UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

VALNEVA AUSTRIA GMBH,
Petitioner,

v.

TAKEDA VACCINES, INC.,
Patent Owner.

Case IPR2025-00776
U.S. Patent No. 11,730,802

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 11,730,802

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MANDATORY NOTICES

Real Parties in Interest (37 C.F.R. § 42.8(b)(1))

Valneva Austria GMBH is the real party-in-interest. No unnamed entity is funding, controlling, or directing this Petition, or otherwise has had an opportunity to control or direct this Petition or Petitioner's participation in any resulting IPR.

Related Matters (37 C.F.R. § 42.8(b)(2))

There are no related litigations.

Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3))

Petitioner designates counsel listed below and consents to electronic service A power of attorney for counsel is being concurrently filed with this Petition.

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I. INTRODUCTION

Valneva Austria GMBH ("Valneva") petitions for *inter partes* review ("IPR") under 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42 of claims 1-67 of U.S. Patent No. 11,730,803 ("the '802 patent") (Ex. 1001), owned by Takeda Vaccines, Inc, ("Patent Owner"). Review should be instituted because claims 1-67 are unpatentable.

II. THE '802 PATENT

A. Brief Description

The '802 patent (EX 1001) is entitled "Zika Vaccines and Immunogenic Compositions, and Methods of Using the Same." The earliest priority is November 3, 2017. EX 1002, ¶38; EX 1001; EX 1008-1010.

The '802 patent is directed to Zika virus vaccines "having one or more antigens from a Zika virus." EX 1002, ¶39; EX 1001 1:29-31. The '802 patent Background teaches that Zika virus is "a flavivirus classified with other mosquito-borne viruses … within the Flaviviridae family …," identifies known Zika virus strain PRVABC59 (EX 1002, ¶39; EX 1001 1:41-43, 48) and recognizes that "Zika continues to pose in particular a significant threat for pregnant women and their unborn babies." EX 1002, ¶39; EX 1001 2:9-18.

The '802 patent states "the present disclosure is based, at least in part, on the finding that clonal isolated Zika viruses harboring an adaptation mutation in protein NS1 grew well and predictably in Vero cells to high titer, and surprisingly, were genetically stable/genetically homogenous without any detectable mutations in the

viral envelope protein" (EX 1002, ¶40; EX 1001 2:38-40; 3:16-22 and 3:35-39). However, the inventors never claimed the particular Zika virus strain PRVABC59 with this NS1 mutation instead they claimed an antigen from any Zika virus. EX 1002, ¶¶40, 43.

The inventors admit the techniques and procedures used to develop the claimed Zika vaccine are "generally well understood and commonly employed using conventional methodology by those skilled in the art …" EX 1002, ¶41; EX 1001 17:55-58. They also admit that the culture conditions used "are known and described in a variety of publications" or are commercially available (EX 1001 34:23-28), that vaccine purification is "standard practice," "using standard purification procedures e.g. chromatography, etc." (EX 1002, ¶41; EX 1001 35:40-45) and that antigens may be isolated using "standard methods" of size exclusion chromatography to obtain purity as a function of main peak to total area under the curve (EX 1002, ¶41; EX 1001 37:4-27).

The '802 patent teaches inactivated whole virus vaccines are old and can be "produced and/or purified or otherwise isolated by any suitable method known in the art," including chemical inactivation. EX 1002, ¶42; EX 1001 35:64-36:7, 38:58-60 and 39:5-7. The inventors admit that the use of adjuvants with vaccines is well known (EX 1002, ¶42; EX 1001 42:66-67) and vaccines may be

"conventionally administered" by intramuscular or subcutaneous administration. EX 1002; ¶42; EX 1001 54:62-65.

Everything from the need for a Zika virus vaccine, to the Zika virus strain PRVABC59 with the NS1 mutation, to culturing, purifying, inactivating, adjuvant formulating and administering is admitted to be in the prior art and conventional. EX 1002, ¶¶43, 78. Any effect of this Zika vaccine in the human body, such as antibody generation, is an inherent property resulting from practicing the admitted prior art techniques. *Id*.

While the '802 patent discusses preventing Zika virus disease in a fetus or newborn by vaccinating a pregnant woman, it provides no data to support safety or efficacy of such a method. (e.g., EX 1002, ¶¶44-45, 407; EX 1001 59:13-22, 77:10-78:50).

B. Prosecution History

Relevant portions of the prosecution history are attached. (EX 1003. EX 1002, ¶38. A preliminary amendment cancelled claims 1-54 and added new vaccine claims 55-64 and new method claims 65-73. EX 1002, ¶46; EX 1003, p. 269-275.

Responding to a restriction requirement, the applicant selected the method claims, cancelled claims 55-64 and amended main independent claim 65:

65. (Currently Amended) A method of ~~treating or preventing, in particular preventing~~ vaccinating against Zika virus infection in a

human subject in need thereof,

the method comprising administering to the human subject ~~the~~ a vaccine or immunogenic composition ~~of claim 55~~ comprising a dose of from about 1 µg to about 40 µg of an antigen from a Zika virus, wherein the antigen is an inactivated whole virus.

EX 1002, ¶47; EX 1003, p. 176-182

The applicant added new claims 74 to 124. Dependent claim 70 directed to prime and boost administration and new claim 75 directed to seroconversion rate recited:

70. (Previously Presented) The method of claim 65, wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration.

75. (New) The method of claim 70, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration a seroconversion rate of at least 80%, or at least 90%, or at least 95%, or 100% in a population of at least 20 Zika virus seronegative subjects.

EX 1002, ¶48; EX 1003, p. 146-156.

A non-final office action indicated claims 75 (above), 76, 77, 97-102, 107-119 and 123-124 were objected to but would be allowable if written into independent

form. EX 1002, ¶¶49-51; EX 1003, p. 87.

The Examiner rejected claims 65, 66-72, 78, 79, 80-90 and 96 as anticipated and claims 73-74, 89, 92-93, 94, 95, 103-106, and 121-122 as obvious over Barbero WO2017/109223 ("Barbero"). EX 1002, ¶52-54; EX 1003, pp. 87-89. Barbero taught "a Zika virus vaccine (abstract), purified (page 7 lines 9-12), that is inactivated by formalin (page 108 lines 1-5) … antigen doses of 0.012-12 μg adjuvanted with $AlOH_3$ (page 114 lines 1-5) for human trials (page 115 lines 27-32); and pregnant women (page 116 lines 13-22)." EX 1002, ¶52; EX 1003, p. 88. "Barbero discloses the administration may be intramuscular or subcutaneous one or more times (page 24 lines 1-7)." *Id*. "Barbero discloses administration and a second administration (boost) 3-4 weeks later (page 115 lines 11-25.)" *Id.* "Barbero discloses administering aluminum hydroxide adjuvant at 500 μg/ml (page 112 lines 1-5.)" *Id.*

Responding, the Applicant amended claim 65 to include claim 70's prime and boost administration and allowable claim 75's seroconversion rate. EX 1002, ¶55; EX 1003, p. 52-66.

Claim 74 (adoptive transfer between mother and fetus) was amended to include claim 100's prime and boost administration. *Id.*, ¶56.

Allowable dependent claim 76 (seroconversion rate after prime) was amended to include independent claim 65 and dependent claim 68 (administered one or more times). *Id.*, ¶57.

Rejected dependent claim 91 (10µg virus, 200µg aluminum hydroxide, buffer) was amended to overcome the indefiniteness rejection and include independent claim 65. *Id.*, ¶58.

Dependent claim 107 (purified antigen), 109 (dose between 10µg to 40µg), 115 (aluminum salt adjuvant), 119 (clonal isolate), 120 (10 µg virus, 200 µg aluminum hydroxide and buffer), 123 (Zika endemic region) and 124 (age between 18-29 or 30-49) were amended to include independent claim 74 (adoptive transfer between mother and fetus). *Id.*, ¶¶59-65.

New claims 125 to 133 were added. *Id.*, ¶66.

A Notice of Allowance indicated claims 65-69, 71-99 and 101-133 were allowed, but failed to provide any Statement of Reasons for Allowance. EX 1002, ¶67; EX 1003, p. 28-33.

The claims were allowed, in part, because Barbero did not teach a seroconversion rate of at least 80% in a population of at least 20 Zika virus seronegative subjects 14 and/or 28 days after boost administration. However, Thomas WO 2017/210215 ("Thomas") (EX 1004), which was cited in an IDS but never applied by the Examiner, teaches vaccinating male and female humans with 5

μg prime and boost doses of inactivated, whole Zika virus antigen to achieve a seroconversion rate of at least 80% in a population of at least 20 Zika virus seronegative subjects 14 and/or 28 days after boost administration – the exact subject matter the Examiner thought was not taught by Barbero. Had the Examiner been aware of this teaching in Thomas, the claims would not have been allowable. Ex 1002, ¶77.

C. Technical Considerations

Seroconversion is the process by which a person's immune system produces detectable levels of antibodies in response to an infection or vaccination, going from seronegative (no detectable antibodies) to seropositive (detectable antibodies). EX 1002, ¶¶68-69.

A neutralizing antibody titer, is typically measured by gradually diluting a blood sample and determining the highest dilution at which the antibodies are still able to neutralize the pathogen. The higher the titer, the greater the concentration of neutralizing antibodies. *Id.*, ¶¶70-71.

Neutralizing antibody titers can be determined, e.g., by a plaque reduction neutralization test (PRNT) or microneutralization (MN) assay. In PRNT, serial dilutions of a blood sample are mixed with a fixed number of live virus particles, and the mixture is added to a monolayer of susceptible cells. After incubation, plaques formed on the monolayer (clear zones) are counted. The neutralization titer

is the highest dilution of serum that reduces the number of plaques by a certain percentage (e.g., 50%). MN assay is a modification of PRNT in which neutralization is assessed in a 96-well format, allowing high-throughput testing. "Geometric mean neutralizing antibody titer" or "GMT" is commonly used in vaccine and immunology studies and refers to the average level of neutralizing antibodies in a group of individuals. Using a geometric mean is more accurate than an arithmetic mean. A higher GMT suggests a stronger immune response. *Id.*, ¶72.

An adjuvant enhances the body's immune response to an antigen. Adjuvants, such as aluminum hydroxide (alum), have long been used in vaccines to improve effectiveness. *Id.*, ¶73.

"Adoptive transfer" refers to the production of antibodies in a first subject in response to an antigen (e.g., a pregnant woman), which are then transferred to a second subject (e.g., a fetus). "Passive transfer" refers to the similar process of passing antibodies from one person to another, such as from mother to fetus or infant. *Id.*, ¶74.

III. OVERVIEW OF THE PRIOR ART

A. Thomas

Thomas WO 2017/210215 ("Thomas") (EX 1004) was published December 7, 2017 with International Filing Date of May 30, 2017, which is before the 802 patent's earliest provisional application filing date of November 3, 2017. *Id.*, ¶82.

Thomas teaches in "Example 5. ZIKV PIV Performance in Human Trials" (EX 1004 40:7-43:15), 5 μg doses of a purified whole inactivated Zika virus adjuvanted with aluminum hydroxide were administered by prime and boost injection 28 days later to 55 male and female human volunteers with a mean age of 31.5 years. A group seroconversion rate of 92% was reported. The generation of neutralizing antibody to Zika virus showed a peak geometric mean titer (GMT) greater than 10 times post prime. No serious adverse events were reported. The immunogenicity data indicates moderate to highly immunogenic following two doses measured to study day 57. Titers in the majority of the vaccinated population exceed what is believed to be protective based on pre-clinical animal studies. A passive transfer study was also completed using purified antibody from the human vaccine recipients. EX 1002, ¶84. Thomas Example 5 (EX 1004 40:7-43:15) shows that numerous claims of the '802 patent were clearly known and/or obvious to one of ordinary skill ("POSA"). *Id.*, ¶¶83-84; *See also*, EX 1004 Abstract, 4:15-18; 6:33-7:2; 5:8-9; 5:2-6; 5:8-11; 41:7-8; 4:20-28; 40:18-26; 18:28-30; 3:18-22; 4:20-22; 7:32-33; 7:30-8:2; 6:33-7:6; 7:32-33; 9:1-9; 41:9-10; and 42:4-7.

