. Claims 311-315 have been canceled. Claims 1-295 have canceled by previous amended. Claim 310 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on May 20, 2024. Claims 296-309 and 316-327 are currently under examination.

Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on 4/22/2025 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. An initialed copy is attached hereto.

Claim Rejections - 35 USC § 103 Withdrawn

6. Rejection of claims 296-309 and new claims 316-322 are rejected under 35 U.S.C. 103 as being unpatentable over Porro et al., (WO 2014/118201 A1), priority to 1/31/2013, in view of John J. Mekalanos US 9533032 B and further in view of del Amo et al. (Clinical Microbiology and Infection vol. 20, pp. 684-689, 8 November 2013), is withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Caufield et al. WO 2011/100151 A1, art of record applicants' search report.

Claim Rejections - 35 USC § 102 Maintained

7. Rejection of claims 296, 298, 299, 301, 302, 303, 304, 305, 306, 307, 308 and 309 are rejected under 35 U.S.C. 102(a)(1)/102(a)(2) as being anticipated by Porro et al., (WO 2014/118201 A1), priority to 1/31/2013, is maintained.

Claim 296 is drawn to a pharmaceutical composition comprising at least 2 immunogenic saccharide- polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique Streptococcus pneumoniae serotype, wherein a first serotype comprises 16, 20A, 20B, 24F or 31 and at least one additional serotype is selected from the group consisting of 1, 2, 3, 4,5, 6A, 6B, 6C, 7F, OV, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 22F, 23A, 23B, 24F, 31, 33F, 34, 35B, and 38, wherein the at least one additional serotype is not the first serotype; and wherein the fragment of the capsular polysaccharide is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, a hexasaccharide or an oligosaccharide.

Porro et al. disclose limitations of claims 296, 298, 299 a pharmaceutical or antigenic multivalent molecular construct consisting of a basic unit comprising a helper-T dependent carrier protein covalently bound to a minimum of three carbohydrate structures of different serological specificity, wherein each carbohydrate structure are at least three capsular polysaccharides selected among type 1, 2, 3, 4, 5, 6A, 6B, 6C, 6D, 7F, 8. 9N, 9V,10A, 11A, 11B, 11C, 11F, 12F, 14,

15A, 15B, 15C, 17F, 18C, 19F, 20, 22F, 23A, 23F, 33F and 35B of Streptococcus pneumoniae (see abs, claims specially claims 1, 2, 4, 5, 8, 9, 11. As to amended claim 296, Porro et al. teach serotype 20 which inherently include serotypes 20A and 20 B (see claim 6, pages 3, 20, 81). Porro et al. teach monosaccharide and oligosaccharide (see pages 5, 6, 8, 9, 12, 48, 80). Porro et al. disclose conjugated polypeptides to capsular polysaccharides (see claims). The invention contains each *S. pneumonia* capsular saccharide (see page 8, 12, 68 and claim 5). Porro et al. disclose that examples of carrier proteins which may be used in the present invention are diphtheria toxoid, tetanus toxoid, CRM197, pneumococcal surface protein, PspA and protein D from H. influenzae (see claims 4, 7, 8 and pages 8, 14). meeting the limitation of claims 301, 302, 307). Porro et al. disclose cross-linked polysaccharide to poly peptide limitations of claim 307 see pages 43, 45 and 47. Porro et al. disclose the immunogenic composition may be adjuvanted (pages 26,31, 60, 63 and tables 5,6 and claims 13-14), and may further comprise a buffering agent (pages 36, 38, 43, 47, 52 and fig 4) and a salt (page 38 (meeting the limitation of claim 303). Moreover, the vaccine preparation (claim 11-12; meeting the limitation of claim 304) containing immunogenic compositions may be administered via the intramuscular, intradermal or subcutaneous routes (see page 31,61 and claim 14). As to limitation of claim 305, Porro et al. teach opsonophagocytic response (see pages 20, 61). As to limitation of claims 306 and 309. Porro et al. teach 0.1 to 1.0 microgram saccharide-polypeptide conjugate amount by weight (see claim 12, page 62). As it pertains to claim 308, the Office takes the position that the prior art meets this limitation, particularly, the polypeptide that is a toxoid based upon Applicant's definition: paragraph 035- The term "partly mitigated" in reference to the toxin activity of a polypeptide can refer to a decreased toxicity of the polypeptide as compared to a wild type version of the polypeptide. A CRM197 protein or toxoid is inherently, based upon Applicant's definition, 'partly mitigated'.

The prior art anticipates the claimed invention.

Since the Office does not have the facilities for examining and comparing applicants' composition with the composition of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the prior art.

See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and in re Fitzgerald et al., 205 USPQ 594.

Applicants' Arguments

8. Applicant's arguments filed 5/16/2025 have been fully considered but they are not persuasive. Applicants argue:

The claims are directed to a pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31, and at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38, wherein the at least one additional serotype is not the first serotype; and wherein the fragment of the capsular polysaccharide is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, a hexasaccharide, or an oligosaccharide. According to MPEP 2131, not only does an anticipatory reference have to teach each and every element as set forth in the claim, but it also has to teach the arrangement or combination of the elements as required by the claim.

Porro does not do teach or suggest the immune saccharide- polypeptide conjugates of the claims. In particular, Porro does not disclose immunogenic saccharide-polypeptide conjugates, each comprising a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide. Instead, Porro relates to multivalent molecular constructs comprising at least three carbohydrate structures *(e.g.*, capsular polysaccharides) all bound to a helper-T dependent carrier protein *(see, e.g.*, Abstract and claim 1 of Porro). Porro specifically explains that the multivalent construct structure is beneficial to address carrier protein- dependent immune-suppression and immune interference, noting that the "vaccine formulation encompassing as many as eighteen type-specific conjugate antigens, as an example, will be synthesized by only using one third (or 33%) of the amount of carrier protein needed in the nowadays available single-antigen-associated formulation, so that the

immunogenic burden on the immune-system of the host will be significantly lower and, consequently, safer" (Porro, p. 4). Porro also indicates that the "new generation of conjugate antigens expressing multiple specificities or obtaining vaccines with an always broader spectrum of protection against a variety of bacterial pathogens while drastically reducing the amount of carrier protein" will improve "the cost of production of the vaccines, ... production efficiency, ... production accuracy, ... safety, ... [and] the public utility of such conjugate vaccines" (Porro, pages 9-1O; emphasis added).

Therefore, as Porro does not anticipate the claims, Applicant respectfully requests that this rejection be withdrawn.

Office Response

9. Applicant's arguments filed 5/16/2025 have been fully considered but they are not persuasive.

In response to applicants' arguments, it is the examiner's position that Porro teach immune saccharide- polypeptide conjugates of the claims. In particular, Porro does not disclose immunogenic saccharide-polypeptide conjugates, each comprising a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide (see pages 3, 4, 5, 6, 7, 8, 10, 11 and claims 4, 7, 8, 18, 26). Porro teach glycoconjugates (see pages 7, 10, 11).

Page 10 of Porro recites that ":the present invention summarizes the concepts and the technical procedures above referenced 10 for conjugate antigens composed of protein carrier and a maximum of two different carbohydrate structures. In developing the above state of the art, the preferred (not limitative) embodiment of the basic molecular construct subject of the present invention is composed 15 by a multivalent, preferably a tetra-valent semi synthetic glycoprotein which features built-in multiple epitopes and expresses its helper I-dependent immunogenic specificity *"in vivo"* to the protein CRM197, as well as to three carried type-specific Ps, 20 for example Ps of *S. pneumoniae.* As an example, any triad of the Ps type 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A,11A,

12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F of *S. pneumoniae* such as the triad consisting of the Ps type 3,6A,7F."

In response to applicants' arguments, it is the examiner's position that Porro teach the limitations of amended claim 296. Porro et al. disclose limitations of claims 296, a pharmaceutical or antigenic multivalent molecular construct consisting of a basic unit comprising a helper-T dependent carrier protein covalently bound to a minimum of three carbohydrate structures of different serological specificity, wherein each carbohydrate structure are at least three capsular polysaccharides selected among type 1, 2, 3, 4, 5, 6A, 6B, 6C, 6D, 7F, 8. 9N, 9V,10A, 11A, 11B, 11C, 11F, 12F, 14, 15A, 15B, 15C, 17F, 18C, 19F, **20**, 22F, 23A, 23F, 33F and 35B of Streptococcus pneumoniae (see abs, claims specially claims 1, 2, 4, 5, 8, 9, 11. As to amended claim 296, Porro et al. teach serotype 20 which inherently include serotypes 20A and/or 20 B (see claim 6, pages 3, 20, 81). Porro et al. teach monosaccharide and oligosaccharide (see pages 5, 6, 8, 9, 12, 48, 80). Porro et al. disclose conjugated polypeptides to capsular polysaccharides (see claims). The invention contains each *S. pneumonia* capsular saccharide (see page 8, 12, 68 and claim 5).

Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 103 Maintained

10. Claims 296-309, 316-322 and new claims are rejected under 35 U.S.C. 103 as being unpatentable over Caufield et al. WO 2011/100151 A1, art of record applicants' search report, in view of Porro et al., (WO 2014/118201 A1), priority to 1/31/2013, in view of John J. Mekalanos US 9533032 B and further in view of del Amo et al. (Clinical Microbiology and Infection vol. 20, pp. 684-689, 8 November 2013),

Claim 296 is drawn to a pharmaceutical composition comprising at least 2 immunogenic saccharide- polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination

thereof is from a unique Streptococcus pneumoniae serotype, wherein a first serotype comprises 16, 20A, 20B, 24F or 31 and at least one additional serotype is selected from the group consisting of 1, 2, 3, 4,5, 6A, 6B, 6C, 7F, OV, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 22F, 23A, 23B, 24F, 31, 33F, 34, 35B, and 38, wherein the at least one additional serotype is not the first serotype; and wherein the fragment of the capsular polysaccharide is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, a hexasaccharide or an oligosaccharide.

Caulfield et al. teach an immunogenic composition comprising: a multivalent polysaccharide-protein conjugate mixture consisting of capsular polysaccharides from serotypes **1,** 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, **19F,** 22F, 23F, and 33F of *Streptococcus pneumoniae* conjugated to a carrier protein; and a pharmaceutically acceptable carrier and further comprise a carrier protein CRM197 and a adjuvant. (see claims and abstract).

Caulfield et al. page 5 recites "The present invention provides a multivalent immunogenic composition comprising, consisting essentially of, or alternatively, consisting of 15 distinct polysaccharide- protein conjugates, wherein each of the conjugates contains a different capsular polysaccharide conjugated to a carrier protein, and wherein the capsular polysaccharides are prepared from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F of S. *pneumoniae,* together with a pharmaceutically acceptable carrier. In certain embodiments, the carrier protein is CRM197. " Caulfield et al. teach composition comprising a plurality of at least two immunogenic polysaccharide-protein conjugates containing serotypes 22F and 33F provides robust antibody responses (see page 6). Caulfield et al. do not teach all the serotypes recited in claim 296 and new claims 323-327.

Porro et al. disclose limitations of claims 296, 298, 299 and new claims 323-327 a pharmaceutical or antigenic multivalent molecular construct consisting of a basic unit comprising a helper-T dependent carrier protein covalently bound to a minimum of three carbohydrate structures of different serological specificity, wherein each carbohydrate structure are at least three capsular polysaccharides selected among type 1, 2, 3, 4, 5, 6A, 6B, 6C, 6D, 7F, 8. 9N, 9V,10A,

11A, 11B, 11C, 11F, 12F, 14, 15A, 15B, 15C, 17F, 18C, 19F, 20, 22F, 23A, 23F, 33F and 35B of Streptococcus pneumoniae (see abs, claims specially claims 1, 2, 4, 5, 8, 9, 11. As to amended claim 296, Porro et al. teach serotype 20 which inherently include serotypes 20A and 20 B (see claim 6, pages 3, 20, 81). Porro et al. teach monosaccharide and oligosaccharide (see pages 5, 6, 8, 9, 12, 48, 80). Porro et al. disclose conjugated polypeptides to capsular polysaccharides (see claims). The invention contains each *S. pneumonia* capsular saccharide (see page 8, 12, 68 and claim 5). Porro et al. disclose that examples of carrier proteins which may be used in the present invention are diphtheria toxoid, tetanus toxoid, CRM197, pneumococcal surface protein (see claims 4, 7 8). meeting the limitation of claims 301, 302, 307). Porro et al. disclose cross-linked polysaccharide to poly peptide limitations of claim 307 see pages 43, 45 and 47. Porro et al. disclose the immunogenic composition may be adjuvanted (pages 26,31, 60, 63 and tables 5,6 and claims 13-14), and may further comprise a buffering agent (pages 36, 38, 43, 47, 52 and fig 4) and a salt (page 38 (meeting the limitation of claim 303). Moreover, the vaccine preparation (claim 11-12; meeting the limitation of claim 304) containing immunogenic compositions may be administered via the intramuscular, intradermal or subcutaneous routes (see page 31,61 and claim 14). As to limitation of claim 305, Porro et al. teach opsonophagocytic response (see pages 20, 61). As to limitation of claims 306 and 309. Porro et al. teach 0.1 to 1.0 microgram saccharide-polypeptide conjugate amount by weight (see claim 12 , page 62). As it pertains to claim 308, the Office takes the position that the prior art meets this limitation, particularly, the polypeptide that is a toxoid based upon Applicant's definition: paragraph 035- The term "partly mitigated" in reference to the toxin activity of a polypeptide can refer to a decreased toxicity of the polypeptide as compared to a wild type version of the polypeptide. A CRM197 protein or toxoid is inherently, based upon Applicant's definition, 'partly mitigated'.

Porro et al. do not teach serotypes 16F, 19A, 23B. 24F or 31.
Mekalanos teaches a vaccine composition comprising at least 2 immunogenic saccharide- polypeptide conjugates each comprising individually a capsular polysaccharide (see claims, abstract and columns 17-18). Mekalanos claim 15 teaches

Streptococcus pneumoniae polysaccharide is capsular type 1, 2, 3, 4, 5, 6A, 6B, 7A, 7B, 7C, 7F, 8, 9A, 9L, 9N, 9V, 10A, 10B, 10F, 11A, 11B, 11C, 11D, 11F, 12A, 12B, 12F, 13, 14, 15A, 15B, 15C, 15F, 16A, 16F, 17A, 17F, 18A, 18B, 18C, 18F, 19A, 19B, 19C, 19F, 20, 21, 22F, 23B, 23F, 24A, 24B, 24F, 25A, 25F, 27, 28A, 28F, 29, 31, 32A, 32F, 33A, 33B, 33D, 33F, 34, 35A, 35B, 35F, 36, 37, 38, 39, 40, 41A, 41F, 42, 43, 44, 45, 46, 47A, 47F, or 48. The above serotypes include serotypes 16F, 20, 24F and 31. As to newly added claims 316, 317, 319, 320, 321, 322 the added serotype have been taught by Mekalanos including 19A, 23B and others recited in those claims.

Additionally, del Amo et al. teach plurality of Streptococcal pneumoniae serotypes included in the new generations of conjugate vaccines or pharmaceutical compositions (see title, abstract page 685 and tables 1 and 2). del Amo et al. teach 40 serotypes/serogroups (1, 2, 3, 4, 5, 6A/6B, 6C, 7C/(7B/ 40), 7F/7A, 8, 9N/9L, 9V/9A, 10A, 10F/(10C/33C), 11A/11D, 12F/(12A/44/46), 13, 14, 15A/15F, 15B/15C, 16F, 17F, 18/(18A/ 18B/18C/18F), 19A, 19F, 20, 21, 22F/22A, 23A, 23B, 23F, 24/ (24A/24B/24F), 31, 33F/(33A/37), 34, 35A/(35C/42), 35B, 35F/ 47F, 38/25F, 39) see page 685.

It would have been obvious to combine the teaching of references to obtain the claimed invention. Because, Caulfield et al. teach an immunogenic composition comprising: a multivalent polysaccharide-protein conjugate mixture consisting of capsular polysaccharides from serotypes **1,** 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, **19F,** 22F, 23F, and 33F of *Streptococcus pneumoniae* conjugated to a carrier protein; and a pharmaceutically acceptable carrier and further comprise a carrier protein CRM197 and a adjuvant. (see claims and abstract). Porro et al. disclose limitations of claims 296, 298, 299 and new claims 323-327 a pharmaceutical or antigenic multivalent molecular construct consisting of a basic unit comprising a helper-T dependent carrier protein covalently bound to a minimum of three carbohydrate structures of different serological specificity, wherein each carbohydrate structure are at least three capsular polysaccharides selected among type 1, 2, 3, 4, 5, 6A, 6B, 6C, 6D, 7F, 8. 9N, 9V,10A, 11A, 11B, 11C, 11F, 12F, 14, 15A, 15B, 15C, 17F, 18C, 19F, 20, 22F, 23A, 23F, 33F and 35B of Streptococcus pneumoniae (see abs, claims specially claims 1, 2, 4, 5, 8, 9, 11).

It would have been obvious before the effective filing date of the presently claimed invention to employ serotypes 16F,19A, 23B, 24F, 31 taught by del Amo et al. and Mekalanos together with the claimed serotypes recited by Porro et al. to obtain the claimed invention. Because the extra serotypes further cover infections associated with that serotype with a reasonable expectation of success. One of skill in the art would be motivated because one can prevent those infections also. There is an expectation of success because Porro et al. specifically teach that you can mix any of the ones listed and the conjugates have been made with various mixtures for a long time. All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. See the recent Board decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396). Accordingly, the subject matter of claims w o u l d have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the presently claimed invention, absent evidence to the contrary.

Additionally, *KSR International Co. v. Teleflex Inc.,* 127 S. Ct. 1727, 1741 (2007), discloses combining prior art elements according to known methods to yield predictable results, thus the combination is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.,* 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It is well known to combine known serotypes recited by the claims in a conjugate which function in a predictable manner to yield a reasonable expectation of success along with predictable results to one of ordinary skill in the art at the time of the invention. Thus, it would have been obvious to a person of ordinary skill in the art to combine prior art elements according to known methods that is ready for improvement to yield predictable results. The claimed invention is *prima facie* obvious in view of the teachings of the prior art, absent any convincing evidence to the contrary.

Applicants' Arguments

11. Applicant's arguments filed 5/16/2025 have been fully considered but they are not persuasive. Applicants argue:

The deficiencies of Porro and discussed above. Namely, Porro does not teach or suggest immunogenic saccharide-polypeptide conjugates, each comprising a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide. Mekalanos, cited for its purported disclosure of serotypes 16F, 19A, 23B, 24F, and **31,** describes vaccine compositions comprising an antigen entrapped within a cross-linked carrier protein matrix, and does not remedy the deficiencies of Porro. Similarly, the Examiner cited del Amo for its purported disclosure of numerous serotypes *(e.g.,* 1, 2, 3, 4, 5, 6A/6B, 6C, 7C/(7B/40), 7F/7A, 8, 9N/9L, 9V/9A, 10A, 10F/(10C/33C), 11A/11D, 12F/(12A/44/46), 13, 14, 15A/15F, 15B/15C, 16F, I 7F, 18/(18A/18B/18C/18F), 19A, 19F, 20, 21, 22F/22A, 23A, 23B, 23F, 24/(24A/24B/24F), 31, 33F/(33A/37), 34, 35A/(35C/42), 35B, 35F/47F, 38/25F, and 39); however, the list of serotypes in del Amo includes those that may be detected using an *in vitro* assay, not for conjugation, let alone for inclusion in an immunogenic saccharide-polypeptide conjugate as claimed. Therefore, as none of the cited references, alone or in combination, teaches or suggests the immunogenic saccharide-polypeptide conjugates of the claims, withdrawal of the rejection is respectfully requested.

Office Response

12. Applicant's arguments filed 5/16/2025 have been fully considered but they are not persuasive.

Response to the arguments in regard to Porro has been mentioned above.

Additionally, Mekalanos column 11 teach a conjugate vaccine for a conjugate made between a PS and the carrier protein tetanus toxoid. In this model, only B-cells that display antibody receptors that recognize the PS bind the PS-protein conjugate. Mekalanos column 23 teach various carrier proteins of the invention include, e.g., toxins and toxoids diphtheria toxoid or CRM 197, tetanus toxin, tetanus toxoid.

Caulfield et al. teach an immunogenic composition comprising: a multivalent polysaccharide-protein conjugate mixture consisting of capsular polysaccharides from serotypes **1,** 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, **19F,** 22F, 23F, and 33F of *Streptococcus pneumoniae* conjugated to a carrier protein; and a pharmaceutically acceptable carrier and further comprise a carrier protein CRM197 and a adjuvant. (see claims and abstract).

Caulfield et al. page 5 recites "The present invention provides a multivalent immunogenic composition comprising, consisting essentially of, or alternatively, consisting of 15 distinct polysaccharide- protein conjugates, wherein each of the conjugates contains a different capsular polysaccharide conjugated to a carrier protein, and wherein the capsular polysaccharides are prepared from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F of S. *pneumoniae,* together with a pharmaceutically acceptable carrier. In certain embodiments, the carrier protein is CRM197. " Caulfield et al. teach composition comprising a plurality of at least two immunogenic polysaccharide-protein conjugates containing serotypes 22F and 33F provides robust antibody responses (see page 6).

The combination of references make the claims obvious.

Conclusion

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KHATOL S SHAHNAN SHAH whose telephone number is (571)272-0863. The examiner can normally be reached on Mon-Tue, Thurs-Fri 12pm-8pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Khatol S Shahnan-Shah/
Examiner, Art Unit 1645
June 25, 2025

/JANA A HINES/
Primary Examiner, Art Unit 1645

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/347,435	Forrest et al.
	Examiner	Art Unit
	KHATOL S SHAHNAN SHAH	1645

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
P2E2 all databases	06/25/2025	KSS
PDP inventor, biotech, continuity, priority	06/25/2025	KSS
Google scholar	06/25/2025	KSS
NPL	06/25/2025	KSS
Checked co pending applications	06/25/2025	KSS

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/KHATOL S SHAHNAN SHAH/ Examiner, Art Unit 1645	

Petitioner Merck Ex-1015, 1892

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L3938	48	forrest ADJ bruce	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/06/27 06:39 PM
L3939	22	L3938 AND saccharide-polypeptide	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/06/27 06:40 PM
L3940	22	L3939 AND conjugate	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/06/27 06:40 PM
L3941	15	L3940 AND immunogenic	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB,	OR	ON	ON	2025/06/27 06:41 PM

Petitioner Merck Ex-1015, 1893

			HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)				
L3942	15	L3941 AND capsular	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/06/27 06:41 PM
L3943	15	L3942 AND streptococcus	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/06/27 06:42 PM
L3944	10	L3943 AND pneumoniae	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/06/27 06:43 PM
L3945	10	L3944 AND serotype	(US-PGPUB; USPAT; USOCR; FIT (AU, AP,	OR	ON	ON	2025/06/27 06:43 PM

Petitioner Merck Ex-1015, 1894

			AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)				
L3946	150	love ADJ jack	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/06/27 06:45 PM
L3947	0	L3946 AND (streptococus ADJ pneumoniae)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/06/27 06:50 PM
L3948	9	L3946 AND (streptococcus ADJ pneumoniae)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO;	OR	ON	ON	2025/06/27 06:51 PM

Petitioner Merck Ex-1015, 1895

			JPO; DERWENT)				
L3949	15	L3946 AND saccharide-polypeptide	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/06/27 06:52 PM
L3950	8	L3949 AND immunogenic	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/06/27 06:52 PM
L3951	26	saccharide-polypeptide AND immunogenic	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/06/27 06:53 PM
L3952	26	L3951 AND streptococcus	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO,	OR	ON	ON	2025/06/27 06:54 PM

Petitioner Merck Ex-1015, 1896

			NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)				
L3953	26	L3952 AND conjugate	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/06/27 06:54 PM
L3954	26	L3953 AND composition	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/06/27 06:55 PM
L3955	26	L3954 AND serotype	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/06/27 06:55 PM
L3956	26	L3955 AND capsular	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB,	OR	ON	ON	2025/06/27 06:56 PM

Petitioner Merck Ex-1015, 1897

			HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)				
L3957	11	L3956 AND CRM	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/06/27 06:56 PM
L3958	11	L3957 AND tetanus	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/06/27 06:57 PM
L3959	10	L3958 AND toxoid	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/06/27 06:57 PM

There are no Interference searches to show.