B. Barbero

Barbero Calzado WO2017/109223 ("Barbero") was published June 29, 2017 before the '802 patent's earliest provisional application filing date of November 3, 2017. EX 1002, ¶85; EX 1005.

Barbero, cited during prosecution (EX 1002, ¶85-86) teaches "[t]here is a possible association between Zika virus infection during pregnancy and microcephaly in the fetus/neonate. EX 1002, ¶86; EX 1005 13:11-16. Barbero teaches that inactivated Zika virus vaccines are safe for pregnant women. EX 1005 4:8-10, 13:26-28, 21:32-33, 116:17-20; EX 1002, ¶¶86-88. Barbero teaches assessing seroconversion using PRNT. EX 1002, ¶87; EX 1005 22:25-35. Barbero teaches virus purification greater than 90% using size exclusion chromatography. EX 1002, ¶¶89-90; EX 1005 14:29-31. Barbero teaches using 500 μg of aluminum hydroxide adjuvant and greater than 95% adsorption of viral particles on the adjuvant. EX 1002, ¶89; EX 1005 112:1-7.

C. Murata

Murata et al., Vaccine 29 (2011) 3155-3161 ("Murata") was published online February 26, 2011 which is before the '802 patent's earliest provisional application filing date of November 3, 2017. EX 1002, ¶91; EX 1006.

Murata teaches "[p]laque purification has been used for decades" (EX 1006 p. 3156) and "may be a rapid and efficient means by which vaccine seed virus purity can be enhanced." EX 1002, ¶¶92-96; EX 1006 p. 3156-3159. Murata suggests plaque purification because ["p]laque purification is an approach unencumbered by intellectual property constraints." EX 1002, ¶92; EX 1006 p. 3159.

D. Faucette

Faucette et al., Human Vaccines & Immunotherapeutics 11:11, 2549-2555; November 2015 ("Faucette") was published November 2015 which is before the '802 patent's earliest provisional application filing date of November 3, 2017. EX 1002, ¶97; EX 1007.

Faucette is directed to immunizing pregnant women with transfer of antibodies to the fetus or newborn. EX 1002, ¶98-99; EX 1007 Abstract, p. 2549-2552.

Faucette teaches that "the vaccines effectiveness is due to both passive antibody transport and reduction of maternal exposure." EX 1002, ¶100; EX 1007, p. 2522.

Faucette also teaches that "[m]aternal immunization has emerged as a worldwide public health strategy to protect both pregnant women and infants against infections" (EX 1002, ¶101; EX 1007 p. 2553) and "that consistent efforts are needed to open well-designed vaccine trials to safely include and monitor pregnant women." EX 1002, ¶101; EX 1007 p. 2553-2554.

E. Version 8 of Clinical Trial NCT02952833 ("NCT02952833")

Version 8 of Clinical Trial NCT02952833 ("NCT02952833") was publicly available as of July 2, 2017 which is before the '802 patent's earliest provisional application filing date of November 3, 2017. EX 1002, ¶102; EX 1011; EX 1013.

NCT02952833 describes a Zika vaccine study protocol in men and women between the ages of 18-49, evaluating three dose levels, i.e., "5.0 mcg, 2.5 mcg and 10 mcg of ZPIV" administered by intramuscular (IM) injection on Days 1 and 29. EX 1002, ¶¶103-110; EX 1011 pp. 6, 8, 10-11. The study assesses safety, seroconversion rates and peak Geometric Mean Titer (GMT). EX 1002, ¶105; EX 1011 p. 6.

F. Liu, et al., Clinical and Vaccine Immunology, Vol. 19, No. 1 (January 2012) pp. 73-78 ("Liu")

Liu was published November 23, 2011 which is before the '802 patent's earliest provisional application filing date of November 3, 2017. EX 1002, ¶111; EX 1012.

Liu compares PRNT with enzyme-linked immunospot-based microneutralization assay (ELISPOT-MNT) and reports good correlation was observed between the two assays. EX 1002, ¶112; EX 1012 p. 73: "A good correlation . . . was observed between the two assays." EX 1012 p. 76: "a good relationship between the two assay methods". . . "there was no significant . . . disagreement between them . . . the two assay methods agree reasonably well . . . ." EX 1012 p. 77: "The results of our comparison of PRNT and ELISPOT-MNT show that there was significant agreement . . . between the two methods."

IV. IDENTIFICATION OF CHALLENGE (37 C.F.R § 42.104(b))

A. Claims for Which Review is Requested and Grounds on Which

Challenge is Based

Petitioner requests review of claims 1-67 on the following grounds and that the Board find each claim unpatentable. The '802 patent is to be reviewed under post-AIA 35 U.S.C. §§ 102 and 103. This Petition, supported by the accompanying declaration of Dr. Farshad Guirakhoo (EX 1002), demonstrates a reasonable likelihood that Petitioner will prevail with respect to challenged claims 1-67. Claim limitations are labelled in the Claims Listing Appendix. A detailed claim chart of claims 1-67 and the art relied upon is provided in Exhibit B of EX 1002. *See also* EX 1002, ¶¶ 113, 162, 202, 264, 277, 371, 397, 465, 483, 513, 522.

Ground	Claims	Basis for Unpatentability
Ground I	1-4, 6, 7, 10, 13, 19, 21, 23, 27-31, and 59	Anticipation under 35 U.S.C. §102(a)(2) and/or obviousness under 35 U.S.C. §103 based on Thomas
Ground II	11, 60, 61 and 62	Obviousness under 35 U.S.C. §103 based on Thomas
Ground III	8, 12, 14, 22, and 24	Obviousness under 35 U.S.C. §103 based on Thomas in view of Barbero
Ground IV	25	Obviousness under 35 U.S.C. §103 based on Thomas in view of Murata
Ground V	5, 15-18, and 20	Obviousness under 35 U.S.C. §103 based on Thomas in view of NCT02952833
Ground VI	26 and 63	Obviousness under 35 U.S.C. §103 based on Thomas in view of NCT02952833 and further in view of Barbero

Ground VII	9, 32, 33, 35, 36, 38, 39, 41, 47, 49, 51, 55-58, 65-67	Obviousness under 35 U.S.C. §103 based on Thomas in view of Faucette
Ground VIII	34, 43-46 and 48	Obviousness under 35 U.S.C. §103 based on Thomas in view of Faucette, and further in view of NCT02952833
Ground IX	37, 40, 42, 50 and 52	Obviousness under 35 U.S.C. §103 based on Thomas in view of Faucette and further in view of Barbero
Ground X	54 and 64	Obviousness under 35 U.S.C. §103 based on Thomas in view of Faucette and further in view of NCT02952833 and Barbero
Ground XI	53	Obviousness under 35 U.S.C. §103 based on Thomas in view of Faucette and further in view of Murata

B. 314(a) Discretion Does Not Apply

To Petitioner's knowledge there are no grounds for discretionary denial under § 314(a) because there are no prior petitions challenging validity of the '802 patent, this is not a successive petition, there is no litigation in which the '802 patent is asserted and no reason why the PTAB could not complete this review within a year of institution.

C. 325(d) Discretion Does Not Apply

Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH, IPR2019-01469, Paper 6, at *10 (PTAB Feb. 13, 2020) (precedential) does not support discretionary denial of institution under § 325(d). Becton Factors (c), (e),

and (f) favor institution because the Office erred in a manner material to the patentability of the challenged claims.

1. The Examiner's First Material Error

The Examiner erred indicating the prior art of record did not teach the subject matter of claim 75, namely, where administration of a 5 µg first (prime) dose and a 5 µg second (boost) dose of a purified, inactivated whole Zika antigen induces 14 and/or 28 days after the boost administration a seroconversion rate of at least 80% in a population of at least 20 Zika virus seronegative subjects. Thomas teaches this very subject matter. EX 1002, ¶83-84; EX 1004 42:4-7. Accordingly, the Examiner was wrong to indicate that claim 75 would be allowable. Although cited in an IDS (EX 1003 p. 106), the Examiner did not apply Thomas. Becton Factor (c) supports institution. *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at *17 (PTAB Dec. 15, 2017); *Vizio, Inc. v. Nichia Corporation*, IPR2017-00551, Paper 9 at *8 (PTAB July 7, 2017) (instituting IPR even though references were listed on an IDS submitted to the examiner where there is no evidence that the references were applied); *Mylan Pharmaceuticals Inc. v. Merck Sharpe & Dohme Corp*, IPR2020-00040, Paper 21, at *8 (PTAB May 12, 2020); *Medacta USA, Inc. v. RSB Spine, LLC*, IPR2020-00264, Paper 24, at *17 (PTAB May 22, 2020).

Had the Examiner understood (or even considered) the teachings of Thomas, the Examiner would have rejected claim 75 based on Thomas, rather than indicate

allowability. Claim 65 was amended to include the subject matter of claims 70 and 75 leading to allowability of claim 65 as issued claim 1 and its issued dependent claims 2-8, 10, 12-25, and 27-31. EX 1002, ¶¶55-65; EX 1003, pp. 28-33, 52-66. Becton Factor (e) supports institution. *Advanced Bionics* at *8. *Vudu, Inc. v. Ideahub, Inc.*, IPR2020-01689, Paper 16, at *18-20 (PTAB April 19, 2021); *Amber.IO, Inc. D/B/A Two Tap v. 72Lux, Inc. D/B/A Shoppable*, IPR2020-00015, Paper 8, at *20-21 (PTAB April 1, 2020); *Medacta*, at *17; *Mylan*, at *19.

Dr. Guirakhoo demonstrates that Thomas teaches the subject matter of claim 75. Ex. 1002, ¶¶83-84, 119-121. Becton Factor (f) supports institution. *Medacta*, at *18 ("We find that the additional evidence of Mr. Sherman's testimony and Figure 8 of Fraser '106 further weighs against exercising our discretion to deny institution under 35 U.S.C. § 325(d)."); *Mylan*, at *20.

2. The Examiner's Further Material Errors

A. The Examiner further similarly, materially erred finding claims 76, 77, 97-102, 107-119, and 123-124 allowable despite Thomas. Thomas alone discloses the subject matter of these claims to a POSA. EX 1002, ¶¶167, 399-403, 405-406, 424-431, 436-437, 441, 443, 449, 451. The combination of Thomas and Barbero (disclosing many dependent features) discloses the subject matters of claims 77, 108, 116 and 118 to a POSA. EX 1002, ¶¶215-227, 497-512. The combination of Thomas and NCT02952833 (of which the Examiner was unaware and teaching a 10 μg dose

within claimed ranges) discloses the subject matters of claims 99, 109, 110, 111, 112, 113 and 114 to a POSA. EX 1002, ¶¶466-482. The combination of Thomas and Murata (of which the Examiner was unaware) discloses the subject matter of claim 119. EX 1002, ¶¶523-528. Accordingly, the Examiner was wrong to indicate that claims 76, 77, 97-102, 107-119 and 123-124 would be allowable.

This Petition identifies material error and presents new factual evidence and legal arguments demonstrating unpatentability. Any argument this Petition should be denied under § 325(d) is meritless.

D. Level of Ordinary Skill

A POSA would have an M.D. or Ph.D. degree in virology, immunology, or vaccinology and at least 3 years of experience in one or more of the research, design, development and testing of antiviral vaccines. A POSA may be part of a multidisciplinary team having such experience. EX 1002, ¶81.

E. Claim Construction

All claim terms herein are understandable to a POSA and should be given their ordinary and customary meaning to a POSA as they would be given in a civil action under 35 U.S.C. 282(b). *Id.*, ¶79-80

V. RELEVANT LEGAL STANDARDS

A. Legal Standard for Anticipation

A claim is anticipated when a single prior art reference discloses all of the

limitations of the claim, "arranged or combined in the same way as in the claim." *Net MoneyIN, Inc. v. VeriSign, Inc.,* 545 F.3d 1359, 1370 (Fed. Cir. 2008).