Petitioner Merck Ex-1015, 1899

Conjugate of structurally reassigned pneumococcal serotype 31 polysaccharide with CRM197 elicited potent immune response

T Sun, S Mai, H Mao, H Li, Y Duan, S Meng, J Bao… - Carbohydrate …, 2022 - Elsevier

… The reaction is faster, and the DMF **conjugate** elicited comparable immune responses with the aqueous **conjugate**. S-31-ps **conjugate** vaccine has the potential of being included in the …

☆ Save 99 Cite Cited by 12 Related articles All 6 versions

Novel Polypeptide Automated Synthesis Devices: A Review

Z Chen, Z Zhou, M Zeng, Y Bao, Y Deng… - Journal of …, 2024 - ingentaconnect.com

Peptides are a unique class of proteins and one-dimensional biological nanomaterials that play an exceptionally important role in life science and industrial applications. At present, …

☆ Save 99 Cite Related articles »

Related searches

starch and saccharide-polypeptide conjugate

fiber and saccharide-polypeptide conjugate

ftir and saccharide-polypeptide conjugate

dextran and saccharide-polypeptide conjugate

food and saccharide-polypeptide conjugate

zein and saccharide-polypeptide conjugate

raffinose and saccharide-polypeptide conjugate

forrest and **glucose**-polypeptide conjugate

APPROVED: /K.S.S/

FORM PTO-1449/A and B (modified PTO/SB/08)				APPLICATION NO.: 17/347,435	ATTY. DOCKET NO.: P1143.70000US05
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				FILING DATE: June 14, 2021	CONFIRMATION NO.: 4020
				FIRST NAMED INVENTOR: Bruce D. Forrest	
Sheet	1	of	1	GROUP ART UNIT: 1645	EXAMINER: Khatol S. Shahnan Shah

U.S. PATENT DOCUMENTS

Examiner's Initials #	Cite No.	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication or Issue of Cited Document MM-DD-YYYY
		Number	Kind Code		

FOREIGN PATENT DOCUMENTS

Examiner's Initials #	Cite No.	Foreign Patent Document			Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Translation (Y/N)
		Office/ Country	Number	Kind Code			
/K.S.S/		WO	2018/064444	A1	Biological E Ltd.	04-05-2018	
/K.S.S/		WO	2019/070994	A1	Liffey Biotech Ltd.	04-11-2019	

OTHER ART – NON PATENT LITERATURE DOCUMENTS

Examiner's Initials #	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	Translation (Y/N)
/K.S.S/		Extended European Search Report, mailed March 5, 2025, in connection with Application No. EP 24193141.9 (P1143.70000EP01).	

[NOTE – No copies of U.S. patents, published U.S. patent applications, or pending, unpublished patent applications stored in the USPTO's Image File Wrapper (IFW) system, are included. See 37 CFR § 1.98 and 1287 OG 163. Copies of all other patent(s), publication(s), unpublished, pending U.S. patent applications, or other information listed are provided as required by 37 CFR § 1.98 unless 1) such copies were provided in an IDS in an earlier application that complies with 37 CFR § 1.98, and 2) the earlier application is relied upon for an earlier filing date under 35 U.S.C. § 120.]

05/20/2025

EXAMINER:	DATE CONSIDERED:
/KHATOL S SHAHNAN SHAH/	05/20/2025

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

Docket No.: P1143.70000US05
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Bruce D. Forrest
Application No.:	17/347,435
Confirmation No.:	4020
Filed:	June 14, 2021
For:	SACCHARIDE-POLYPEPTIDE CONJUGATE COMPOSITIONS AND METHODS OF USE THEREOF
Examiner:	Khatol S. Shahnan Shah
Art Unit:	1645

Certificate of Electronic Filing under 37 C.F.R. § 1.8
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: October 2, 2025 Signature: /Emma Dereberry/ (Emma Dereberry)

RESPONSE TO OFFICE ACTION UNDER 37 C.F.R. § 1.111

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

In response to the Office Action dated July 2, 2025, Applicant respectfully requests entrance of the following Amendment and consideration of the following Remarks. The deadline for responding to the Office Action is October 2, 2025. Applicant thus submits that the present Response is timely submitted on Thursday, October 2, 2025.

Please amend the above-identified Application as follows:

Amendments to the Claims are reflected in the Listing of Claims, which begins on page 2 of this Response.

Remarks begin on page 7 of this response.

AMENDMENTS TO THE CLAIMS

This Listing of Claims will replace all prior versions, and listings, of claims in the Application:

Listing of Claims

1-295. (Canceled)

296. (Currently Amended) A pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates, each immunogenic saccharide-polypeptide conjugate ~~comprising individually~~ consisting of a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31, and at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38, wherein the at least one additional serotype is not the first serotype; and wherein the fragment of the capsular polysaccharide is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, a hexasaccharide, or an oligosaccharide.

297. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 31.

298. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 24F.

299. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 20A.

Petitioner Merck Ex-1015, 1903

300. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 16F.

301. (Currently Amended) The pharmaceutical composition of claim 296, wherein the polypeptide comprises cross-reacting material 197 (CRM_{197})~~a mixture of polypeptides~~.

302. (Currently Amended) The pharmaceutical composition of claim 296, wherein the polypeptide comprises ~~cross-reacting material 197 (CRM_{197}),~~ tetanus toxoid, a diphtheria toxoid, cholera toxoid, pertussis toxoid, inactivated or mutant pneumococcal pneumolysin, pneumococcal surface protein A, pneumococcal adhesion protein A, pneumococcal lipoprotein PsaA, C5a peptidase group A or group B *Streptococcus*, a non-typable *H. influenzae* P4 protein, a non-typable *H. influenzae* P6 protein, *M. catarrhalis* uspA, keyhole limpet haemocyanin (KLH), outer membrane protein complex (OMPC) from *N. meningitidis*, a purified protein derivative of tuberculin(PPD), protein D from *H. influenzae*, PspA, any fragment thereof, or any combination thereof.

303. (Previously Presented) The pharmaceutical composition of claim 296, further comprising an adjuvant; a chelating agent; a surfactant; an emulsifier; a buffering agent; a preservative; a salt; an anti-fungal compound; or a combination thereof.

304. (Previously Presented) The pharmaceutical composition of claim 296, wherein the pharmaceutical composition is in the form of an intramuscularly injectable composition, intradermally injectable composition, subcutaneously injectable composition, or an intranasally administrable composition.

305. (Previously Presented) The pharmaceutical composition of claim 296, wherein at least one of the immunogenic saccharide-polypeptide conjugates elicits an opsonophagocytic response.

306. (Canceled)

Petitioner Merck Ex-1015, 1904

307. (Previously Presented) The pharmaceutical composition of claim 296, wherein the immunogenic saccharide-polypeptide conjugates comprise: (i) the capsular polysaccharide at least partially embedded in the polypeptide, (ii) the capsular polysaccharide chemically cross-linked to the polypeptide, and/or (iii) the capsular polysaccharide at least partially chemically cross-linked to the polypeptide.

308. (Previously Presented) The pharmaceutical composition of claim 296, wherein a toxin activity of the polypeptide is at least partly mitigated.

309. (Previously Presented) The pharmaceutical composition of claim 296, wherein each of the immunogenic saccharide-polypeptide conjugates is present in an amount of at least 0.001%, by weight, based on the weight of the pharmaceutical composition.

310. (Withdrawn) A method comprising administering to a subject the pharmaceutical composition of claim 296.

311.-315. (Cancelled)

316. (Currently Amended) The pharmaceutical composition of claim 296, wherein the first serotype comprises 16F, and the at least one additional serotype comprises 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, and 15A.

317. (Currently Amended) The pharmaceutical composition of claim 296, wherein the first serotype comprises 20A, and the at least one additional serotype comprises 7F, 8, 9N, 15A, 15C, 16F, 19A, 22F, 23A, and 23B.

Petitioner Merck Ex-1015, 1905

318. (Currently Amended) The pharmaceutical composition of claim 296, wherein the first serotype comprises 23B, and the at least one additional serotype comprises 16F, 20A, 22F, 23A, 24F, 31, 33F, and 35B.

319. (Currently Amended) The pharmaceutical composition of claim 296, wherein the first serotype comprises 24F, and the at least one additional serotype comprises 3, 7F, 8, 9N, 10A, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, and 31.

320. (Currently Amended) The pharmaceutical composition of claim 296, wherein the first serotype comprises 16F, and the at least one additional serotype comprises 3, 7F, 8, 9N, 10A, 12F, 15A, 15C, 17F, 20A, 22F, 23A, 23B, 31, 33F, and 35B.

321. (Currently Amended) The pharmaceutical composition of claim 296, wherein the first serotype comprises 24F, and the at least one additional serotype comprises 3, 6A, 7F, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 19A, 20A, 22F, 23B, 31, and 35B.

322. (Currently Amended) The pharmaceutical composition of claim 296, wherein the first serotype comprises 31, and the at least one additional serotype comprises 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 22F, 33F, and 35B.

323. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 20B.

324. (Previously Presented) The pharmaceutical composition of claim 323, wherein the at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 16F, 17F, 18C, 19A, 19F, 22F, 23A, 23B, 23F, 31, 33F, and 35B.

Petitioner Merck Ex-1015, 1906

325. (Previously Presented) The pharmaceutical composition of claim 298, wherein the at least one additional serotype comprises 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 23F, 31, 33F, and 35B.

326. (Currently Amended) The pharmaceutical composition of claim 296, wherein the first serotype is 16F, and the at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 17F, 18C, 19A, 19F, 20B, 22F, 23A, 23B, 23F, 31, 33F, and 35B.

327. (Currently Amended) The pharmaceutical composition of claim 296, wherein the first serotype is 16F, and the at least one additional serotype comprises 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 17F, 19A, 20A, 22F, 23A, 23B, 23F, 24F, 31, 33F, and 35B.

Petitioner Merck Ex-1015, 1907

REMARKS

Claims 296-310 and 316-327 are pending in the Application before entrance of the present Amendment, of which claim 310 is withdrawn from consideration by the Examiner at this time. By the present Amendment, claims 296, 301, 302, 316-322, 326, and 327 are amended and claim 306 is cancelled. Applicant reserves the right to pursue the subject matter canceled from the claims in one or more future continuing applications claiming priority to the present Application. Support for the amendments to claim 296 can be found throughout the originally filed Application, *e.g.*, paragraph [0042]. Claim 301 is amended to incorporate subject matter from claim 302 and claim 302 is amended to remove the subject matter in amended claim 301. Claims 316-322, 326, and 327 are amended to correct minor grammatical errors. After entrance of the present Amendment, claims 296-305, 307-310, and 316-327 will be pending in the Application, with claim 310 being withdrawn from consideration by the Examiner. Applicant submits that no new matter is added to the Application by this Amendment.

Amendment or cancellation of the claims during prosecution of this Application is not to be construed as acquiescence to any of the objections or rejections set forth in the Office Action and was done solely to expedite prosecution of the Application. Applicant reserves the right to pursue the claims as originally filed or similar claims in this particular Application or one or more continuing patent applications claiming priority to this Application.

Each of the rejections levied by the Examiner is addressed in turn below.

Claim Rejections under 35 U.S.C. § 102

The Examiner rejected claims 296, 298, 299, and 301-309 under 35 U.S.C. § 102 as allegedly being anticipated by Porro (WO 2014/118201). The Examiner states “it is the examiner’s position that Porro teach immune saccharide-polypeptide conjugates of the claims” (p. 6). Applicant respectfully disagrees.

However, without conceding the correctness of the Examiner’s position and solely in the interest of advancing prosecution, the claims have been amended and are directed to a pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates, *each immunogenic saccharide-polypeptide conjugate consisting of* a

Petitioner Merck Ex-1015, 1908

capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31, and at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38, wherein the at least one additional serotype is not the first serotype; and wherein the fragment of the capsular polysaccharide is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, a hexasaccharide, or an oligosaccharide.

According to MPEP 2131, not only does an anticipatory reference have to teach each and every element as set forth in the claim, but it also has to teach the arrangement or combination of the elements as required by the claim. Porro does not do teach or suggest the immune saccharide-polypeptide conjugates of the claims. In particular, Porro, which is titled "**Multivalent** Glycoconjugate Vaccines," does not disclose a composition comprising **individual** immunogenic saccharide-polypeptide conjugates, **each** consisting of a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide.

Instead, Porro relates to **multivalent** molecular constructs comprising **at least three** carbohydrate structures (*e.g.*, capsular polysaccharides) all bound to a helper-T dependent carrier protein (*see, e.g.*, Abstract and claim 1 of Porro). Porro specifically explains that the **multivalent** construct structure is beneficial to address carrier protein-dependent immune-suppression and immune interference, noting that the "vaccine formulation encompassing as many as eighteen type-specific conjugate antigens, as an example, will be synthesized by only using one third (or 33%) of the amount of carrier protein needed in the nowadays available single-antigen-associated formulation, so that the immunogenic burden on the immune-system of the host will be significantly lower and, consequently, safer" (Porro, p. 4). Porro also indicates that the "new generation of conjugate antigens expressing multiple specificities or obtaining vaccines with an always broader spectrum of protection against a variety of bacterial pathogens while drastically reducing the amount of carrier protein" will improve "the cost of production of the vaccines, … production efficiency, … production accuracy, … safety, … [and] the public utility of such conjugate vaccines" (Porro, pages 9-10; emphasis added). Therefore, Porro does not describe the individual

Petitioner Merck Ex-1015, 1909

immunogenic saccharide-polypeptide conjugates as claimed, but rather multivalent structures, where multiple antigens are conjugated to a single carrier protein.

The Examiner points to pages 3-11 and claims 4, 7, 8, 18, and 26 of Porro, which purportedly describe the individual saccharide-polypeptide conjugates of the present claims; however, none of the cited passages describe the pharmaceutical compositions of the pending claims. Instead, the cited passages describe prior art vaccines and how Porro's multivalent vaccine, multiple antigens are conjugated to a single carrier protein, is superior to existing vaccines because the multivalent vaccine requires less carrier protein:

- Page 3 describes "the possibility to reduce the amount of the carrier protein in the whole conjugate formulations is becoming a prioritary issue," and that children undergoing existing vaccine protocols for the prevention of broad-spectrum invasive pneumococcal disease will be "injected with eighteen conjugated antigens which have the relevant burden of eighteen times the single-type-specific, dose of carrier protein;"
- Page 4 distinguishes Porro's "present invention" from existing vaccines, noting that Porro's multivalent vaccines feature "a new category of conjugate antigens which feature the expression of multiple carbohydrate specificities, pre-determined and built-in the molecular construct, which uses one mole (or micromole or nanomole or picomole, all representative for a fraction of it) of protein carrier for carrying at least one mole (or micromole or nanomole or picomole, all representative for a fraction of it) of each of at least three different type (or group)-specific carbohydrate antigens" and indicates the proposed benefit of the multivalent vaccine as "a vaccine formulation encompassing as many as eighteen type-specific conjugate antigens, as an example, will be synthesized by only using one third (or 33%) of the amount of carrier protein needed in the nowadays available single-antigen-associated formulation, so that the immunogenic burden on the immune-system of the host will be significantly lower and, consequently, safer;"

Petitioner Merck Ex-1015, 1910

- Page 5 describes the phenomenon of "carrier protein-dependent immune-suppression and immune interference" which occurs when "the immune system … becomes overwhelmed by the amount of protein antigen administered in repeated doses, for instance as a conjugate entity, especially when significant serological titers of pre-existing, carrier protein-specific, memory IgG antibodies, are present in the treated host" and notes that Porro's multivalent vaccines address this issue: "[t]he significant reduction of the protein carrier dosage by the present molecular model, however, warrants the full expression of helper T-dependency, according to the previous experimental work;"
- Page 6 describes prior art patents, one directed to a molecular model of tri-valent glycoprotein that "induced serological specificity to the carrier protein and to each of the two carried carbohydrate structures" and the second directed to "oligosaccharide conjugate vaccines and an improved method for producing said oligosaccharide-based conjugate vaccines;"
- Page 7 describes a prior art patent application disclosing "a new method of producing HMW poly-disperse, cross-linked, polysaccharide-based conjugate antigens in high yield," and journal articles describing "the activation chemistry of a meningococcal group B oligosaccharide" and the "activation chemistry of a pneumococcal type 6A oligosaccharide;"
- Page 8 references a further article, in which the authors describe "a two-steps conjugation process to the same carrier protein, CRM197, of two capsular oligosaccharides;"
- Page 9 references an additional paper in which the authors describe "conjugate antigens composed of protein carrier and a maximum of two different carbohydrate structure" which differs from Porro's multivalent vaccine that "is composed by a multivalent, preferably a tetra-valent semi-synthetic glycoprotein which features built-in multiple epitopes and expresses its helper T-dependent immunogenic specificity '*in vivo*' to the protein CRM197 as well as to three carried type-specific Ps, for example Ps of *S. pneumoniae*;"

Petitioner Merck Ex-1015, 1911

- Page 10 describes the multivalent vaccine as a "semi-synthetic tetravalent antigen can be considered as the novel new precursor of a new generation of conjugate antigens expressing multiple specificities for obtaining vaccines with an always broader spectrum of protection … while drastically reducing the amount of carrier protein" and describes benefits of the multivalent vaccine including its cost, production efficiency, production accuracy, and safety; and
- Page 11 describes additional benefits of the multivalent vaccines, noting that the "built-in multiple antigenicity of the disclosed molecular construct, specific for different bacterial antigens, actually parallels, in the innovative field of poly-pharmacology, the synthesis of a drug designed a priori for simultaneously reaching multiple receptors of pharmacological relevance, so allowing the reduction of the number of drugs to be administered in associated form."

The Examiner also cites claims 4, 7, 8, 18, and 26 in support of its assertion that the present claims are anticipated by Porro. Applicant respectfully notes that each of the claims is directly or indirectly related to a "multivalent molecular construct consisting of a basic unit comprising a helper-T dependent carrier protein covalently bound to a minimum of three carbohydrate structures of different serological specificity" and not a composition comprising individual immunogenic saccharide-polypeptide conjugates, each comprising a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide, as claimed.

Therefore, as Porro does not describe a composition comprising individual immunogenic saccharide-polypeptide conjugates, each comprising a capsular polysaccharide, fragment thereof, the reference does not anticipate the claims. Applicant respectfully requests that this rejection be withdrawn.

Claim Rejections under 35 U.S.C. § 103

The Examiner rejected claims 296-309 and 316-322 under 35 U.S.C. § 103 as allegedly being obvious over Caufield *et al.* (WO 2011/100151; hereinafter "Caufield") in view of Porro, Mekalanos (US 9,533,032), and further in view of del Amo *et al.*, "High invasiveness of

Petitioner Merck Ex-1015, 1912

pneumococcal serotypes included in the new generation of conjugate vaccines." *Clin. Microbiol. Infect.* 2013, 20(7):684-9 (hereinafter "del Amo"). Applicant respectfully disagrees.

As noted above, the claims have been amended and are directed to a pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates, each immunogenic saccharide-polypeptide conjugate consisting of a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31, and at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38, wherein the at least one additional serotype is not the first serotype; and wherein the fragment of the capsular polysaccharide is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, a hexasaccharide, or an oligosaccharide.

None of the cited references, alone or in combination, teach the composition of the amended claims. Caufield, cited for its purported disclosure of a multivalent polysaccharide-protein conjugate mixture consisting of capsular polysaccharides from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F of *Streptococcus pneumoniae* conjugated to a carrier protein (*e.g.*, CRM197), does not describe the combination of serotypes recited in claim 296, nor does it remedy the deficiencies of Porro discussed above. Mekalanos, cited for its purported disclosure of serotypes 16F, 19A, 23B, 24F, and 31, describes vaccine compositions comprising an antigen entrapped within a cross-linked carrier protein matrix, and does not remedy the deficiencies of Porro and Caufield. Similarly, the Examiner cited del Amo for its purported disclosure of numerous serotypes (*e.g.*, 1, 2, 3, 4, 5, 6A/6B, 6C, 7C/(7B/40), 7F/7A, 8, 9N/9L, 9V/9A, 10A, 10F/(10C/33C), 11A/11D, 12F/(12A/44/46), 13, 14, 15A/15F, 15B/15C, 16F, 17F, 18/(18A/18B/18C/18F), 19A, 19F, 20, 21, 22F/22A, 23A, 23B, 23F, 24/(24A/24B/24F), 31, 33F/(33A/37), 34, 35A/(35C/42), 35B, 35F/47F, 38/25F, and 39); however, the list of serotypes in del Amo includes those that may be detected using an *in vitro* assay, not for conjugation, let alone for inclusion in a composition comprising immunogenic saccharide-polypeptide conjugates as claimed. Moreover, using the assays described in del Amo, the authors found that serotypes 1, 3, 5, 7F, and 19A are the most invasive

Petitioner Merck Ex-1015, 1913

serotypes and serotypes 6A, 6C, 19A, 19F, and 23B are the most common serotypes in carriage (Abstract). The most common serotypes, 1, 3, 5, 6A, 6C, 7F, 19A, 19F, and 23B, are not those required by the claim. In addition, del Amo suggests that the other serotypes should not be included in a vaccine, concluding that "all serotypes with high attack rate are included in PCV13 and that the remaining serotypes circulating in our regions have a low invasive disease potential" (p. 687).

Therefore, as none of the cited references, alone or in combination, teaches or suggests the claimed composition comprising immunogenic saccharide-polypeptide conjugates, withdrawal of the rejection is respectfully requested.

General Comments on Dependent Claims

Each of the dependent claims depends from a base claim that is believed to be in condition for allowance, and Applicant therefore believes that it is unnecessary at this time to argue the allowability of each of the dependent claims individually. Applicant does not, however, necessarily concur with the interpretation of the dependent claims as set forth in the Office Action, nor does Applicant concur that the basis for the rejection of any of the dependent claims is proper. Therefore, Applicant reserves the right to specifically address the patentability of the dependent claims in the future.

Petitioner Merck Ex-1015, 1914

In view of the foregoing, this Application should now be in condition for allowance. A notice to that effect is respectfully requested. If the Examiner believes, after this Response, the Application is not in condition for allowance, the Examiner is requested to call the undersigned at the telephone number indicated below to discuss any outstanding issues.

If this Response is not considered timely filed, and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time.

Applicant believes all fees due with this Response are being paid by credit card. However, if any additional fees are due, please charge them, or credit any overpayment, to our Deposit Account No. 23/2825, under Docket No. P1143.70000US05, from which the undersigned is authorized to draw.

Dated: October 2, 2025

Respectfully submitted,

Electronic signature: /Jessica A. von Reyn/
Jessica A. von Reyn
Registration Number: 76,839
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

Petitioner Merck Ex-1015, 1915

Doc Code: TRAN.LET
Document Description: Transmittal Letter

USED IN LIEU OF PTO/SB/21 (07-09)

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	

Application Number	17/347,435-Conf. #4020
Filing Date	June 14, 2021
First Named Inventor	Bruce D. Forrest
Art Unit	1645
Examiner Name	Khatol S. Shahnan Shah
Attorney Docket Number	P1143.70000US05

ENCLOSURES (*Check all that apply*)

- [ ] Fee Transmittal Form
  - [ ] Fee Attached
- [x] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) (please Identify below):

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	WOLF, GREENFIELD & SACKS, P.C.		
Signature	/Jessica A. von Reyn/		
Printed name	Jessica A. von Reyn		
Date	October 2, 2025	Reg. No.	76,839

Certificate of Electronic Filing under 37 C.F.R. § 1.8

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: October 2, 2025 Signature: /Emma Dereberry/ (Emma Dereberry)

14461378

Docket No.: P1143.70000US05
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Bruce D. Forrest
Application No.:	17/347,435
Confirmation No.:	4020
Filed:	June 14, 2021
For:	SACCHARIDE-POLYPEPTIDE CONJUGATE COMPOSITIONS AND METHODS OF USE THEREOF
Examiner:	Khatol S. Shahnan Shah
Art Unit:	1645

Certificate of Electronic Filing under 37 C.F.R. § 1.8
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: October 2, 2025 Signature: /Emma Dereberry/ (Emma Dereberry)

RESPONSE TO OFFICE ACTION UNDER 37 C.F.R. § 1.111

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

In response to the Office Action dated July 2, 2025, Applicant respectfully requests entrance of the following Amendment and consideration of the following Remarks. The deadline for responding to the Office Action is October 2, 2025. Applicant thus submits that the present Response is timely submitted on Thursday, October 2, 2025.

Please amend the above-identified Application as follows:

Amendments to the Claims are reflected in the Listing of Claims, which begins on page 2 of this Response.

Remarks begin on page 7 of this response.