B. Legal Standard for Obviousness

The question of obviousness requires analyzing (1) scope and content of the prior art; (2) differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co*., 383 U.S. 1, 17-18 (1966).

VI. SPECIFIC GROUNDS FOR UNPATENTABILITY

A. Claims 1-4, 6, 7, 10, 13, 19, 21, 23, 27-31, and 59 are Anticipated by, or in the Alternative, Rendered Obvious in View of Thomas

1. Independent Claim 1

a. Element [1A] A method of vaccinating against Zika virus infection in a human subject in need thereof, the method comprising

Thomas teaches immunizing a human against ZIKV infection (EX 1002, ¶115; EX 1004 4:15-18; 5:2-6; 6:33-7:2; 5:8-9) and that extrapolation from animal models to humans is reasonable for single dose or a booster dose. EX 1004 18:16-20. Thomas Example 5 concludes that "vaccines comprising inactivated ZIKV are protective against infection with ZIKV." EX 1002, ¶115; EX 1004 42:21-43:1. Accordingly, Thomas teaches this limitation. EX 1002, ¶115.

b. Element [1B] administering to the human subject a vaccine or immunogenic composition comprising a

dose of from about 1 μg to about 40 μg of an antigen from a Zika virus

Thomas teaches administering a 5 μg dose of a Zika virus antigen. EX 1002, ¶116; EX 1004 41:7-8: "Two doses were administered at 0 and 28 days, 5 μg per dose, and adjuvanted with alum." Accordingly, Thomas teaches this limitation. EX 1002, ¶116.

c. Element [1C] wherein the antigen is an inactivated whole virus, as a first (prime) and a second (boost) administration

Thomas teaches that the antigen is an inactivated whole virus. EX 1002, ¶117; EX 1004 18:28-30. Thomas teaches a first (prime) and a second (boost) administration. EX 1002, ¶118. EX 1004 4:20-22, 7:32-33, 41:7-8 ("Two doses were administered at 0 and 28 days, 5 μg per dose, and adjuvanted with alum."). Accordingly, Thomas teaches this limitation. EX 1002, ¶117-118.

d. Element [1D] wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration a seroconversion rate of at least 80% in a population of at least 20 Zika virus seronegative subjects

Thomas teaches a seroconversion rate of 92% for 55 humans at day 57 (28 days after the boost administration). EX 1002, ¶¶68, 120; EX 1004 42:4-7 ("Seroconversion measured by the MN50 assay, >1:10 titer, at study day 57 was 92% across the Trial 2 Group, Trial 3 Group, and Trial 1 Group study sites with a range of site specific seroconversion rates of Trial 2 Group 92%, Trial 1 Group 88%,

and Trial 3 Group 100%."); Table at 42:19 for Trial Group 1 (N=25), Trial Group 2 (N=20), Trial Group 3 (N=10) and All participants N=55. Accordingly, Thomas teaches this limitation of claim 1 and each and every limitation of claim 1. EX 1002, ¶119-121.

Alternatively, claim 1 would have been obvious, as Thomas teaches all of the claim limitations including human clinical trials with the claimed dosage and achieving the claimed seroconversion rates. EX 1002, ¶122.

It is within the level of a POSA to use Thomas's Example 5 disclosing all limitations of the claim with no modification. EX 1002, ¶123.

Additionally, a POSA would have been motivated to optimize the Thomas Example 5 vaccine dose by either the amount of antigen and/or adjuvant or the type of adjuvant to induce the claimed seroconversion rate, because Thomas teaches to do just that. EX 1002, ¶124; EX 1004 40:19-21 ("ZPIV is explored across a range of antigen doses in an attempt to define the optimal dose of antigen as well as lower limits of antigen concentration required to effectively immunize a recipient"). EX 1004 42:4-8; 28:19-22.

Based on Thomas, a POSA would have been motivated to explore doses and seroconversion rates with the goal of creating a vaccine with the claimed seroconversion rate of at least 80% because the amount of antigen and/or adjuvant

or the type of adjuvant make the vaccine dose a result-effective variable, as Thomas demonstrates that vaccine dose affects seroconversion. EX 1002, ¶125.

A POSA would have had a reasonable expectation of successfully modifying the vaccine dose of Thomas Example 5 to induce the claimed seroconversion rate because Thomas teaches that 5 μg dose achieves 92% seroconversion and only routine optimization of dose/adjuvant is needed to affect seroconversion. EX 1002, ¶126; EX 1004 42:4-7.

Accordingly, claim 1 is also obvious in view of Thomas. EX 1002, ¶127.

2. Dependent Claims 2-4, 6, 7, 10, 13, 19, 21, 23, 27-31, and 59

The limitations of dependent claims 2-4, 6, 7, 10, 13, 19, 23, 27-31 and 59 are taught by Thomas. EX 1002, ¶¶128-161. Thomas teaches or renders obvious every limitation of claim 1. EX 1002, ¶¶113-127. Accordingly, these dependent claims are either anticipated by or rendered obvious over Thomas.

a. Claim 2

Claim 2 recites the subject is pregnant, intends to be pregnant or is a woman of childbearing potential. EX 1002, ¶128; EX 1001 122:65-67. Thomas teaches use of purified inactivated whole virus in a pregnant woman because of "superior safety profile" (EX 1002, ¶129; EX 1004 18:28-30). Example 5 teaches women of child bearing potential as subjects. EX 1002, ¶129; EX 1004 41:12-13. Accordingly, Thomas anticipates claim 2. Claim 2 is also obvious in view of Thomas for the same

reasons expressed with respect to claim 1 and further that selecting a women of child bearing potential is an option expressly taught by Thomas. EX 1002, ¶129.

b. Claim 3

Claims 3 recites intramuscular or subcutaneous administration. EX 1002, ¶130; Ex. 1001 123:1-3. Thomas teaches intramuscular or subcutaneous injection. EX 1002, ¶131; EX 1004 7:12-14. Accordingly, Thomas anticipates claim 3. Claim 3 is also obvious in view of Thomas for the same reasons expressed with respect to claim 1, and that selecting intramuscular or subcutaneous administration are options expressly taught by Thomas. EX 1002, ¶131.

c. Claim 4

Claim 4 recites administering one or more times. EX 1002, ¶132; Ex. 1001 123:4-5. Thomas not only teaches that a single dose is effective for humans (e.g., EX 1002, ¶133; EX 1004 4:18-20, 7:30-8:2), but also that two doses (i.e., "one or more") is effective (EX 1002, ¶133; EX 1004 41:7-8). Accordingly, Thomas anticipates claim 4. Claim 4 is also obvious in view of Thomas for the same reasons expressed with respect to claim 1, and that selecting administration one or more times is an option expressly taught by Thomas. EX 1002, ¶133.

d. Claims 6, 7, 10, 13, 19, 21, 23, 27-31, and 59

As detailed in Exhibit 1002 Exhibit B, claims 6, 7, 10, 13, 19, 21, 23, 27-31 and 59 add limitations reciting prime and boost timing (Claim 6 and 7), seroconversion rates (Claims 10 and 59), purified antigen (Claim 13), dosage (Claim

19), adjuvant (Claims 21 and 23), the lack of adverse events (Claims 27 and 28), and subjects (Claims 29-31). EX 1002, ¶¶70, 134, 136, 138, 141, 143, 145, 148, 150, 152, 154, 156, 158, and 160; Ex. 1001 123:9-16, 123:35-39, 123:63, 124:13-17, 124:21-23, 124:30-31, 124:49-61, 127:20-23. Thomas teaches each of these specific limitations and therefore anticipates these claims.

- Claim 6, Thomas teaches administration of two doses 4 weeks (28 days) apart (EX 1002, ¶135; EX 1004 41:7-8, 40:24-27)
- Claim 7, Thomas teaches a boost administration 28 days after prime (EX 1002, ¶137; EX 1004 41:7-8, 40:24-27);
- Claim 10, Thomas teaches the claimed seroconversion greater than 90% after day 28 from administration. EX 1002, ¶139-140; EX 1004, 42:4-7, 19 (Seroconversion at study day 57 [28 days from boost administration] was 92% across the Trial 2 Group (N=20) and ALL (N=55));
- Claim 13, Thomas teaches purified ZIKV antigen. EX 1002, ¶142; EX 1004 3:18-22 ("A novel purified, inactivated ZIKV is described, including compositions and vaccines comprising it, methods for producing the same, and methods of using the same …"), 18:28-30;
- Claim 19, Thomas teaches a 5 μg dose. EX 1002, ¶144; EX 1004 41:7-8 ("Two doses were administered at 0 and 28 days, 5 μg per dose…");

- Claims 21 and 23, Thomas teaches using an aluminum salt alum) adjuvant. EX 1002, ¶¶146-147, 149; EX 1004 28:18-25 ("Suitable inorganic adjuvants include, but are not limited to, for example, an aluminum salt, such as aluminum hydroxide gel (alum) or aluminum phosphate.") and 41:7-8;
- Claims 27 and 28, Thomas teaches that there were no serious adverse events, including a fever of 39° C. or higher, resulting from administration of the vaccine. EX 1002, ¶¶151, 153; EX 1004 41:16, (no "…serious adverse events related to vaccination…"), 43:14;
- Claim 29, Thomas teaches administering the vaccine to subjects from the Zika endemic region of Puerto Rico. EX 1002, ¶155; EX 1004 40:27-32 ("ZPIV will be administered in an area of Puerto Rico with a high rate of dengue virus priming as well as an areas having recently experienced a large Zika outbreak ..."");
- Claim 30, Thomas teaches that the mean age of the volunteers was 31.5 years which is within the claimed range of 30 to 49 years of age. EX 1002, ¶157; EX 1004 41:13-15;
- Claim 31, Thomas teaches that the subjects are female. EX 1002, ¶159; EX 1004 18:28-30, 41:12-13 (subjects being 48% female);

- Claim 59, Thomas teaches that Trial 3 Group exhibited a seroconversion rate of 100%, meeting the seroconversion rate limitation of at least 95% or 100% in claim 59. EX 1002, ¶161; EX 1004 42:6-7.

A POSA would have been motivated with a reasonable expectation of success to select each of these dependent claim features from options expressly taught by Thomas. (EX 1002, ¶¶135, 137, 139-140, 142, 146-147, 149, 151, 153, 155, 157, 159, 161). Accordingly, these claims are obvious.

B. GROUND II: Claim 11, 60, 61 and 62 Rendered Obvious Over Thomas.

1. Independent Claim 11

a. Elements [11A]-[11D]

Elements [11A]-[11D] are nearly identical to [1A]-[1D] except that [11D] recites that the vaccine or immunogenic composition "is administered one or more times" as opposed to "a first (prime) and second (boost) administration" in Claim 1. EX 1002, ¶¶75, 163-167; EX 1001 121:61-122:64, 123:40-52. Thomas' teaching of administration including a first (prime) and a second (boost) in Claim 1 teaches limitation [11D]. EX 1002, ¶¶117-118, 167; EX 1004 4:20-22, 7:32-33, 18:28-30, 41:7-8. For the reasons set forth above with respect to [1A]-[1D], Thomas teaches Elements [11A]-[11D]. EX 1002, ¶¶163-167.

b. Element [11E] wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after a single dose or prime administration a seroconversion rate of at least 60% in a population of at least 20 Zika virus seronegative subjects.

Thomas teaches a seroconversion rate of 92% (within at least 60%) for 55 humans 28 days after a boost administration. EX 1002, ¶169; EX 1004 42:4-7, Table at 42:19. Accordingly, Thomas teaches a seroconversion rate of at least 60% in a population of at least 20 Zika virus seronegative subjects. *Id.; See also* EX 1002, ¶168.

Thomas does not teach this rate after a single dose. EX 1002, ¶173. However, Thomas teaches a single dose is effective to provide 100% complete protection. EX 1002, ¶¶170, 174; EX 1004 4:15-22. Thomas teaches a slight rise in antibody after the first (prime) dose. EX 1002, ¶174; EX 1004 42:9-10, Table at 42:19 Day 1 after prime administration, GMT of 5.0 for N=55 volunteers. Thomas teaches that "[i]deally, only one dose is needed." EX 1002, ¶174; EX 1004 7:30-32. Thomas also teaches that a booster dose is not required. EX 1002, ¶174; EX 1004 4:15-22 and 7:11.

Thomas teaches that a POSA can determine without undue experimentation whether an initial dose is sufficient. EX 1002, ¶¶175-176; EX 1004 7:30-8:2. Thomas teaches that "someone skilled in this art can determine a safe and effective dose and schedule for this ZIKV PIV, as needed for persons of any age and size."

EX 1002, ¶¶175-176; EX 1004 4:24-28. Thomas teaches extrapolation to human use is reasonable for safe and effective dosages (e.g., a single dose, or a booster dose at 4 weeks as described below. EX 1002, ¶¶176; EX 1004 18:17-20.

Thomas teaches that administering a dose of an inactivated, whole Zika virus antigen vaccine including an adjuvant affects seroconversion. A vaccine dose including an inactivated, whole Zika virus antigen and an adjuvant would be recognized by POSA as a result-effective variable. Both the amount of antigen and adjuvant, as well as the adjuvant type, in the vaccine dose can be altered to affect seroconversion. EX 1002, ¶¶171, 172, 177.

It is within the level of POSA to use Thomas's method to arrive at a seroconversion rate for a population of at least 20 Zika virus seronegative subjects after a single or prime administration, as the method would require no modification. EX 1002, ¶175. Alternatively a POSA would have been motivated to modify/optimize the vaccine dose of Thomas Example 5 by either the amount of antigen and/or adjuvant or the type of adjuvant to induce a seroconversion rate of at least 60% in a population of at least 20 Zika virus seronegative subjects 14 and/or 28 days after a single dose or prime administration, because Thomas teaches that "[i]deally, only one dose is needed to effect protection against Zika infection for mammals, including humans." EX 1002, ¶176; EX 1004 7:3-32. Thomas teaches that "a single immunization of the vaccine can be shown to provide 100% complete

protection in susceptible mammals against challenge with ZIKV." EX 1002, ¶176; EX 1004 4:15-22.

A POSA would have been motivated to explore seroconversion rates after a single prime administration, because Thomas teaches that a single dose is effective and increasing the antibody titer after a single dose administration provides more effective protection earlier against the Zika virus, and would decrease the need for a booster administration. Further, the amount of antigen and/or adjuvant or the type of adjuvant make the vaccine dose a result-effective variable, as Thomas demonstrates that dose affects seroconversion after a first dose, as well as after a boost dose. EX 1002, ¶177.

A POSA would have had a reasonable expectation of successfully modifying/optimizing Thomas Example 5 to induce the claimed seroconversion rate after a single dose or prime administration, because Thomas teaches that "a single immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against challenge with ZIKV" (EX 1002, ¶178; EX 1004 4:15-22) and that single dose is safe and effective. EX 1002, ¶178; EX 1004 18:17-20. A seroconversion rate of at least 60% results merely from routine optimization of the amount of antigen and/or adjuvant or the type of adjuvant in the vaccine based on Thomas teaching that vaccine dose is a result-effective variable affecting seroconversion. EX 1002, ¶178.

Accordingly, claim 11 is obvious in view of Thomas. EX 1002, ¶¶169-179.

2. Dependent Claims 60-62

Claims 60-62 depend from claim 11 and the additional limitations of these claims increase the seroconversion rate to 80% (claim 60), 90% (claim 61), and 95% (claim 62). EX 1002, ¶¶180-181, 187-188, and 194-195; EX 1001 127:24-128:9. Thomas teaches in Example 5 a seroconversion rate of 92% for 55 humans at day 57. EX 1002, ¶¶169, 181, 188, 195; EX 1004 42:4-7, Table at 42:19. For the same reason as above with respect to [11E], it is within the skill of POSA to use Thomas's method to arrive at the seroconversion rates of claims 60, 61 and 62 using a single or prime administration. EX 1002, ¶¶169-179, 181, 188, 195. A POSA would have been motivated to modify/optimize the dose of Thomas Example 5 by either the amount of antigen and/or adjuvant or the type of adjuvant to induce a seroconversion rate of at least that claimed in claims 60-62 after a single dose or prime administration, because Thomas teaches that: "[i]deally, only one dose is needed to effect protection against Zika infection for mammals, including humans." (EX 1004 7:30-32); and "a single immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against challenge with ZIKV." (EX 1004 4:15-22); and based on animal models in the field of flavivirus PIVs, a single dose is a safe and effective dosage (EX 1004 18:17-20). EX 1002, ¶¶183, 190, 197, 198; EX 1004, 42:4-23.

A POSA would have been motivated to explore seroconversion rates after a single or prime administration because Thomas teaches that a single dose is effective and increasing the antibody titer after a single dose provides more effective protection earlier against the Zika virus, and would decrease the need for a booster. The amount of antigen and/or adjuvant or the type of adjuvant make the vaccine dose optimizable as a result-effective variable, as Thomas demonstrates that vaccine dose affects seroconversion after a first dose. EX 1002, ¶¶184, 191, 199.

POSA would have had a reasonable expectation of successfully modifying/optimizing the vaccine dose of Thomas Example 5 to induce a seroconversion rate of at least the percentages claimed in claims 60-62 after a single dose or prime administration, because Thomas teaches that "a single immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against challenge with ZIKV" (EX 1004 4:15-22) and that a single dose is a safe and effective dosage. EX 1004 18:17-20. Achieving a seroconversion rate of at least the claimed percentages in claims 60-62 results from routine optimization of the amount of antigen and/or adjuvant or the type of adjuvant in the vaccine dose based on Thomas teaching that vaccine dose is a result-effective variable affecting seroconversion. EX 1002, ¶¶185, 192, 200.

Accordingly, claims 60-62 are obvious in view of Thomas. EX 1002, ¶¶180-201.

C. GROUND III: Claims 8, 12, 14, 22, and 24 are Rendered Obvious by Thomas and Barbero

1. Motivation to Combine

Thomas and Barbero are in the same field of endeavor, i.e. making, testing and using purified, inactivated whole virus antigen Zika vaccines for use in humans. EX 1002, ¶¶205, 217, 230, 242, 256. Thomas and Barbero describe well-known alternatives. POSA would have looked to the art for examples of well-known alternatives as a matter of routine skill and would have been aware of Barbero. *Id.* POSA would have been motivated to select such known alternatives with a reasonable expectation of success as routine optimization of result effective variables or as routine substitution of known methods with no unexpected results. *Id.*

2. Claim 8

Claim 8 depends from claim 1 and requires generation of neutralizing antibodies titers to Zika virus 14 or 28 days after the boost in a subject of greater than 1000, as determined by PRNT. EX 1002, ¶203; EX 1001 123:17-23.

As shown above in Ground I, Thomas teaches each and every limitation of claim 1. *See also* EX 1002, ¶204.

Further, Thomas teaches to determine generation of neutralizing antibodies using a "high-throughput ZIKV microneutralization (MN) assay" as described in Larocca et al. EX 1002, ¶206; EX 1004 34:26-28. Thomas reports peak titers 14

days after boost between 500 and 1000. EX 1002, ¶206; EX 1004 42:12-13. Figure 21 shows that at day 57 "[a]pproximately 10% of the cohort has titers of 1000." EX 1002, ¶206; EX 1004 15:22-27. Figure 20 demonstrates geometric mean antibody titers determined by the MN_{50} assay (EX 1004 15:20-21) and shows that group Z0001 5 mcg ZPIV generated neutralizing antibodies greater than 1000, as demonstrated by the error bars at around day 43 and day 57. Ex. 1002, ¶206. Figure 21 shows that group Z0001 5 mcg ZPIV generated neutralizing antibodies greater than 1000 at day 43 (2 weeks or 14 days post boost) and at day 57 (4 weeks or 28 days post boost). EX 1002, ¶206; EX 1004, Fig. 21. Accordingly, Thomas meets the limitation of "wherein 14 and/or 28 days after the boost administration of the vaccine or immunogenic composition the generation of neutralizing antibodies titers to Zika virus in a subject of greater than 1000," albeit by using the microneutralization (MN) assay. EX 1002, ¶206; EX 1004 3:2-5.

Thomas does not measure by the PRNT. Barbero teaches that "seroconversion of a subject is assessed by performing… PRNT." EX 1002, ¶207; EX 1005 22:25-35, 114:9-30 (describing use of PRNT in mice). Barbero teaches use of the microneutralization (MN) assay. EX 1002, ¶208; EX 1005 114:32-35. Accordingly, Barbero teaches both the microneutralization assay and the PRNT to assess neutralizing antibody titer. EX 1002, ¶207-208.

The PRNT and microneutralization (MN) assay are valid methods of

measuring the antibody titer, which reflects seroconversion. EX 1002, ¶209. Liu reports good correlation was observed between the two assays. EX 1002, ¶209; EX 1012 p. 73, 76, 77. Since Barbero teaches to use both the microneutralization assay and the PRNT assay, POSA would have understood from Barbero that the methods were interchangeable and would produce similar results regarding antibody titer reflecting seroconversion. EX 1002, ¶209.

A POSA would apply the PRNT method of Barbero to determine neutralizing antibody titers using routine skill because Barbero teaches how to use the PRNT assay to determine neutralizing antibody titers. EX 1002, ¶¶209-211.

POSA would have been motivated to use PRNT instead of MN50 because Barbero teaches PRNT and MN50 are known methods for measuring neutralizing antibody titers from a Zika vaccine, as an indication of seroconversion. POSA would have been motivated to achieve a higher neutralizing antibody titer, e.g., by adjusting the dosage of antigen, to obtain the desired immune protection. EX 1002, ¶¶205, 212.

POSA would have had a reasonable expectation of successfully using PRNT instead of MN50 because Barbero teaches successful use of each method to determine neutralizing antibody titers from a Zika vaccine. Substitution of one known method for another known method to achieve the same purpose does not result in patentability absent unexpected results. PRNT is used for the same objective

as MN50, *i.e.*, to measure neutralizing antibody titers, and produces no unexpected result. EX 1002, ¶213.

Accordingly, claim 8 is obvious in view of Thomas and Barbero. EX 1002, ¶214

3. Claim 12

Claim 12 depends from 1 and requires 14 and/or 28 days after boost, geometric mean neutralizing antibody titers ("GMT") in a population of at least 20 Zika virus seronegative subjects, which are at least 10 times higher than the GMT induced 28 days after the prime administration, as determined by the PRNT. EX 1002, ¶¶215-216, EX 1001 123:53-62.

Thomas teaches Geometric Mean Antibody Titers that are greater than 10 times higher compared to 28 days (day 29) after the first (prime) administration, albeit using the MN50 assay. EX 1002, ¶¶218-219; EX 1004 3:2-5, 42:4, 42:19-20, Table.

Thomas does not determine seroconversion and geometric mean neutralizing antibody titers by PRNT. EX 1002, ¶220. However, as detailed above with respect to claim 8, Barbero teaches determining seroconversion using PRNT and the microneutralization assay and the assays have good correlation. POSA would have been motivated to use PRNT instead of MN50 because Barbero teaches the methods are interchangeable. EX 1002, ¶¶205-209, 211, 212, 220-222, 224, 225. POSA

would have had a reasonable expectation of successfully using PRNT instead of MN50 because Barbero teaches successful use of each method. EX 1002, ¶¶213, 226. The substitution of one known method for another to achieve the same purpose is not patentable.

Accordingly claim 12 is obvious in view of Thomas and Barbero. EX 1002, ¶¶223, 227.

4. Claim 14

Claim 14 depends from claim 13 which depends from claim 1 and recites that the main peak of the purified antigen when analyzed by size exclusion chromatography is more than 85% of the total area under the curve. EX 1002, ¶¶228-229, EX 1001, 123:62-67.

Thomas teaches that ZIKV can be purified according to FDA guidelines. EX 1002, ¶231; EX 1004 3:2-5, 3:23-27. Thomas teaches that "[p]urification of the ZIKV may be performed by physical or chemical techniques or any combinations thereof that are routinely used in the art. Physical methods … include but are not limited to size-exclusion chromatography, and the like." EX 1002, ¶231; EX 1004 20:19-24.