AMENDMENTS TO THE CLAIMS

This Listing of Claims will replace all prior versions, and listings, of claims in the Application:

Listing of Claims

1-295. (Canceled)

296. (Currently Amended) A pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates, each immunogenic saccharide-polypeptide conjugate ~~comprising individually~~ consisting of a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31, and at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38, wherein the at least one additional serotype is not the first serotype; and wherein the fragment of the capsular polysaccharide is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, a hexasaccharide, or an oligosaccharide.

297. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 31.

298. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 24F.

299. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 20A.

Petitioner Merck Ex-1015, 1918

300. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 16F.

301. (Currently Amended) The pharmaceutical composition of claim 296, wherein the polypeptide comprises cross-reacting material 197 (CRM_{197})~~a mixture of polypeptides~~.

302. (Currently Amended) The pharmaceutical composition of claim 296, wherein the polypeptide comprises ~~cross-reacting material 197 (CRM_{197}),~~ tetanus toxoid, a diphtheria toxoid, cholera toxoid, pertussis toxoid, inactivated or mutant pneumococcal pneumolysin, pneumococcal surface protein A, pneumococcal adhesion protein A, pneumococcal lipoprotein PsaA, C5a peptidase group A or group B *Streptococcus*, a non-typable *H. influenzae* P4 protein, a non-typable *H. influenzae* P6 protein, *M. catarrhalis* uspA, keyhole limpet haemocyanin (KLH), outer membrane protein complex (OMPC) from *N. meningitidis*, a purified protein derivative of tuberculin(PPD), protein D from *H. influenzae*, PspA, any fragment thereof, or any combination thereof.

303. (Previously Presented) The pharmaceutical composition of claim 296, further comprising an adjuvant; a chelating agent; a surfactant; an emulsifier; a buffering agent; a preservative; a salt; an anti-fungal compound; or a combination thereof.

304. (Previously Presented) The pharmaceutical composition of claim 296, wherein the pharmaceutical composition is in the form of an intramuscularly injectable composition, intradermally injectable composition, subcutaneously injectable composition, or an intranasally administrable composition.

305. (Previously Presented) The pharmaceutical composition of claim 296, wherein at least one of the immunogenic saccharide-polypeptide conjugates elicits an opsonophagocytic response.

306. (Canceled)

Petitioner Merck Ex-1015, 1919

307. (Previously Presented) The pharmaceutical composition of claim 296, wherein the immunogenic saccharide-polypeptide conjugates comprise: (i) the capsular polysaccharide at least partially embedded in the polypeptide, (ii) the capsular polysaccharide chemically cross-linked to the polypeptide, and/or (iii) the capsular polysaccharide at least partially chemically cross-linked to the polypeptide.

308. (Previously Presented) The pharmaceutical composition of claim 296, wherein a toxin activity of the polypeptide is at least partly mitigated.

309. (Previously Presented) The pharmaceutical composition of claim 296, wherein each of the immunogenic saccharide-polypeptide conjugates is present in an amount of at least 0.001%, by weight, based on the weight of the pharmaceutical composition.

310. (Withdrawn) A method comprising administering to a subject the pharmaceutical composition of claim 296.

311.-315. (Cancelled)

316. (Currently Amended) The pharmaceutical composition of claim 296, wherein the first serotype comprises 16F, and the at least one additional serotype comprises 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, and 15A.

317. (Currently Amended) The pharmaceutical composition of claim 296, wherein the first serotype comprises 20A, and the at least one additional serotype comprises 7F, 8, 9N, 15A, 15C, 16F, 19A, 22F, 23A, and 23B.

Petitioner Merck Ex-1015, 1920

318. (Currently Amended) The pharmaceutical composition of claim 296, wherein the first serotype comprises 23B, and the at least one additional serotype comprises 16F, 20A, 22F, 23A, 24F, 31, 33F, and 35B.

319. (Currently Amended) The pharmaceutical composition of claim 296, wherein the first serotype comprises 24F, and the at least one additional serotype comprises 3, 7F, 8, 9N, 10A, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, and 31.

320. (Currently Amended) The pharmaceutical composition of claim 296, wherein the first serotype comprises 16F, and the at least one additional serotype comprises 3, 7F, 8, 9N, 10A, 12F, 15A, 15C, 17F, 20A, 22F, 23A, 23B, 31, 33F, and 35B.

321. (Currently Amended) The pharmaceutical composition of claim 296, wherein the first serotype comprises 24F, and the at least one additional serotype comprises 3, 6A, 7F, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 19A, 20A, 22F, 23B, 31, and 35B.

322. (Currently Amended) The pharmaceutical composition of claim 296, wherein the first serotype comprises 31, and the at least one additional serotype comprises 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 22F, 33F, and 35B.

323. (Previously Presented) The pharmaceutical composition of claim 296, wherein the first serotype is 20B.

324. (Previously Presented) The pharmaceutical composition of claim 323, wherein the at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 16F, 17F, 18C, 19A, 19F, 22F, 23A, 23B, 23F, 31, 33F, and 35B.

Petitioner Merck Ex-1015, 1921

325. (Previously Presented) The pharmaceutical composition of claim 298, wherein the at least one additional serotype comprises 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 23F, 31, 33F, and 35B.

326. (Currently Amended) The pharmaceutical composition of claim 296, wherein the first serotype is 16F, and the at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 17F, 18C, 19A, 19F, 20B, 22F, 23A, 23B, 23F, 31, 33F, and 35B.

327. (Currently Amended) The pharmaceutical composition of claim 296, wherein the first serotype is 16F, and the at least one additional serotype comprises 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 17F, 19A, 20A, 22F, 23A, 23B, 23F, 24F, 31, 33F, and 35B.

Petitioner Merck Ex-1015, 1922

REMARKS

Claims 296-310 and 316-327 are pending in the Application before entrance of the present Amendment, of which claim 310 is withdrawn from consideration by the Examiner at this time. By the present Amendment, claims 296, 301, 302, 316-322, 326, and 327 are amended and claim 306 is cancelled. Applicant reserves the right to pursue the subject matter canceled from the claims in one or more future continuing applications claiming priority to the present Application. Support for the amendments to claim 296 can be found throughout the originally filed Application, *e.g.*, paragraph [0042]. Claim 301 is amended to incorporate subject matter from claim 302 and claim 302 is amended to remove the subject matter in amended claim 301. Claims 316-322, 326, and 327 are amended to correct minor grammatical errors. After entrance of the present Amendment, claims 296-305, 307-310, and 316-327 will be pending in the Application, with claim 310 being withdrawn from consideration by the Examiner. Applicant submits that no new matter is added to the Application by this Amendment.

Amendment or cancellation of the claims during prosecution of this Application is not to be construed as acquiescence to any of the objections or rejections set forth in the Office Action and was done solely to expedite prosecution of the Application. Applicant reserves the right to pursue the claims as originally filed or similar claims in this particular Application or one or more continuing patent applications claiming priority to this Application.

Each of the rejections levied by the Examiner is addressed in turn below.

Claim Rejections under 35 U.S.C. § 102

The Examiner rejected claims 296, 298, 299, and 301-309 under 35 U.S.C. § 102 as allegedly being anticipated by Porro (WO 2014/118201). The Examiner states "it is the examiner's position that Porro teach immune saccharide-polypeptide conjugates of the claims" (p. 6). Applicant respectfully disagrees.

However, without conceding the correctness of the Examiner's position and solely in the interest of advancing prosecution, the claims have been amended and are directed to a pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates, *each immunogenic saccharide-polypeptide conjugate consisting of* a

Petitioner Merck Ex-1015, 1923

capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31, and at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38, wherein the at least one additional serotype is not the first serotype; and wherein the fragment of the capsular polysaccharide is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, a hexasaccharide, or an oligosaccharide.

According to MPEP 2131, not only does an anticipatory reference have to teach each and every element as set forth in the claim, but it also has to teach the arrangement or combination of the elements as required by the claim. Porro does not do teach or suggest the immune saccharide-polypeptide conjugates of the claims. In particular, Porro, which is titled "**Multivalent** Glycoconjugate Vaccines," does not disclose a composition comprising **individual** immunogenic saccharide-polypeptide conjugates, **each** consisting of a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide.

Instead, Porro relates to **multivalent** molecular constructs comprising **at least three** carbohydrate structures (*e.g.*, capsular polysaccharides) all bound to a helper-T dependent carrier protein (*see, e.g.*, Abstract and claim 1 of Porro). Porro specifically explains that the **multivalent** construct structure is beneficial to address carrier protein-dependent immune-suppression and immune interference, noting that the "vaccine formulation encompassing as many as eighteen type-specific conjugate antigens, as an example, will be synthesized by only using one third (or 33%) of the amount of carrier protein needed in the nowadays available single-antigen-associated formulation, so that the immunogenic burden on the immune-system of the host will be significantly lower and, consequently, safer" (Porro, p. 4). Porro also indicates that the "new generation of conjugate antigens expressing multiple specificities or obtaining vaccines with an always broader spectrum of protection against a variety of bacterial pathogens while drastically reducing the amount of carrier protein" will improve "the cost of production of the vaccines, … production efficiency, … production accuracy, … safety, … [and] the public utility of such conjugate vaccines" (Porro, pages 9-10; emphasis added). Therefore, Porro does not describe the individual

Petitioner Merck Ex-1015, 1924

immunogenic saccharide-polypeptide conjugates as claimed, but rather multivalent structures, where multiple antigens are conjugated to a single carrier protein.

The Examiner points to pages 3-11 and claims 4, 7, 8, 18, and 26 of Porro, which purportedly describe the individual saccharide-polypeptide conjugates of the present claims; however, none of the cited passages describe the pharmaceutical compositions of the pending claims. Instead, the cited passages describe prior art vaccines and how Porro's multivalent vaccine, multiple antigens are conjugated to a single carrier protein, is superior to existing vaccines because the multivalent vaccine requires less carrier protein:

- Page 3 describes "the possibility to reduce the amount of the carrier protein in the whole conjugate formulations is becoming a prioritary issue," and that children undergoing existing vaccine protocols for the prevention of broad-spectrum invasive pneumococcal disease will be "injected with eighteen conjugated antigens which have the relevant burden of eighteen times the single-type-specific, dose of carrier protein;"
- Page 4 distinguishes Porro's "present invention" from existing vaccines, noting that Porro's multivalent vaccines feature "a new category of conjugate antigens which feature the expression of multiple carbohydrate specificities, pre-determined and built-in the molecular construct, which uses one mole (or micromole or nanomole or picomole, all representative for a fraction of it) of protein carrier for carrying at least one mole (or micromole or nanomole or picomole, all representative for a fraction of it) of each of at least three different type (or group)-specific carbohydrate antigens" and indicates the proposed benefit of the multivalent vaccine as "a vaccine formulation encompassing as many as eighteen type-specific conjugate antigens, as an example, will be synthesized by only using one third (or 33%) of the amount of carrier protein needed in the nowadays available single-antigen-associated formulation, so that the immunogenic burden on the immune-system of the host will be significantly lower and, consequently, safer;"

Petitioner Merck Ex-1015, 1925

- Page 5 describes the phenomenon of "carrier protein-dependent immune-suppression and immune interference" which occurs when "the immune system … becomes overwhelmed by the amount of protein antigen administered in repeated doses, for instance as a conjugate entity, especially when significant serological titers of pre-existing, carrier protein-specific, memory IgG antibodies, are present in the treated host" and notes that Porro's multivalent vaccines address this issue: "[t]he significant reduction of the protein carrier dosage by the present molecular model, however, warrants the full expression of helper T-dependency, according to the previous experimental work;"
- Page 6 describes prior art patents, one directed to a molecular model of tri-valent glycoprotein that "induced serological specificity to the carrier protein and to each of the two carried carbohydrate structures" and the second directed to "oligosaccharide conjugate vaccines and an improved method for producing said oligosaccharide-based conjugate vaccines;"
- Page 7 describes a prior art patent application disclosing "a new method of producing HMW poly-disperse, cross-linked, polysaccharide-based conjugate antigens in high yield," and journal articles describing "the activation chemistry of a meningococcal group B oligosaccharide" and the "activation chemistry of a pneumococcal type 6A oligosaccharide;"
- Page 8 references a further article, in which the authors describe "a two-steps conjugation process to the same carrier protein, CRM197, of two capsular oligosaccharides;"
- Page 9 references an additional paper in which the authors describe "conjugate antigens composed of protein carrier and a maximum of two different carbohydrate structure" which differs from Porro's multivalent vaccine that "is composed by a multivalent, preferably a tetra-valent semi-synthetic glycoprotein which features built-in multiple epitopes and expresses its helper T-dependent immunogenic specificity '*in vivo*' to the protein CRM197 as well as to three carried type-specific Ps, for example Ps of *S. pneumoniae*;"

Petitioner Merck Ex-1015, 1926

- Page 10 describes the multivalent vaccine as a "semi-synthetic tetravalent antigen can be considered as the novel new precursor of a new generation of conjugate antigens expressing multiple specificities for obtaining vaccines with an always broader spectrum of protection … while drastically reducing the amount of carrier protein" and describes benefits of the multivalent vaccine including its cost, production efficiency, production accuracy, and safety; and
- Page 11 describes additional benefits of the multivalent vaccines, noting that the "built-in multiple antigenicity of the disclosed molecular construct, specific for different bacterial antigens, actually parallels, in the innovative field of poly-pharmacology, the synthesis of a drug designed a priori for simultaneously reaching multiple receptors of pharmacological relevance, so allowing the reduction of the number of drugs to be administered in associated form."

The Examiner also cites claims 4, 7, 8, 18, and 26 in support of its assertion that the present claims are anticipated by Porro. Applicant respectfully notes that each of the claims is directly or indirectly related to a "multivalent molecular construct consisting of a basic unit comprising a helper-T dependent carrier protein covalently bound to a minimum of three carbohydrate structures of different serological specificity" and not a composition comprising individual immunogenic saccharide-polypeptide conjugates, each comprising a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide, as claimed.

Therefore, as Porro does not describe a composition comprising individual immunogenic saccharide-polypeptide conjugates, each comprising a capsular polysaccharide, fragment thereof, the reference does not anticipate the claims. Applicant respectfully requests that this rejection be withdrawn.

Claim Rejections under 35 U.S.C. § 103

The Examiner rejected claims 296-309 and 316-322 under 35 U.S.C. § 103 as allegedly being obvious over Caufield *et al.* (WO 2011/100151; hereinafter "Caufield") in view of Porro, Mekalanos (US 9,533,032), and further in view of del Amo *et al.*, "High invasiveness of

Petitioner Merck Ex-1015, 1927

pneumococcal serotypes included in the new generation of conjugate vaccines." *Clin. Microbiol. Infect.* 2013, 20(7):684-9 (hereinafter "del Amo"). Applicant respectfully disagrees.

As noted above, the claims have been amended and are directed to a pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates, each immunogenic saccharide-polypeptide conjugate consisting of a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31, and at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38, wherein the at least one additional serotype is not the first serotype; and wherein the fragment of the capsular polysaccharide is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, a hexasaccharide, or an oligosaccharide.

None of the cited references, alone or in combination, teach the composition of the amended claims. Caufield, cited for its purported disclosure of a multivalent polysaccharide-protein conjugate mixture consisting of capsular polysaccharides from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F of *Streptococcus pneumoniae* conjugated to a carrier protein (*e.g.*, CRM197), does not describe the combination of serotypes recited in claim 296, nor does it remedy the deficiencies of Porro discussed above. Mekalanos, cited for its purported disclosure of serotypes 16F, 19A, 23B, 24F, and 31, describes vaccine compositions comprising an antigen entrapped within a cross-linked carrier protein matrix, and does not remedy the deficiencies of Porro and Caufield. Similarly, the Examiner cited del Amo for its purported disclosure of numerous serotypes (*e.g.*, 1, 2, 3, 4, 5, 6A/6B, 6C, 7C/(7B/40), 7F/7A, 8, 9N/9L, 9V/9A, 10A, 10F/(10C/33C), 11A/11D, 12F/(12A/44/46), 13, 14, 15A/15F, 15B/15C, 16F, 17F, 18/(18A/18B/18C/18F), 19A, 19F, 20, 21, 22F/22A, 23A, 23B, 23F, 24/(24A/24B/24F), 31, 33F/(33A/37), 34, 35A/(35C/42), 35B, 35F/47F, 38/25F, and 39); however, the list of serotypes in del Amo includes those that may be detected using an *in vitro* assay, not for conjugation, let alone for inclusion in a composition comprising immunogenic saccharide-polypeptide conjugates as claimed. Moreover, using the assays described in del Amo, the authors found that serotypes 1, 3, 5, 7F, and 19A are the most invasive

Petitioner Merck Ex-1015, 1928

serotypes and serotypes 6A, 6C, 19A, 19F, and 23B are the most common serotypes in carriage (Abstract). The most common serotypes, 1, 3, 5, 6A, 6C, 7F, 19A, 19F, and 23B, are not those required by the claim. In addition, del Amo suggests that the other serotypes should not be included in a vaccine, concluding that "all serotypes with high attack rate are included in PCV13 and that the remaining serotypes circulating in our regions have a low invasive disease potential" (p. 687).

Therefore, as none of the cited references, alone or in combination, teaches or suggests the claimed composition comprising immunogenic saccharide-polypeptide conjugates, withdrawal of the rejection is respectfully requested.

General Comments on Dependent Claims

Each of the dependent claims depends from a base claim that is believed to be in condition for allowance, and Applicant therefore believes that it is unnecessary at this time to argue the allowability of each of the dependent claims individually. Applicant does not, however, necessarily concur with the interpretation of the dependent claims as set forth in the Office Action, nor does Applicant concur that the basis for the rejection of any of the dependent claims is proper. Therefore, Applicant reserves the right to specifically address the patentability of the dependent claims in the future.

Petitioner Merck Ex-1015, 1929

In view of the foregoing, this Application should now be in condition for allowance. A notice to that effect is respectfully requested. If the Examiner believes, after this Response, the Application is not in condition for allowance, the Examiner is requested to call the undersigned at the telephone number indicated below to discuss any outstanding issues.

If this Response is not considered timely filed, and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time.

Applicant believes all fees due with this Response are being paid by credit card. However, if any additional fees are due, please charge them, or credit any overpayment, to our Deposit Account No. 23/2825, under Docket No. P1143.70000US05, from which the undersigned is authorized to draw.

Dated: October 2, 2025

Respectfully submitted,

Electronic signature: /Jessica A. von Reyn/
Jessica A. von Reyn
Registration Number: 76,839
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

Petitioner Merck Ex-1015, 1930

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/347,435	**10/02/2025 01:25:27 PM Z ET**	**P1143.70000US05**

Title of Invention

SACCHARIDE-POLYPEPTIDE CONJUGATE COMPOSITIONS AND METHODS OF USE THEREOF

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	
CONFIRMATION #	4020	FILED BY	Emma Dereberry
PATENT CENTER #	72559922	FILING DATE	06/14/2021
CUSTOMER #	23628	FIRST NAMED INVENTOR	Bruce D. Forrest
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	JESSICA VON REYN

Documents

TOTAL DOCUMENTS: 4

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
P114370000US05-TRN-JXV.pdf		1	Miscellaneous Incoming Letter	25 KB
P114370000US05-AMN-JXV.pdf		14	-	79 KB
P114370000US05-AMN-JXV-A....pdf	(1-1)	1	Amendment/Request for Reconsideration-After Non-Final Rejection	25 KB
P114370000US05-AMN-JXV-CLM.pdf	(2-6)	5	Claims	37 KB
P114370000US05-AMN-JXV-REM.pdf	(7-14)	8	Applicant Arguments/Remarks Made in an Amendment	57 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
P114370000US05-TRN-JXV.pdf	0125399D893F6248D936E53787D41FAF563C675243DC68FB7D471108A57BD1CB1A9764F5C98C0DF3AF76A645D10F128775FB12CE893B7BF551D3F105F01E5806
P114370000US05-AMN-JXV.pdf	4AA9140784951D069B596FBC63487B5661CBEED23085F5E264713F93FCA97681F4FBE3E29EDCC5D36769DCCF44C6AB08376BCDC5F144C48D89C98D06CDE13B5E
P114370000US05-AMN-JXV-A....pdf	3F88063C7C0ADB6C3EFB7F0CDBCC4C586A7880CA2CE2989889CB73194898C57CAB09FD3E22E50D3F4629DF1579E7E88010E61D86780A3B76B370ADE41101DD54
P114370000US05-AMN-JXV-CLM.pdf	64D64EB9C6C868AA96AD14D01B845F9B0E0B42FD1AC12A3B0A929CF0976449376FB41E4ABBDCDDB0BF957004F65DCBA24DFB5EBC9C9FEF9E7A0C8DF68764AFBB
P114370000US05-AMN-JXV-REM.pdf	34A32531B50D5EDC7A0E136AD0D1696742C8414B5781834495213C27C3329723ADCDAAF268FB871D7538E2B0972F4A0C83D92DF2B0A0C702281A72C71298FD3F

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 17/347,435	Filing Date 06/14/2021	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $240 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	10/02/2025	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 26	Minus	** 27	= 0		x $80 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $240 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/JACQUELYN L WILLIAMS/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/347,435	06/14/2021	Bruce D. Forrest	P1143.70000US05	4020

23628 7590 01/21/2026
WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER
SHAHNAN SHAH, KHATOL S

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
01/21/2026	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents_eOfficeAction@WolfGreenfield.com
WGS_eOfficeAction@WolfGreenfield.com

Office Action Summary	Application No. 17/347,435	Applicant(s) Forrest et al.	
	Examiner KHATOL S SHAHNAN SHAH	Art Unit 1645	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 10/2/2025.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 296-305,307-310 and 316-327 is/are pending in the application.

5a) Of the above claim(s) 310 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 296-305,307-309 and 316-327 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Petitioner Merck Ex-1015, 1935

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

2. Applicants' amendment and response of 10/2/2025 are acknowledged. Claims 301, 302, 317-322 and 326-327 have been amended. Claim 306 has been canceled.

Status of Claims

3. Claims 296-305, 307-310 and 316-327 are pending. Claims 301, 302, 308 and 310 have been amended. New claims 323-327 have been added. Claims 301, 302, 317-322 and 326-327 have been amended. Claim 306 has been canceled.

Claims 1-295 and 311-315 have canceled by previous amended. Claim 310 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on May 20, 2024. Claims 296-305, 307-309 and 316-327 are currently under examination.

Rejections Moot

Claim Rejections - 35 USC § 102 Moot

4. Rejection of claim 306 under 35 U.S.C. 102(a)(1)/102(a)(2) as being anticipated by Porro et al., (WO 2014/118201 A1), priority to 1/31/2013, is moot in view of cancelation of said claim.

Claim Rejections - 35 USC § 103 Moot

5. Rejection of claim 306 rejected under 35 U.S.C. 103 as being unpatentable over Caufield et al. WO 2011/100151 A1, art of record applicants' search report, in view of Porro et al., (WO 2014/118201 A1), priority to 1/31/2013, in view of John J. Mekalanos US 9533032 B and further in view of del Amo et al. (Clinical Microbiology and Infection vol. 20, pp. 684-689, 8 November 2013), is moot in view of cancelation of said claim.

Claim Rejections - 35 USC § 102 Withdrawn

6. Rejection of claims 296, 298, 299, 301, 302, 303, 304, 305, 307, 308 and 309 under 35 U.S.C. 102(a)(1)/102(a)(2) as being anticipated by Porro et al., (WO 2014/118201 A1), priority to 1/31/2013, is withdrawn in view of application's amendment and response of 10/2/2025.

Claim Rejections - 35 USC § 103 Maintained

7. Rejection of claims 296-305, 307-309, 316-327 claims under 35 U.S.C. 103 as being unpatentable over Caufield et al. WO 2011/100151 A1, art of record applicants' search report, in view of Porro et al., (WO 2014/118201 A1), priority to 1/31/2013, in view of John J. Mekalanos US 9533032 B and further in view of del Amo et al. (Clinical Microbiology and Infection vol. 20, pp. 684-689, 8 November 2013), is maintained.

Claim 296 is drawn to a pharmaceutical composition comprising at least 2 immunogenic saccharide- polypeptide conjugates each comprising individually a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique Streptococcus pneumoniae serotype, wherein a first serotype comprises 16, 20A, 20B, 24F or 31 and at least one additional serotype is selected from the group consisting of 1, 2, 3, 4,5, 6A, 6B, 6C, 7F, OV, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 22F, 23A, 23B, 24F, 31, 33F, 34, 35B, and 38, wherein the at least one additional serotype is not the first serotype; and wherein the fragment of the capsular polysaccharide is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, a hexasaccharide or an oligosaccharide.