Thomas does not teach the main peak of the antigen being more than 85% of the total area under the curve in size exclusion chromatography, but this is a known and admitted manner of determining purity. EX 1002, ¶¶231-232; EX 1001 37:16-

19. Barbero teaches "the residual impurity of the final virus preparation with respect to all impurities in the crude harvest is less than 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, preferably less than 5% as determined by SEC-HPLC (Size Exclusion Chromatography – HPLC)." EX 1002, ¶232; EX 1005 14:29-31. Since Barbero teaches an impurity of less than 10% as determined by size exclusion chromatography, Barbero teaches a purity of greater than 90% as determined by size exclusion chromatography. EX 1002, ¶¶232-234.

A POSA would have been motivated to obtain a desired purity level for an antigen preparation for vaccination that is more than 85%, because Barbero teaches greater than 90% purity as determined by size exclusion chromatography. POSA would have had a reasonable expectation of successfully using size exclusion chromatography because Barbero teaches its successful use. It is not inventive to discover the optimum or workable ranges by routine experimentation. EX 1002, ¶¶236-238.

Accordingly, claim 14 is obvious in view of Thomas and Barbero. EX 1002, ¶¶235, 239.

5. Claim 22

Claim 22 depends from claim 21 and recites between 100 μg to about 600 μg of an aluminum salt adjuvant. EX 1002, ¶¶240-241; EX 1001 124:21-29.

Thomas teaches an aluminum salt adjuvant (EX 1002, ¶243; EX 1004 28:18-24) in a suitable amount (EX 1004 17:1). Thomas teaches to POSA that amount of adjuvant is a result-effective variable affecting immune response. EX 1002, ¶243; EX 1004 28:19-22. Barbero teaches a suitable amount of 500 μg of an aluminum hydroxide adjuvant per ml of ZIKV vaccine. EX 1002, ¶244; EX 1005 112:1-4.

Optimizing the amount of adjuvant is within the routine skill of POSA. POSA would have been motivated to use the 500 μg of Barbero with a reasonable expectation of success because Thomas teaches the use of adjuvants in a suitable amount and selection of amount of adjuvant is routine optimization of a result-effective variable affecting immune response, i.e. seroconversion. EX 1002, ¶¶246-248; EX 1004 17:1, 28:18-22.

Accordingly claim 22 is obvious in view of Thomas and Barbero. EX 1002, ¶¶245, 249.

6. Claim 24

Claim 24 depends from claim 21 which depends from claim 1 and recites that the vaccine further includes an aluminum salt adjuvant where at least 75% of the antigen is adsorbed on the adjuvant. EX 1002, ¶¶250-251; EX 1001 124:32-35.

Thomas teaches an aluminum salt adjuvant (EX 1002, ¶252; EX 1004 3:2-5, 4:31-5:1, 28:18-24) in a suitable amount (EX 1004 17:1). Thomas teaches POSA that amount of adjuvant is a result-effective variable affecting immune response. EX

1002, ¶¶252-255; EX 1004 41:6-81:24-29, 1:41-43, 4:24-28, 28:19-22, 31:27-28, 41:28-42:3. Barbero teaches greater than 95% adsorption of Zika virus particles to an aluminum salt adjuvant. EX 1002, ¶257; EX 1005 112:1-7.

Optimizing the amount of Zika virus adsorbed to an aluminum salt adjuvant is within the routine skill of POSA. POSA would have been motivated to optimize the amount of Zika virus adsorbed to an aluminum salt adjuvant with a reasonable expectation of success because Thomas teaches the use of adjuvants in a suitable amount, Barbero teaches greater than 95% adsorption and selection of the amount of adsorption is routine optimization of a result-effective variable affecting immune response, i.e. seroconversion. EX 1002, ¶¶258-262; EX 1005 112:4-7.

Accordingly claim 24 is obvious in view of Thomas and Barbero. EX 1002, ¶¶251, 263.

D. GROUND IV: Claim 25 is Obvious Over Thomas and Murata

1. Motivation to Combine

Thomas and Murata are in the same field of endeavor, i.e. making, testing, and using purified, inactivated whole virus antigen vaccines for use in humans. EX 1002, ¶270. POSA would have looked to the art for examples of isolating and purifying Zika virus as a routine matter and would have been aware of Murata. *Id.*

2. Dependent Claim 25

Claim 25 depends from claim 1 and recites that the Zika virus is a plaque purified clonal Zika virus isolate. EX 1002, ¶265; Ex. 1001 124:36-38.

As discussed in Ground I, Thomas teaches all the limitations of claim 1. EX 1002, ¶266. Thomas also teaches purifying ZIKV concentrate. EX 1002, ¶267; EX 1004 5:25-32, 6:4-10, 22:21-22, 23:10-21, 32:1-3. Thomas teaches that "ZIKV can be purified to be free of pathogens and adventitious agents." EX 1002, ¶268; EX 1004 3:23-36, 19:15-16. Thomas teaches that "[p]urification of the ZIKV may be performed by physical or chemical techniques or any combinations thereof that are routinely used in the art." EX 1002, ¶¶268, 269; EX 1004 20:19-20.

Murata teaches use of plaque purification to purify virus. EX 1002, ¶¶271-272; EX 1006 p. 3156, 3158. Murata uses plaque purification to purify influenza virus from the adventitious agents of replicating and non-replicating viruses. EX 1002, ¶¶271-272; EX 1006 p. 3157-3158, sections 3.2 and 3.3 and "Plaque purification is an approach unencumbered by intellectual property constraints …" EX 1002, ¶¶271-272; EX 1006 p. 3159.

Using plaque purification is within the routine skill of POSA. POSA would have been motivated to use plaque purification with a reasonable expectation of success because Thomas teaches to purify virus using routine methods and Murata teaches plaque purification is a routine method and the substitution of one known

method for another does not result in patentability absent unexpected results. EX 1002, ¶¶273-275; EX 1004 3:24-26; 20:19-20; EX 1006 p. 3158-3159.

Accordingly claim 25 is obvious in view of Thomas and Murata. EX 1002, ¶276.

E. GROUND V: Claims 5, 15-18, and 20 are Obvious Over Thomas in view of NCT02952833

1. Motivation to Combine

Thomas and NCT02952833 are in the same field of endeavor, i.e. making, testing, and using purified, inactivated whole virus antigen vaccines for use in humans. EX 1002, ¶¶282, 299, 314, 330, 345, 360. A POSA would have looked to the art for examples of dosage amounts as a routine matter and would have been aware of NCT02952833. *Id.*

2. Claim 5

Claim 5 depends from claim 1 and recites a dose of 10 μg administered one time. EX 1002, ¶¶278, 281; EX 1001 123:6-8.

Thomas teaches administering a 5 μg dose of a Zika virus antigen two times. EX 1002, ¶¶116, 279; EX 1004 41:7-8: "Two doses were administered at 0 and 28 days, 5 μg per dose, and adjuvanted with alum."

Thomas teaches "someone skilled in this art can determine a safe and effective dose and schedule for this ZIKV PIV, as needed for persons of any age and size." EX 1002, ¶279; EX 1004 4:24-28. Thomas teaches that from what is already known

in the field of flavivirus PIVs, extrapolation to human use is reasonable for safe and effective dosages (e.g., a single dose) EX 1002, ¶279; EX 1004 4:24-28, 18:17-20, 42:4-28. Thomas further teaches at EX 1004 40:18-22 that in "Trial 2 ZPIV is explored across a range of antigen doses in an attempt to define the optimal dose of antigen as well as lower limits of antigen concentration required to effectively immunize a recipient." Thomas further teaches at EX 1004 40:23-26 that in "Trial 3 ZPIV is explored across a range of schedules in an attempt to define the optimal dosing schedule to effectively immunize a recipient and the potential requirement for booster doses to create durable immune responses." EX 1002, ¶¶283, 290. Thomas demonstrated that two 5 μg doses (a total of 10 μg) were safe and provided significant immune response. EX 1002, ¶¶287, 291; EX 1004, 4:24-28. Thomas demonstrated a greater immunological response and, therefore greater protection, after a second (boost) 5 μg dose. EX 1002, ¶291; EX 1004 42:9-11.

Accordingly, a vaccine dose including an inactivated, whole Zika virus antigen and an adjuvant which results in seroconversion and, a seroconversion rate, would be recognized by POSA as a result-effective variable. Both the amount of antigen and adjuvant, as well as the adjuvant type, in the vaccine dose can be altered to affect seroconversion, and also provide a safe and effective dose and schedule for persons of any size and age. EX 1002, ¶280.

NCT02952833 evaluates three dose levels of "5.0 mcg, 2.5 mcg and 10mcg of ZPIV" that are administered "by intramuscular (IM) injection on Days 1 and 29." EX 1002, ¶284; EX 1011 p. 6. "The Primary objectives of this study are to 1. Assess the safety and reactogenicity of a homologous prime boost regimen of ZPIV given at three different dose levels …" *Id.* "The secondary objectives of this study are to 1. Assess … seroconversion rates, and peak Geometric Mean Titer (GMT) …" *Id.*

Eligible study participants in Group 1 (5.0 mcg ZPIV), Group 2 (2.5 mcg ZPIV) and Group 3 (10.0 mcg ZPIV) included both men and women (nonpregnant) between the ages of 18 and 49. EX 1002, ¶¶285, 287; EX 1011 p. 8, 11. Experimental Group 3 will be administered 10 mcg ZPIV (aluminum hydroxide adjuvant) in a homologous prime-boost regimen on Day 1 and Day 29. Experimental Group 3 includes 25 subjects of which 5 are given a placebo. EX 1002, ¶285; EX 1011 p. 8. The Peak GMT overall and by dosage group is measured by ZIKV ELISA and neutralization assay. EX 1002, ¶286; EX 1011 p. 10. The proportion of subjects overall and by dosage group that seroconvert to ZIKV at each post-vaccination visit is assessed by ELISA responses in comparison with baseline and by neutralization titers in comparison with baseline. *Id*.

Optimizing the dose amount and schedule of ZIKV is within the routine skill of POSA. EX 1002, ¶¶289-293. POSA would have been motivated to optimize the dose amount to 10 μg and administer one time, with a reasonable expectation of

success because Thomas teaches to optimize dose amounts and schedules. NCT02952833 teaches a dose amount of 10 μg, dose is a result-effective variable, and the selection of the dose amount and schedule is routine optimization of a result-effective variable affecting immune response, i.e. seroconversion. POSA would have reasonably expected that the higher 10 μg dose, for example as administered as the boost, would provide a similar if not greater immunological response and protection against Zika virus compared to a 5 μg boost dose, because the higher antigen content of the 10 μg boost dose would be expected to elicit a greater immunological response compared to a 5 μg boost dose. *Id*. In general POSA would understand that a greater amount of antigen exposure leads to a stronger and more rapid immune response. EX 1002, ¶280.

Accordingly claim 5 is obvious in view of Thomas and NCT02952833. EX 1002, ¶¶277, 288, 294.

3. Dependent Claims 15-18, and 20

Claims 15-18, and 20 depend from claim 1 and like claim 5 also recite a dose amount with a lower limit of about 10 μg. (EX 1002, ¶¶ 295, 310, 326, 341, 356) and are obvious for the same reasons as claim 5 discussed above. EX 1002, ¶¶277, 296-309, 311-325, 327-340, 342-355, 357-370. NCT02952833 teaches a dose amount of 10 μg within the claimed ranges, dose is a result-effective variable, and

the selection of the dose amount is routine optimization of a result-effective variable affecting immune response, i.e. seroconversion. *Id*.

F. GROUND VI: Claims 26 and 63 are Obvious Over Thomas and NCT02952833 and further in view of Barbero

1. Motivation to Combine

Thomas, NCT02952833 and Barbero are in the same field of endeavor, i.e. making, testing, and using purified, inactivated whole virus antigen vaccines for use in humans. EX 1002, ¶¶282, 299, 314, 330, 345, 360, 384. A POSA would have looked to the art for examples of dose, adjuvants and other components of a vaccine such as buffers and sugars, as a matter of routine skill and would have been aware of Barbero. EX 1002, ¶384.

2. Independent Claim 26

Elements [26A]-[26C] are nearly identical to [1A]-[1C] except that [26C] does not require that administration of the antigen be "as a first (prime) and second (boost) administration" as in [1C]. EX 1002, ¶¶372-373, EX 1001 124:39-45. Accordingly for the reasons set forth above with respect to [1A]-[1C], Thomas teaches Elements [26A]-[26C]. EX 1002, ¶374.

Element [26D] adds requirements that the vaccine comprises: (1) a dose of about 10 μg of purified inactivated whole virus; (2) 200 μg aluminum hydroxide; (3) a buffer; and (4) optionally a sugar. EX 1002, ¶¶76, 373-374, Thomas teaches to use suitable amount of aluminum hydroxide adjuvant (EX 1004 28:18-25 "Suitable

inorganic adjuvants include, but are not limited to, for example, an aluminum salt, such as aluminum hydroxide gel (alum) or aluminum phosphate …"); a sugar (EX 1004 28:27 "acylated sugars" and EX 1004 30:20 a "sucrose solution"); and a buffer (EX 1004 30:18-21 "pharmaceutically acceptable buffer solutions."). EX 1002, ¶374.

Thomas does not teach 10 μg of purified inactivated whole virus. EX 1002, ¶375. However, adopting the analysis of claim 5 above, POSA would have been motivated to optimize the dose amount to 10 μg with a reasonable expectation of success because Thomas teaches to optimize dose amounts, NCT02952833 teaches a dose amount of 10 μg, dose is a result-effective variable, and the selection of the dose amount of 10 μg is routine optimization of a result-effective variable affecting immune response, i.e. seroconversion. A POSA would have reasonably expected that the higher 10 μg dose would provide a similar if not greater immunological response and protection compared to a 5 μg dose, because the higher antigen content of the 10 μg dose would be expected to elicit a greater immunological response. In general POSA would understand that a greater amount of antigen exposure leads to a stronger and more rapid immune response. EX 1002, ¶¶376-382; EX 1004 3:2-5, 4:24-28, 42:9-11; EX 1011 p. 6, 8, 10, 11.

Thomas does not teach 200 μg aluminum hydroxide adjuvant. EX 1002, ¶383.

Adopting the analysis of claim 22 above, Thomas teaches an aluminum salt adjuvant (EX 1002, ¶385; EX 1004 28:18-24) in a suitable amount (EX 1002, ¶385; EX 1004 17:1). Thomas teaches the amount of adjuvant is a result-effective variable affecting immune response. EX 1002, ¶¶385, 389; EX 1004 p. 28:19-22. Barbero teaches a suitable amount of 500 μg of an aluminum hydroxide adjuvant per ml of ZIKV vaccine. EX 1002, ¶386; EX 1005 112:1-4.

Optimizing the amount of adjuvant is within the routine skill of POSA. POSA would have been motivated to use the 500 μg of Barbero with a reasonable expectation of success because Thomas teaches the use of adjuvants in a suitable amount and the selection of amount of adjuvant is routine optimization of a result-effective variable. EX 1002, ¶¶387-389; EX 1004 17:1, 28:18-22.

POSA would modify the 500 μg to 200 μg as a matter of routine optimization using ordinary skill, simply by lowering the amount of adjuvant combined with the inactivated whole Zika virus antigen. POSA would have had a reasonable expectation of success because Thomas teaches to use "a suitable amount of adjuvant" (EX 1004 17:1) and Barbero teaches that inactivated Zika virus will adsorb to aluminum hydroxide so as to function as an adjuvant. POSA would have understood that the inactivated Zika virus antigen adsorbed to 200 μg aluminum hydroxide would affect seroconversion rate. Where the general conditions of a claim are disclosed in the prior art, e.g., an amount of aluminum hydroxide adjuvant in a

vaccine dose, it is not inventive to discover the optimum or workable ranges by routine experimentation. EX 1002, ¶¶389-390.

Accordingly claim 26 is obvious in view of Thomas, NCT02952833, and Barbero. EX 1002, ¶¶371, 391.

3. Dependent Claim 63

Claim 63 depends from claim 26 and recites that the sugar is sucrose. EX 1002, ¶¶392, 394; EX 1001, 128:11. Thomas teaches that the sugar is sucrose. EX 1002, ¶395; EX 1004 30:20 (a "sucrose solution"). Accordingly claim 63 is rendered obvious in view of Thomas, NCT02952833, and Barbero. EX 1002, ¶¶393, 395-396.

G. GROUND VII: Claims 9, 32,33, 35, 36, 38, 39, 41, 47, 49, 51, 55-58, and 65-67 are Obvious Over Thomas in view of Faucette

1. Motivation to Combine

Thomas and Faucette are in the same field of endeavor, i.e. making, testing, and using purified, inactivated whole virus antigen vaccines for use in humans. EX 1002, ¶412. A POSA would have looked to the art for examples of adoptive transfer of vaccine-induced neutralizing antibodies from a pregnant woman to a fetus and would have been aware of Faucette. *Id.*

2. Independent Claim 9

a. Element [9A] A method of vaccinating against Zika virus disease in a fetus or newborn in need thereof, the method comprising

Element [9A] is nearly identical to [1A] except that [9A] further requires that the human subject is a fetus or newborn. EX 1001, 121:61-62, 123:24-25; EX 1002 ¶¶74, 398. For the reasons set forth above with respect to [1A], Thomas teaches Element [9A] being a human subject. EX 1002 ¶399; EX 1004 Abstract, 4:15-18, 5:2-6, 5:8-9, 6:33-7:2, 18:16-20, 42:21-43:1. Thomas teaches that the human subject can be a fetus or newborn. EX 1002 ¶¶400-402; EX 1004 2:13-24 (need for a Zika virus vaccine that protects pregnant women and fetuses), EX 1004 3:2-12 (mechanism of action administering a vaccine to a pregnant woman "could include … protecting the fetus during maternal infection (infection during pregnancy occurs but vaccine induced immunity prevents fetal infection from taking hold."), 4:2-7, 18:26-30. Accordingly, Thomas teaches element [9A]. EX 1002 ¶403.

b. Element [9B] administering to a pregnant human subject a vaccine or immunogenic composition comprising a dose of from about 1 µg to about 40 µg of an antigen from a Zika virus

Element [9B] is nearly identical to [1B] except that [9B] further requires that the administration be to a pregnant human subject. EX 1001, 121:63-65, 123:26-28; EX 1002, ¶398. For the reasons set forth above with respect to [1B] and just above with respect to [9A], Thomas teaches Element [9B]. EX 1002, ¶404; EX 1004 41:7-8.

c. Element [9C] wherein the antigen is an inactivated whole virus and Element [9E] wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration,

The combination of Elements [9C] and [9E] is identical to [1C]. EX, 1002 ¶398. Accordingly for the reasons set forth above respect to [1C] Thomas teaches Elements [9C] and [9E]. EX 1002, ¶¶405-406, 421-22; EX 1004 18:28-30.

d. Element [9D] wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn,

Thomas does not expressly teach that the pregnant human adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn. Thomas does teach a mechanism of action administering a vaccine to a pregnant woman "could include … protecting the fetus during maternal infection (infection during pregnancy occurs but vaccine induced immunity prevents fetal infection from taking hold)." EX 1004 3:2-12; EX 1002, ¶¶408, 413, 415; *see also* EX 1004 2:13-24, 4:2-7, 18:26-30, 39:15-16.

Thomas further teaches adoptive transfer studies in rhesus monkeys and in mice similar to that described in the '802 patent. EX 1002, ¶409. Thomas teaches that "[a]doptive transfer studies are conducted demonstrating that the ZIKV PIV created antibodies and these antibodies protect against infection." EX 1004 33:8-10. Thomas states that "taken together, these data demonstrated that purified IgG

from ZIKV PIV vaccinated rhesus monkeys provided passive protection following adoptive transfer in both rodents and primates." EX 1004 38:24-26. Thomas concludes that "[t]he adoptive transfer studies demonstrate that vaccine-elicited antibodies are sufficient for protection against ZIKV challenge. Moreover, passive protection in mice and rhesus monkeys is observed at relatively low antibody titers (Figs. 11, 12). Such antibody titers are likely achievable by these vaccine platforms in humans, thus raising optimism for the development of a ZIKV vaccine for humans." EX 1004 38:30-39:2; *See also* EX 1002, ¶409, EX 1004, 33:21-25, 38:17-22.

Thomas teaches with respect to the adoptive transfer data in mice and rhesus monkeys that "taken together, these data are reasonably predictive for how ZIKV vaccines will perform in humans." EX 1004 39:15-16; See also EX 1002, ¶¶410-411; EX 1004 8:24-26, 26:26-30, 38:5-22, 38:30-39:2.

Faucette teaches benefits of immunizing pregnant women are to "generate maternal immune protection as well as elicit the production and transfer of antibodies cross the placenta … to provide early infant protection" (EX 1007 Abstract, p. 2549, 2552, Introduction) and that "[m]aternal vaccination aims to protect both the mother and neonate." EX 1007 p. 2550. Faucette further teaches that "maternally derived antibodies have a profound and long-lasting effect in promoting the development of infant B cells and their antibody diversification and production,

as well as the selection against potentially autoreactive B cell populations." EX 1007, p. 2552; See also EX 1002, ¶¶414-415; EX 1007, pp. 2549-2550, 2552.

Accordingly, Thomas and Faucette teach this limitation of claim 9. EX 1002, ¶416.

Administering a Zika virus vaccine to a pregnant woman is within the routine skill of POSA. EX 1002, ¶417.

POSA would have been motivated to vaccinate a pregnant woman to adoptively transfer a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn (EX 1002, ¶418) because Thomas teaches a need for a vaccine to protect both a pregnant woman and the fetus and to vaccinate the pregnant mother provides protection of the fetus and newborn to Zika virus infection. EX 1004 2:13-24, 4:2-7, 18:26-30. Faucette teaches immunizing pregnant women to "generate maternal immune protection as well as elicit the production and transfer of antibodies cross the placenta … to provide early infant protection." EX 1007 Abstract, p. 2549.

POSA would have had a reasonable expectation of successfully vaccinating a pregnant woman to adoptively transfer a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn (EX 1002, ¶419) because Thomas provides animal studies of successful adoptive transfer. EX 1004 38:5-39:2. Faucette teaches that maternal antibody transfer occurs across the placenta by

neonatal Fc receptor (FcRn) expressed on trophoblasts across, conferring fetal and early infant immune protection (Fig. 1A). EX 1007 p. 2552. Faucette acknowledges that inactivated virus vaccines have successfully been used to immunize pregnant women. EX 1007 p. 2549.

Based on the above, Claim 9 is obvious in view of Thomas and Faucette. EX 1002, ¶¶420, 423.

3. Independent Claims 41 and 49, 57, and 58

The limitations of Claims 41, 49, 57, and 58 except for the purified antigen (claim 41), the vaccine having an aluminum salt adjuvant (claim 49), the pregnant human subject being from a Zika endemic region or from a Zika non-endemic region travelling to an endemic region (claim 57), and the pregnant human subject being 18 to 29 years of age or 30 to 49 years of age (claim 58) are all found in independent claim 9. EX 1002, ¶¶74, 436, 437, 440, 441, 448-451. A POSA would have a motivation to combine Thomas and Faucette with a reasonable expectation of success for the reasons discussed with respect to claim 9. The additional limitations of Claims 41, 49, 57, and 58 are the same limitations recited in other previously discussed dependent claims taught and rendered obvious by Thomas as detailed above with respect to Claim 13 (EX 1002, ¶437), Claim 21 (EX 1002, ¶441), Claim 29 (EX 1002, ¶449), and Claim 30 (EX 1002, ¶451). Accordingly, claims 41, 49, 57 and 58 are obvious over Thomas and Faucette. EX 1002, ¶¶437, 441, 449, 451.