Porro et al. disclose limitations of claims 296, 298, 299 a pharmaceutical or antigenic multivalent molecular construct consisting of a basic unit comprising a helper-T dependent carrier protein covalently bound to a minimum of three carbohydrate structures of different serological specificity, wherein each carbohydrate structure are at least three capsular polysaccharides selected among type 1, 2, 3, 4, 5, 6A, 6B, 6C, 6D, 7F, 8. 9N, 9V,10A, 11A, 11B, 11C, 11F, 12F, 14, 15A, 15B, 15C, 17F, 18C, 19F, 20, 22F, 23A, 23F, 33F and 35B of Streptococcus pneumoniae (see abs, claims

specially claims 1, 2, 4, 5, 8, 9, 11. As to amended claim 296, Porro et al. teach serotype 20 which inherently include serotypes 20A and 20 B (see claim 6, pages 3, 20, 81). Porro et al. teach monosaccharide and oligosaccharide (see pages 5, 6, 8, 9, 12, 48, 80). Porro et al. disclose conjugated polypeptides to capsular polysaccharides (see claims). The invention contains each *S. pneumonia* capsular saccharide (see page 8, 12, 68 and claim 5). Porro et al. disclose that examples of carrier proteins which may be used in the present invention are diphtheria toxoid, tetanus toxoid, CRM197, pneumococcal surface protein, PspA and protein D from H. influenzae (see claims 4, 7, 8 and pages 8, 14). meeting the limitation of claims 301, 302, 307). Porro et al. disclose cross-linked polysaccharide to poly peptide limitations of claim 307 see pages 43, 45 and 47. Porro et al. disclose the immunogenic composition may be adjuvanted (pages 26,31, 60, 63 and tables 5,6 and claims 13-14), and may further comprise a buffering agent (pages 36, 38, 43, 47, 52 and fig 4) and a salt (page 38 (meeting the limitation of claim 303). Moreover, the vaccine preparation (claim 11-12; meeting the limitation of claim 304) containing immunogenic compositions may be administered via the intramuscular, intradermal or subcutaneous routes (see page 31,61 and claim 14). As to limitation of claim 305, Porro et al. teach opsonophagocytic response (see pages 20, 61). As to limitation of claims 306 and 309. Porro et al. teach 0.1 to 1.0 microgram saccharide-polypeptide conjugate amount by weight (see claim 12, page 62). As it pertains to claim 308, the Office takes the position that the prior art meets this limitation, particularly, the polypeptide that is a toxoid based upon Applicant's definition: paragraph 035- The term "partly mitigated" in reference to the toxin activity of a polypeptide can refer to a decreased toxicity of the polypeptide as compared to a wild type version of the polypeptide. A CRM197 protein or toxoid is inherently, based upon Applicant's definition, 'partly mitigated'.

Caulfield et al. teach an immunogenic composition comprising: a multivalent polysaccharide-protein conjugate mixture consisting of capsular polysaccharides from serotypes **1,** 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, **19F,** 22F, 23F, and 33F of *Streptococcus pneumoniae* conjugated to a carrier protein; and a pharmaceutically acceptable carrier and further comprise a carrier protein CRM197 and a adjuvant. (see claims and abstract).

Caulfield et al. page 5 recites "The present invention provides a multivalent immunogenic composition comprising, consisting essentially of, or alternatively, consisting of 15 distinct polysaccharide protein conjugates, wherein each of the conjugates contains a different capsular polysaccharide conjugated to a carrier protein, and wherein the capsular polysaccharides are prepared from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F of S. *pneumoniae,* together with a pharmaceutically acceptable carrier. In certain embodiments, the carrier protein is CRM197. " Caulfield et al. teach composition comprising a plurality of at least two immunogenic polysaccharide-protein conjugates containing serotypes 22F and 33F provides robust antibody responses (see page 6). Caulfield et al. do not teach all the serotypes recited in claim 296 and new claims 323-327.

Porro et al. disclose limitations of claims 296, 298, 299 and new claims 323-327 a pharmaceutical or antigenic multivalent molecular construct consisting of a basic unit comprising a helper-T dependent carrier protein covalently bound to a minimum of three carbohydrate structures of different serological specificity, wherein each carbohydrate structure are at least three capsular polysaccharides selected among type 1, 2, 3, 4, 5, 6A, 6B, 6C, 6D, 7F, 8. 9N, 9V,10A, 11A, 11B, 11C, 11F, 12F, 14, 15A, 15B, 15C, 17F, 18C, 19F, 20, 22F, 23A, 23F, 33F and 35B of Streptococcus pneumoniae (see abs, claims specially claims 1, 2, 4, 5, 8, 9, 11. As to amended claim 296, Porro et al. teach serotype 20 which inherently include serotypes 20A and 20 B (see claim 6, pages 3, 20, 81). Porro et al. teach monosaccharide and oligosaccharide (see pages 5, 6, 8, 9, 12, 48, 80). Porro et al. disclose conjugated polypeptides to capsular polysaccharides (see claims). The invention contains each *S. pneumonia* capsular saccharide (see page 8, 12, 68 and claim 5). Porro et al. disclose that examples of carrier proteins which may be used in the present invention are diphtheria toxoid, tetanus toxoid, CRM197, pneumococcal surface protein (see claims 4, 7 8). meeting the limitation of claims 301, 302, 307). Porro et al. disclose cross-linked polysaccharide to poly peptide limitations of claim 307 see pages 43, 45 and 47. Porro et al. disclose the immunogenic composition may be adjuvanted (pages 26,31, 60, 63 and tables 5,6 and claims 13-14), and may further comprise a buffering agent (pages 36, 38, 43, 47, 52 and fig 4) and a salt (page 38 (meeting the limitation of claim 303).

Moreover, the vaccine preparation (claim 11-12; meeting the limitation of claim 304) containing immunogenic compositions may be administered via the intramuscular, intradermal or subcutaneous routes (see page 31,61 and claim 14). As to limitation of claim 305, Porro et al. teach opsonophagocytic response (see pages 20, 61). As to limitation of claims 306 and 309. Porro et al. teach 0.1 to 1.0 microgram saccharide-polypeptide conjugate amount by weight (see claim 12 , page 62). As it pertains to claim 308, the Office takes the position that the prior art meets this limitation, particularly, the polypeptide that is a toxoid based upon Applicant's definition: paragraph 035- The term "partly mitigated" in reference to the toxin activity of a polypeptide can refer to a decreased toxicity of the polypeptide as compared to a wild type version of the polypeptide. A CRM197 protein or toxoid is inherently, based upon Applicant's definition, 'partly mitigated'.

Porro et al. do not teach serotypes 16F, 19A, 23B. 24F or 31.

Mekalanos teaches a vaccine composition comprising at least 2 immunogenic saccharide- polypeptide conjugates each comprising individually a capsular polysaccharide (see claims, abstract and columns 17-18). Mekalanos claim 15 teaches *Streptococcus pneumoniae* polysaccharide is capsular type 1, 2, 3, 4, 5, 6A, 6B, 7A, 7B, 7C, 7F, 8, 9A, 9L, 9N, 9V, 10A, 10B, 10F, 11A, 11B, 11C, 11D, 11F, 12A, 12B, 12F, 13, 14, 15A, 15B, 15C, 15F, 16A, 16F, 17A, 17F, 18A, 18B, 18C, 18F, 19A, 19B, 19C, 19F, 20, 21, 22F, 23B, 23F, 24A, 24B, 24F, 25A, 25F, 27, 28A, 28F, 29, 31, 32A, 32F, 33A, 33B, 33D, 33F, 34, 35A, 35B, 35F, 36, 37, 38, 39, 40, 41A, 41F, 42, 43, 44, 45, 46, 47A, 47F, or 48. The above serotypes include serotypes 16F, 20, 24F and 31. As to newly added claims 316, 317, 319, 320, 321, 322 the added serotype have been taught by Mekalanos including 19A, 23B and others recited in those claims.

Additionally, del Amo et al. teach plurality of Streptococcal pneumoniae serotypes included in the new generations of conjugate vaccines or pharmaceutical compositions (see title, abstract page 685 and tables 1 and 2). del Amo et al. teach 40 serotypes/serogroups (1, 2, 3, 4, 5, 6A/6B, 6C, 7C/(7B/ 40), 7F/7A, 8, 9N/9L, 9V/9A, 10A, 10F/(10C/33C), 11A/11D, 12F/(12A/44/46), 13, 14, 15A/15F, 15B/15C, 16F, 17F, 18/(18A/ 18B/18C/18F), 19A, 19F, 20, 21, 22F/22A, 23A, 23B, 23F, 24/ (24A/24B/24F), 31, 33F/(33A/37), 34, 35A/(35C/42), 35B, 35F/ 47F, 38/25F, 39) see page 685.

It would have been obvious to combine the teaching of references to obtain the claimed invention. Because, Caulfield et al. teach an immunogenic composition comprising: a multivalent polysaccharide-protein conjugate mixture consisting of capsular polysaccharides from serotypes **1,** 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F of *Streptococcus pneumoniae* conjugated to a carrier protein; and a pharmaceutically acceptable carrier and further comprise a carrier protein CRM197 and a adjuvant. (see claims and abstract). Porro et al. disclose limitations of claims 296, 298, 299 and new claims 323-327 a pharmaceutical or antigenic multivalent molecular construct consisting of a basic unit comprising a helper-T dependent carrier protein covalently bound to a minimum of three carbohydrate structures of different serological specificity, wherein each carbohydrate structure are at least three capsular polysaccharides selected among type 1, 2, 3, 4, 5, 6A, 6B, 6C, 6D, 7F, 8. 9N, 9V,10A, 11A, 11B, 11C, 11F, 12F, 14, 15A, 15B, 15C, 17F, 18C, 19F, 20, 22F, 23A, 23F, 33F and 35B of Streptococcus pneumoniae (see abs, claims specially claims 1, 2, 4, 5, 8, 9, 11).

It would have been obvious before the effective filing date of the presently claimed invention to employ serotypes 16F,19A, 23B, 24F, 31 taught by del Amo et al. and Mekalanos together with the claimed serotypes recited by Porro et al. to obtain the claimed invention. Because the extra serotypes further cover infections associated with that serotype with a reasonable expectation of success. One of skill in the art would be motivated because one can prevent those infections also. There is an expectation of success because Porro et al. specifically teach that you can mix any of the ones listed and the conjugates have been made with various mixtures for a long time. All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. See the recent Board decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396). Accordingly, the subject matter of claims would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the presently claimed invention, absent evidence to the contrary.

Additionally, *KSR International Co. v. Teleflex Inc.,* 127 S. Ct. 1727, 1741 (2007), discloses combining prior art elements according to known methods to yield predictable results, thus the combination is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.,* 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It is well known to combine known serotypes recited by the claims in a conjugate which function in a predictable manner to yield a reasonable expectation of success along with predictable results to one of ordinary skill in the art at the time of the invention. Thus, it would have been obvious to a person of ordinary skill in the art to combine prior art elements according to known methods that is ready for improvement to yield predictable results. The claimed invention is *prima facie* obvious in view of the teachings of the prior art, absent any convincing evidence to the contrary.

Applicants' Arguments

8. Applicant's arguments filed 10/2/2025 have been fully considered but they are not persuasive. Applicants argue:

As noted above, the claims have been amended and are directed to a pharmaceutical composition comprising a plurality of at least two immunogenic saccharide-polypeptide conjugates, each immunogenic saccharide-polypeptide conjugate consisting of a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique *Streptococcus pneumoniae* serotype, wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31, and at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, lOA, l lA, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, 23A, 23B, 23F, 24F, 31, 33F, 34, 35B, or 38, wherein the at least one additional serotype is not the first serotype; and wherein the fragment of the capsular polysaccharide is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, a hexasaccharide, or an oligosaccharide.