4. Dependent Claims 32, 33, 35, 36, 38, 39, 51, and 55-56

Claims 32, 33, 35, 36, 38, 39, 51, and 55-56 depend from claim 9 and add limitations that are the same as those recited in previously discussed dependent claims wherein each limitation is taught or rendered obvious by Thomas as shown above. The following table sets forth where those limitations appear in other dependent claims and are taught or rendered obvious by Thomas:

Current Claim	Limitation Duplicative of Claim Limitation Discussed Above
32	Claim 3 – EX 1002, ¶¶424-425
33	Claim 4 – EX 1002, ¶¶426-427
35	Claim 6 – EX 1002, ¶¶428-429
36	Claim 7 – EX 1002, ¶¶430-431
38	Claim Limitation [1D] – EX 1002, ¶¶432-433
39	Claim Limitation [11E] – EX 1002, ¶¶434-435
47	Claim 13 and Claim Limitation [1B] – EX 1002, ¶¶438-439
51	Claim 23 – EX 1002, ¶¶442-443
55	Claim 27 – EX 1002, ¶¶444-445
56	Claim 28 – EX 1002, ¶¶446-447

As previously demonstrated, claim 9 is rendered obvious by Thomas and Faucette. As detailed above, Thomas teaches or renders obvious the additional limitations in claims 32, 33, 35, 36, 38, 39, 51, 55 and 56. Accordingly the combination of Thomas and Faucette render these claims obvious.

5. Dependent Claims 65-67

Claim 65 depends from claim 39 which depends from claim 9 and increases the seroconversion rate of claim 39 from at least 60% to 70%. EX 1002, ¶452, EX 1001 128:13-17. The analysis of claim 39 and claim 11 above applies equally to this claim. Thomas renders this feature obvious for the same reason discussed with respect to claims 11 and 39. EX 1002, ¶453. Thomas Example 5 discloses a seroconversion rate of 92% for 55 humans at day 57 after a boost administration. A seroconversion rate of 92% is above the claimed value of 70%. As discussed with respect to claims 11 and 39, a vaccine dose would be recognized by a POSA as a result-effective variable as the antigen and adjuvant, as well as the adjuvant type, can be altered to affect seroconversion rate. *Id.*, EX 1004, 42:4-23.

Thomas does not teach a seroconversion rate of 70% in a population of at least 20 Zika virus seronegative subjects 14 and/or 28 days after a single dose or prime administration. EX 1002, ¶454.

Thomas does teach 100% complete protection after a single immunization of the ZIKV vaccine. EX 1002, ¶455; EX 1004 4:15-22. Thomas teaches a slight rise

in antibody after the first (prime) dose of vaccine. EX 1002, ¶455; EX 1004 42:9-10. Thomas teaches that "[i]deally, only one dose is needed to effect protection against Zika infection for mammals, including humans." EX 1002, ¶455; EX 1004 7:30-32. Thomas also teaches that a booster is not required. EX 1002, ¶455; EX 1004 4:15-22, 7:11. Thomas teaches a 92% seroconversion rate in a population of at least 20 Zika virus seronegative subjects at day 57 after a boost administration. EX 1002, ¶455; EX 1004 42:4-7.

POSA would have been motivated to explore seroconversion rates after a single dose or prime administration with the goal of creating a vaccine with a seroconversion rate of 70% in a population of at least 20 Zika virus seronegative subjects 14 and/or 28 days after a single dose or prime administration, because Thomas teaches that a single dose is effective and increasing the antibody titer after a single dose provides more effective protection earlier against the Zika virus, and would decrease the need for a booster administration. Further, the amount of antigen and/or adjuvant or the type of adjuvant make the vaccine dose a result-effective variable, as Thomas demonstrates that vaccine dose affects seroconversion after a first (prime) dose. EX 1002, ¶¶456-458; EX 1004 4:15-22, 7:30-32, 18:17-20, 42:4-10.

POSA would have had a reasonable expectation of successfully achieving a seroconversion rate of 70% after a single dose because Thomas teaches that "a single

immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against challenge with ZIKV" (EX 1004 4:15-22) and that a single dose is a safe and effective dosage. EX 1004 18:17-20. Thomas demonstrated that a seroconversion rate of 92% was achieved, and so POSA would reasonably expect that a lower seroconversion rate of 70% could be achieved from routine optimization of the amount of antigen and/or adjuvant or the type of adjuvant in the vaccine dose based on Thomas teaching that vaccine dose is a result-effective variable. EX 1002, ¶459.

Accordingly, claim 65 is obvious in view of Thomas and Faucette for essentially the same reasons that claim 9 and 39 are obvious in view of Thomas and Faucette. EX 1002, ¶460.

Dependent claims 66-67 depend from claim 39 and add limitations increasing the seroconversion rate to 80% and 90% respectively that are the same as limitations recited in previously discussed dependent claims where those additional limitations are rendered obvious by Thomas for the reasons set forth in grounds previously discussed. The following table sets forth where those limitations appear in previously discussed claims rendered obvious by Thomas:

Current Claim	Limitation Duplicative of Claim Limitation Discussed Above
66	Claim 60 – EX 1002, ¶¶461-462

67	Claim 61 – EX 1002, ¶¶463-464

As previously demonstrated, claim 39 (and independent claim 9) is rendered obvious by Thomas and Faucette. Thomas also teaches or renders obvious the specific additional limitations in claims 66-67. Accordingly, Thomas and Faucette render claims 66-67 obvious.

H. GROUND VIII: Claims 34, 43-46 and 48 are Obvious Over Thomas in view of Faucette and further in view of NCT02952833

1. Motivation to Combine

Thomas, Faucette, and NCT02952833 are in the same field of endeavor, i.e. making, testing, and using purified, inactivated whole virus antigen vaccines for use in humans. EX 1002, ¶¶282, 299, 314, 330, 345, 360, 412. In vaccinating pregnant women, a POSA would have looked to the art for examples of doses and would have been aware of Version 8 of NCT02952833. *Id.*

2. Independent Claim 43

Elements [43A]-[43D] are identical to [9A]-[9D]. EX 1002, ¶¶473-474. For the reasons set forth above with respect to limitations [9A]-[9D], Thomas and Faucette teach these limitations. Limitation [43E] is identical to the limitations recited in dependent claims 13 and 15. EX 1002, ¶474. For the reasons set forth above with respect to dependent claim 13 and 15, Thomas and NCT02952833 teach this limitation. *Id*.

Following the analysis of claim 15, a POSA would have been motivated by Thomas, Faucette and NCT02952833 to optimize a 10 μg dose as a result-effective variable on a pregnant woman with a reasonable expectation of successfully vaccinating her and having adoptive transfer to the fetus. *Id*. Accordingly, claim 43 is obvious over Thomas and Faucette, and further in view of NCT02952833. *Id.*

3. Dependent Claims 34, 44-46, and 48

Claims 34, 44-46, and 48 depend from claim 9. As previously demonstrated, claim 9 is obvious over Thomas and Faucette. These dependent claims add the same limitations previously discussed with respect to other dependent claims and shown above to be taught or rendered obvious by Thomas and NCT02952833. The following table sets forth where those limitations appear in other dependent claims and are taught or rendered obvious by Thomas and NCT02952833:

Current Claim	Limitation Duplicative of Claim Limitation Discussed Above
34	Claim 5 – EX 1002, ¶¶466-472
44	Claims 13 and 16 – EX 1002, ¶¶475-476
45	Claims 13 and 17 – EX 1002, ¶¶477-478
46	Claims 13 and 18 – EX 1002, ¶¶479-480
48	Claims 13 and 20 – EX 1002, ¶¶481-482

As demonstrated above, claim 9 is obvious over Thomas and Faucette. Claim 43 reciting about 10 μg to about 40 μg purified inactivated whole virus is obvious

over Thomas, Faucette and NCT 02952833. Claims 44-46 and 48 reciting a lower limit of about 10 μg, similarly are obvious over Thomas, Faucette and NCT02952833. EX 1002, ¶¶476, 478, 480, 482.

I. GROUND IX: Claims 37, 40, 42, 50 and 52 are Invalid as Being Obvious Over Thomas in view of Faucette and further in view of Barbero

1. Motivation to Combine

Thomas, Faucette and Barbero are in the same field of endeavor, i.e. making, testing, and using purified, inactivated whole virus antigen vaccines for use in humans. EX 1002, ¶¶205, 217, 230, 242, 256, 412. In vaccinating pregnant women, a POSA would have looked to the art for examples of neutralizing antibody titers, geometric mean neutralizing antibody titers, purification by size exclusion chromatography, adjuvant and adjuvant amounts and would have been aware of Barbero. *Id.*

2. Dependent Claims 37, 40, 42, 50, and 52

Claims 37, 40, 42, 50, and 52 depend from claim 9. As previously demonstrated, claim 9 is obvious over Thomas and Faucette. These dependent claims add limitations that are the same as additional limitations of other dependent claims previously discussed. The following table sets forth where those limitations appear in other dependent claims and are taught or rendered obvious by Thomas and Barbero:

Current Claim	Limitation Duplicative of Claim Limitation Discussed Above
37	Claim 8 – EX 1002, ¶¶484-489
40	Claim 12 – EX 1002, ¶¶490-496
42	Claim 14 – EX 1002, ¶¶497-501
50	Claim 22 – EX 1002, ¶¶502-507
52	Claim 24 – EX 1002, ¶¶508-512

Accordingly, the combination of Thomas, Faucette, and Barbero render these claims obvious.

J. GROUND X: Claims 54 and 64 are Obvious Over Thomas in view of Faucette, and further in view of Version 8 of NCT02952833 and Barbero

1. Motivation to Combine

Thomas, Faucette, NCT02952833 and Barbero are in the same field of endeavor, i.e. making, testing, and using purified, inactivated whole virus antigen vaccines for use in humans. EX 1002, ¶¶205, 217, 230, 242, 256, 282, 299, 314, 330, 345, 360, 412. In vaccinating pregnant women, a POSA would have looked to the art for examples of dose, amount of adjuvant and other vaccine components and would have been aware of NCT02952833 and Barbero.

2. Independent Claim 54

Elements [54A]-[54D] are identical to [9A]-[9D]. EX 1002, ¶¶514-515. For the reasons set forth above with respect to limitations [9A]-[9D], Thomas and Faucette teach these limitations. Limitation [54E] is identical to limitation [26D]. For the reasons set forth above with respect to limitation [26D], the combination of Thomas, NCT02952833, and Barbero teach this limitation. *Id.*

Following the analysis for claim 26, POSA would have understood that selecting the 10 μg dose based on NCT02952833 is routine optimization of a result-effective variable and selecting 200 μg aluminum hydroxide as adjuvant based on Barbero is routine optimization of a result-effective variable. EX 1002, ¶¶516-518.

Accordingly, claim 54 is obvious over Thomas and Faucette, and further in view of NCT02952833 and Barbero. EX. 1002, ¶519.

3. Dependent Claim 64

Claim 64 depends from claim 54 and adds the limitation that the sugar is sucrose (the same additional limitation recited in claim 63). EX 1002, ¶520-521; EX 1001, 128:12. As demonstrated above, the combination of Thomas, Faucette, NCT02952833, and Barbero render claim 54 obvious. As set forth above with respect to Claim 63, Thomas teaches the sugar is sucrose. Accordingly, claim 64 is obvious over Thomas and Faucette, and further in view of Version 8 of NCT02952833 and Barbero. *Id*.

K. GROUND XI: Claim 53 is Obvious Over Thomas in view of Faucette, and further in view of Murata

1. Motivation to Combine

Thomas, Faucette and Murata are in the same field of endeavor, i.e. making, testing, and using purified, inactivated whole virus antigen vaccines for use in humans. EX 1002, ¶¶270, 412. In vaccinating pregnant women, a POSA would have looked to the art for examples of purification, such as PRNT and would have been aware of Murata. *Id*.

2. Claim 53

Elements [53A]-[53D] are identical to [9A]-[9D]. EX 1002, ¶¶523-524. For the reasons set forth above with respect to limitations [9A]-[9D], Thomas and Faucette teach these limitations. Limitation [53E] is identical to the limitation recited in dependent claim 25. For the reasons set forth above with respect to dependent claim 25, the combination of Thomas and Murata, teach this limitation. *Id*.