None of the cited references, alone or in combination, teach the composition of the amended claims. Caufield, cited for its purported disclosure of a multivalent polysaccharide-protein conjugate mixture consisting of capsular polysaccharides from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F of *Streptococcus pneumoniae* conjugated to a carrier protein *(e.g.,* CRM197), does not describe the combination of serotypes recited in claim 296, nor does it remedy the deficiencies of Porro discussed above. Mekalanos, cited for its purported disclosure of serotypes 16F, 19A, 23B, 24F, and 31, describes vaccine compositions comprising an antigen entrapped within a cross-linked carrier protein matrix, and does not remedy the deficiencies of Porro and Caufield. Similarly, the Examiner cited del Amo for its purported disclosure of numerous serotypes *(e.g.,* 1, 2, 3, 4, 5, 6A/6B, 6C, 7C/(7B/40), 7F/7A, 8, 9N/9L, 9V/9A, lOA, 10F/(10C/33C), l lA/11D, 12F/(12A/44/46), 13, 14, 15A/15F, 15B/15C, 16F, l 7F, 18/(18A/18B/18C/18F), 19A, 19F, 20, 21, 22F/22A, 23A, 23B, 23F, 24/(24A/24B/24F), 31, 33F/(33A/37), 34, 35A/(35C/42), 35B, 35F/47F, 38/25F, and 39); however, the list of serotypes in del Amo includes those that may be detected using an *in vitro* assay, not for conjugation, let alone for inclusion in a composition comprising immunogenic saccharide-polypeptide conjugates as claimed. Moreover, using the assays described in del Amo, the authors found that serotypes 1, 3, 5, 7F, and 19A are the most invasive serotypes and serotypes 6A, 6C, 19A, 19F, and 23B are the most common serotypes in carriage (Abstract). The most common serotypes, 1, 3, 5, 6A, 6C, 7F, 19A, 19F, and 23B, are not those required by the claim. In addition, del Amo suggests that the other serotypes should not be included in a vaccine, concluding that "all serotypes with high attack rate are included in PCV13 and that the remaining serotypes circulating in our regions have a low invasive disease potential" (p. 687).

Therefore, as none of the cited references, alone or in combination, teaches or suggests the claimed composition comprising immunogenic saccharide-polypeptide conjugates, withdrawal of the rejection is respectfully requested.

General Comments on Dependent Claims Each of the dependent claims depends from a base claim that is believed to be in condition for allowance, and Applicant therefore believes that it is unnecessary at this time to argue the allowability of each of the

dependent claims individually. Applicant does not, however, necessarily concur with the interpretation of the dependent claims as set forth in the Office Action, nor does Applicant concur that the basis for the rejection of any of the dependent claims is proper. Therefore, Applicant reserves the right to specifically address the patentability of the dependent claims in the future.

Office Response

9. Applicant's arguments filed 10/2//2025 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicants' arguments, it is the examiner's position that Porro teach immune saccharide polypeptide conjugates of the claims. In particular, Porro does not disclose immunogenic saccharide-polypeptide conjugates, each comprising a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide (see pages 3, 4, 5, 6, 7, 8, 10, 11 and claims 4, 7, 8, 18, 26). Porro teach glycoconjugates (see pages 7, 10, 11).

Page 10 of Porro recites that ":the present invention summarizes the concepts and the technical procedures above referenced 10 for conjugate antigens composed of protein carrier and a maximum of two different carbohydrate structures. In developing the above state of the art, the preferred (not limitative) embodiment of the basic molecular construct subject of the present invention is composed 15 by a multivalent, preferably a tetra-valent semi synthetic glycoprotein which features built-in multiple epitopes and expresses its helper I-dependent immunogenic specificity *"in vivo"* to the protein CRM197, as well as to three carried type-specific Ps, 20 for example Ps of *S. pneumoniae.* As an example, any triad of the Ps type 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A,11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F of *S. pneumoniae* such as the triad consisting of the Ps type 3,6A,7F."

In response to applicants' arguments, it is the examiner's position that Porro teach the limitations of amended claim 296. Porro et al. disclose limitations of claims 296, a pharmaceutical or antigenic multivalent molecular construct consisting of a basic unit comprising a helper-T dependent carrier protein covalently bound to a minimum of three carbohydrate structures of different serological specificity, wherein each carbohydrate structure are at least three capsular polysaccharides selected among type 1, 2, 3, 4, 5, 6A, 6B, 6C, 6D, 7F, 8. 9N, 9V,10A, 11A, 11B, 11C, 11F, 12F, 14, 15A, 15B, 15C, 17F, 18C, 19F, **20**, 22F, 23A, 23F, 33F and 35B of Streptococcus pneumoniae (see abs, claims specially claims 1, 2, 4, 5, 8, 9, 11. As to amended claim 296, Porro et al. teach serotype 20 which inherently include serotypes 20A and/or 20 B (see claim 6, pages 3, 20, 81). Porro et al. teach monosaccharide and oligosaccharide (see pages 5, 6, 8, 9, 12, 48, 80). Porro et al. disclose conjugated polypeptides to capsular polysaccharides (see claims). The invention contains each *S. pneumonia* capsular saccharide (see page 8, 12, 68 and claim 5).

Additionally, Mekalanos column 11 teach a conjugate vaccine for a conjugate made between a PS and the carrier protein tetanus toxoid. In this model, only B-cells that display antibody receptors that recognize the PS bind the PS-protein conjugate. Mekalanos column 23 teach various carrier proteins of the invention include, e.g., toxins and toxoids diphtheria toxoid or CRM 197, tetanus toxin, tetanus toxoid.

Caulfield et al. teach an immunogenic composition comprising: a multivalent polysaccharide-protein conjugate mixture consisting of capsular polysaccharides from serotypes **1,** 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F of *Streptococcus pneumoniae* conjugated to a carrier protein; and a pharmaceutically acceptable carrier and further comprise a carrier protein CRM197 and a adjuvant. (see claims and abstract).

Caulfield et al. page 5 recites "The present invention provides a multivalent immunogenic composition comprising, consisting essentially of, or alternatively, consisting of 15 distinct polysaccharide protein conjugates, wherein each of the conjugates contains a different capsular polysaccharide conjugated to a carrier protein, and wherein the capsular polysaccharides are prepared from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F of S. *pneumoniae,* together with a

pharmaceutically acceptable carrier. In certain embodiments, the carrier protein is CRM197. " Caulfield et al. teach composition comprising a plurality of at least two immunogenic polysaccharide-protein conjugates containing serotypes 22F and 33F provides robust antibody responses (see page 6).

The combination of references make the claims obvious.

Conclusion

10. No claims are allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any nonprovisional extension fee (37 CFR 1.17(a)) pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KHATOL S SHAHNAN SHAH whose telephone number is (571)272-0863. The examiner can normally be reached on Mon-Tue, Thurs-Fri 12pm-8pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Daniel Kolker can be reached on 571-272-3181

. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published

applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Khatol S Shahnan-Shah/
Examiner, Art Unit 1645
January 13, 2026

/JANA A HINES/
Primary Examiner, Art Unit 1645

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/347,435	Forrest et al.
	Examiner	Art Unit
	KHATOL S SHAHNAN SHAH	1645

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
P2E2 all databases	01/10/2026	KSS
PDP inventor, biotech, continuity, priority	01/10/2026	KSS
Google scholar	01/10/2026	KSS
NPL	01/10/2026	KSS
Checked co pending applications	01/10/2026	KSS
Consulted Primary Hines	01/08/2026	KSS
Consulted SPE Mondesi	12/25/2025	KSS
checked PTAB application 16089040	01/08/2026	KSS

/KHATOL S SHAHNAN SHAH/ Examiner, Art Unit 1645	

Petitioner Merck Ex-1015, 1948

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/347,435	Forrest et al.
	Examiner	Art Unit
	KHATOL S SHAHNAN SHAH	1645

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/KHATOL S SHAHNAN SHAH/ Examiner, Art Unit 1645	

Petitioner Merck Ex-1015, 1949

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L4710	11	bruce ADJ forrest	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2026/01/10 07:41 PM
L4711	151	love ADJ jack	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2026/01/10 07:41 PM
L4712	9	L4711 AND polysaccharide-polypeptide	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2026/01/10 07:42 PM
L4713	215	conjugate AND polysaccharide-polypeptide	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB,	OR	ON	ON	2026/01/10 07:43 PM

Petitioner Merck Ex-1015, 1950

			HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)				
L4714	119	L4713 AND (streptococcus ADJ pneumoniae)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2026/01/10 07:43 PM
L4715	108	L4714 AND immunogenic	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2026/01/10 07:44 PM
L4716	104	L4715 AND serotypes	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2026/01/10 07:44 PM
L4717	58	L4716 AND plurality	(US-PGPUB; USPAT; USOCR; FIT (AU, AP,	OR	ON	ON	2026/01/10 07:45 PM

Petitioner Merck Ex-1015, 1951

			AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)				
L4718	22	L4717 AND CRM197	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2026/01/10 07:45 PM
L4719	18	L4718 AND (6A OR 7F OR 9N OR 15A OR 16F OR 19A OR 22F OR 23A OR 23B OR 24F OR 33f OR 35B)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2026/01/10 07:49 PM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

Petitioner Merck Ex-1015, 1952

Interactions between polysaccharides and polypeptides

D Magnin, S Dumitriu - Polysaccharides: Structural diversity and …, 2005 - books.google.com

… The key consideration is that under specific conditions, **polysaccharide-polypeptide** hybrids enhance functional properties in comparison to polysaccharides and polypeptides alone [52]…

☆ Save 99 Cite Cited by 19 Related articles

OMNIPRESENCE OF CARBOHYDRATES IN LIFE

N Basu - … DEVELOPMENT: an eConSus Book Series Vol. 2 - books.google.com

… Gram-positive bacteria contain a **polysaccharide/polypeptide** framework in their cell wall … been accepted globally, against **Streptococcus pneumonia** causing **pneumonia**, meningitis and …

☆ Save 99 Cite Related articles

Bioactive peptides from edible mushrooms—the preparation, mechanisms, structure—activity relationships and prospects

H Li, J Gao, F Zhao, X Liu, B Ma - Foods, 2023 - mdpi.com

… be edible, and about 200 are collected as food or **pharmaceutical** ingredients [10]. Therefore, edible … (PSP) from Coriolus versicolor; **polysaccharide polypeptide** complexes (PSPC) from …

☆ Save 99 Cite Cited by 38 Related articles All 7 versions »

Recent advancement in nanocarriers for oral vaccination

P Kour, G Rath, G Sharma, AK Goyal - Artificial cells, nanomedicine …, 2018 - Taylor & Francis

… release behaviour and other favourable **pharmaceutical** properties … antigen of **Streptococcus pneumonia** encapsulated in … **Polysaccharide/polypeptide**/polymer-coated liposomes were …

☆ Save 99 Cite Cited by 22 Related articles All 7 versions »

Aspects of immunochemistry (concluded)

M Stacey - Quarterly Reviews, Chemical Society, 1947 - pubs.rsc.org

… in the immunity pattern, and the chemical **composition** of each major component of the cell is … shigze ; however, the " reconstituted " **polysaccharide-polypeptide** complex 122 (made by …

☆ Save 99 Cite Cited by 8 Related articles All 2 versions »

Enzymes as green catalysts for precision macromolecular synthesis

S Shoda, H Uyama, J Kadokawa, S Kimura… - Chemical …, 2016 - ACS Publications

The present article comprehensively reviews the macromolecular synthesis using enzymes as catalysts. Among the six main classes of enzymes, the three classes, oxidoreductases, …

☆ Save 99 Cite Cited by 588 Related articles All 4 versions »

Agaricus blazei bioactive compounds and their effects on human health: benefits and controversies

A Cristine da Silva de Souza… - … pharmaceutical …, 2017 - benthamdirect.com

… its chemical **composition** and clinical investigations. … to protect against lethal **Streptococcus pneumoniae** infection in … , glycopeptides and **polysaccharidepolypeptide** complexes) and …

☆ Save 99 Cite Cited by 46 Related articles All 5 versions »

Bacteriology

H Al-Haideri - csw.uobaghdad.edu.iq

▪ Bacteriology: is the science that deals with the study of microorganisms known as bacteria▪ The term includes a large group of typically unicellular microscopic organisms which are …

☆ Save 99 Cite Related articles »

Exploring bacterial diversity: from cell to sequence

R Nazir, S Rehman, M Nisa, U ali Baba - Freshwater Microbiology, 2019 - Elsevier

Microorganisms comprise a huge reservoir of resources providing innovative applications useful to mankind. Microbes are responsible for vital biogeochemical cycling without which all …

☆ Save 99 Cite Cited by 18 Related articles All 2 versions »

INTRODUCTION TO MICROBIOLOGY

A Kumar - academia.edu

It's with great happiness that, I would like to acknowledge a great deal of people that get helped me extremely through the entire difficult, challenging, but a rewarding and interesting …

☆ Save 99 Cite Related articles »

Related searches

streptococcus pneumoniae polysaccharide **peptide**

streptococcus pneumoniae polysaccharide **structure**

streptococcus pneumoniae **virulence factors**

streptococcus pneumoniae **biofilm**