Applying the above analysis of claim 25 to claim 53, purifying virus using plaque purification is within the routine skill of POSA. POSA would have been motivated to use plaque purification with a reasonable expectation of success because Thomas teaches to purify virus using routine methods. EX 1002, ¶¶525-527. Murata teaches plaque purification is a routine method and the substitution of one know method for another is well within ordinary skill and does not result in patentability absent unexpected results. *Id*.

Accordingly, claim 53 is obvious over Thomas and Faucette, and further in view of Murata. EX 1002, ¶528.

L. NO SECONDARY CONSIDERATIONS OF NON-OBVIOUSNESS EXIST

The Petitioner has considered but is not aware of any evidence of secondary considerations of non-obviousness of the claims, such as failure of others, unexpected results, praise in the industry, long-felt, but unmet need, copying or commercial success. EX 1002, ¶529.

VII. GROUNDS FOR STANDING AND PAYMENT OF FEES

Petitioner hereby certifies that the '802 patent is eligible for and Petitioner is not barred or estopped from requesting *inter partes* review challenging claims 1-67 on the grounds identified in the present Petition.

This Petition requests review of claims 1-67 of the '802 patent and is accompanied by a payment of $118,145, comprising a $23,750 request fee, a $28,125 post-institution fee, a $22,090 request fee for 47 claims in excess of 20, and a $44,180 post-institution fee for 47 claims in excess of 20. 37 C.F.R. § 42.15(a)(1)-(4). This Petition meets the fee requirements of 35 U.S.C. § 312(a)(1). Petitioner authorizes the Board to charge any additional fees to Deposit Account 19-0733.

VIII. CONCLUSION

Inter partes review should be instituted and claims 1-67 of United States Patent No. 11,730,802 should be canceled.

BANNER & WITCOFF, LTD

Dated: March 31, 2025

By: /Robert F. Altherr, Jr./

Robert F. Altherr, Jr
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CERTIFICATION UNDER 37 CFR § 42.24(d)

Under the provisions of 37 CFR § 42.24(d), the undersigned hereby certifies that the word count for the foregoing Petition for *Inter Partes* Review totals 13,837, which is less than the 14,000 allowed under 37 CFR § 42.24(a)(1)(i). The total words were counted by the Word Count feature of Microsoft Word.

Pursuant to 37 C.F.R. § 42.24(a)(1), this count does not include the table of contents, the table of authorities, mandatory notices under § 42.8, the certificate of service, this certification of word count, the claims listing appendix, or appendix of exhibits.

Dated: March 31, 2025

By: /Robert F. Altherr, Jr./

Robert F. Altherr, Jr
Reg. No. 31,810

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.105, I hereby certify that I caused a true and correct copy of this Petition for *Inter Partes* Review in connection with U.S. Patent No. 11,730,802 and supporting evidence to be served via FedEx Priority Overnight on March 31, 2025, on the following:

HONIGMAN LLP/ MPI (114119)
650 TRADE CENTRE WAY
SUITE 200
KALAMAZOO, MI 49002

Dated: March 31, 2025

By: /Robert F. Altherr, Jr./

Robert F. Altherr, Jr
Reg. No. 31,810

CLAIM APPENDIX

Claim Feature	'802 Patent Claims
1A	A method of vaccinating against Zika virus infection in a human subject in need thereof, the method comprising
1B	administering to the human subject a vaccine or immunogenic composition comprising a dose of from about 1 μg to about 40 μg of an antigen from a Zika virus,
1C	wherein the antigen is an inactivated whole virus, as a first (prime) and a second (boost) administration,
1D	wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration a seroconversion rate of at least 80% in a population of at least 20 Zika virus seronegative subjects.
2	The method of claim 1, wherein the subject is pregnant or intends to become pregnant or is a woman of childbearing potential.
3	The method of claim 1, wherein the vaccine or immunogenic composition is administered by intramuscular or subcutaneous administration.
4	The method of claim 1, wherein the vaccine or immunogenic composition is administered one or more times.
5	The method of claim 1, wherein the vaccine or immunogenic composition comprising a dose of 10 μg is administered one time.
6	The method of claim 1, wherein the prime and boost administration takes place from about 1 to about 16 weeks apart or from about 1 to about 6 weeks apart or from about 1 to about 4 weeks apart or from about 3 to about 5 weeks apart.
7	The method of claim 1, wherein the second (boost) administration is administered from about 25 days to about 30 days after the first (prime) administration.

Claim Feature	'802 Patent Claims
8	The method of claim 1, wherein 14 and/or 28 days after the boost administration of the vaccine or immunogenic composition the generation of neutralizing antibodies titers to Zika virus in a subject of greater than 1000, or of greater than 1500, or of greater than 2000, or of greater than 3000 are induced, as determined by the plaque reduction neutralization test (PRNT).
9A	A method of vaccinating against Zika virus disease in a fetus or newborn in need thereof, the method comprising
9B	administering to a pregnant human subject a vaccine or immunogenic composition comprising a dose of from about 1 μg to about 40 μg of an antigen from a Zika virus,
9C	wherein the antigen is an inactivated whole virus, and
9D	wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn,
9E	wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration.
10	The method of claim 1, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration a seroconversion rate of at least 90% in a population of at least 20 Zika virus seronegative subjects.
11A	A method of vaccinating against Zika virus infection in a human subject in need thereof, the method comprising
11B	administering to the human subject a vaccine or immunogenic composition comprising a dose of from about 1 μg to about 40 μg of an antigen from a Zika virus,
11C	wherein the antigen is an inactivated whole virus,
11D	wherein the vaccine or immunogenic composition is administered one or more times,
11E	wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after a single dose or prime administration a seroconversion rate of at least 60% in a population of at least 20 Zika virus seronegative subjects.

Claim Feature	'802 Patent Claims
12	The method of claim 1, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration, geometric mean neutralizing antibody titers in a population of at least 20 flavivirus naïve subjects and/or at least 20 Zika virus seronegative subjects, which are at least 10 times, or at least 15 times, or at least 20 times, or at least 25 times higher than the geometric mean neutralizing antibody titers induced 28 days after the prime administration, as determined by the plaque reduction neutralization test (PRNT).
13	The method of claim 1, wherein the antigen is purified.
14	The method of claim 13, wherein the main peak of the antigen when analyzed by size exclusion chromatography is more than 85% of the total area under the curve in the size exclusion chromatography.
15	The method of claim 1, wherein the vaccine or immunogenic composition comprises a dose of from about 10 μg to about 40 μg of purified inactivated whole virus.
16	The method of claim 1, wherein the vaccine or immunogenic composition comprises a dose of from about 10 μg to about 30 μg of purified inactivated whole virus.
17	The method of claim 1, wherein the vaccine or immunogenic composition comprises a dose of from about 10 μg to about 20 μg of purified inactivated whole virus.
18	The method of claim 1, wherein the vaccine or immunogenic composition comprises a dose of about 10 μg to about 15 μg of purified inactivated whole virus.
19	The method of claim 1, wherein the vaccine or immunogenic composition comprises a dose of about 2 μg, or about 5 μg, or about 10 μg of purified inactivated whole virus.

Claim Feature	'802 Patent Claims
20	The method of claim 1, wherein the vaccine or immunogenic composition comprises a dose of about 10 μg of purified inactivated whole virus.
21	The method of claim 1, wherein the vaccine or immunogenic composition further comprises an aluminum salt adjuvant.
22	The method of claim 21, wherein the vaccine or immunogenic composition comprises from about 100 μg to about 600 μg or from about 100 μg to about 450 μg or from about from about 100 μg to about 300 μg or from about 150 μg to about 250 μg or from about 100 μg to about 225 μg or about 200 μg of an aluminum salt as adjuvant.
23	The method of claim 21, wherein the adjuvant is aluminum hydroxide.
24	The method of claim 21, wherein at least 75%, or at least 85%, or at least 90%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99%, or 100% of the antigen are adsorbed to the adjuvant.
25	The method of claim 1, wherein the Zika virus is a clonal isolate, in particular from a plaque purified clonal Zika virus isolate.
26A	A method of vaccinating against Zika virus infection in a human subject in need thereof, the method comprising
26B	administering to the human subject a vaccine or immunogenic composition comprising a dose of from about 1 μg to about 40 μg of an antigen from a Zika virus,
26C	wherein the antigen is an inactivated whole virus,
26D	wherein the vaccine or immunogenic composition comprises a dose of about 10 μg of purified inactivated whole virus, about 200 μg aluminum hydroxide, a buffer; and optionally a sugar.
27	The method of claim 1, wherein administration of the vaccine or immunogenic composition to the human subject does not result in the subject having a severe adverse event as a result of the administration.
28	The method of claim 27, wherein the severe adverse event is a fever of a temperature of 39° C. or higher.

Claim Feature	'802 Patent Claims
29	The method of claim 1, wherein the subject is from a Zika endemic region or from a Zika non-endemic region travelling to an endemic region.
30	The method of claim 1, wherein the subject is 18 to 29 years of age or 30 to 49 years of age.
31	The method of claim 1, wherein the subject is a female subject.
32	The method of claim 9, wherein the vaccine or immunogenic composition is administered by intramuscular or subcutaneous administration.
33	The method of claim 9, wherein the vaccine or immunogenic composition is administered one or more times.
34	The method of claim 9, wherein the vaccine or immunogenic composition comprising a dose of 10 μg is administered one time.
35	The method of claim 9, wherein the prime and boost administration takes place from about 1 to about 16 weeks apart or from about 1 to about 6 weeks apart or from about 1 to about 4 weeks apart or from about 3 to about 5 weeks apart.
36	The method of claim 9, wherein the second (boost) administration is administered from about 25 days to about 30 days after the first (prime) administration.
37	The method of claim 9, wherein 14 and/or 28 days after the boost administration of the vaccine or immunogenic composition the generation of neutralizing antibodies titers to Zika virus in the pregnant human subject of greater than 1000, or of greater than 1500, or of greater than 2000, or of greater than 3000 are induced, as determined by the plaque reduction neutralization test (PRNT).

Claim Feature	'802 Patent Claims
38	The method of claim 9, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration a seroconversion rate of at least 80%, or at least 90%, or at least 95%, or 100% in a population of at least 20 Zika virus seronegative subjects.
39	The method of claim 9, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after a single dose or prime administration a seroconversion rate of at least 60% in a population of at least 20 Zika virus seronegative subjects.
40	The method of claim 9, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration, geometric mean neutralizing antibody titers in a population of at least 20 flavivirus naïve subjects and/or at least 20 Zika virus seronegative subjects, which are at least 10 times, or at least 15 times, or at least 20 times, or at least 25 times higher than the geometric mean neutralizing antibody titers induced 28 days after the prime administration, as determined by the plaque reduction neutralization test (PRNT).
41	A method of vaccinating against Zika virus disease in a fetus or newborn in need thereof, the method comprising administering to a pregnant human subject a vaccine or immunogenic composition comprising a dose of from about 1 μg to about 40 μg of an antigen from a Zika virus, wherein the antigen is an inactivated whole virus, and wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn, wherein the antigen is purified.
42	The method of claim 41, wherein the main peak of the antigen when analyzed by size exclusion chromatography is more than 85% of the total area under the curve in the size exclusion chromatography.
43A	A method of vaccinating against Zika virus disease in a fetus or newborn in need thereof, the method comprising

Claim Feature	'802 Patent Claims
43B	administering to a pregnant human subject a vaccine or immunogenic composition comprising a dose of from about 1 μg to about 40 μs of an antigen from a Zika virus,
43C	wherein the antigen is an inactivated whole virus,
43D	and wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn,
43E	wherein the vaccine or immunogenic composition comprises a dose of from about 10 μg to about 40 μg of purified inactivated whole virus.
44	The method of claim 9, wherein the vaccine or immunogenic composition comprises a dose of from about 10 μg to about 30 μg of purified inactivated whole virus.
45	The method of claim 9, wherein the vaccine or immunogenic composition comprises a dose of from about 10 μg to about 20 μg of purified inactivated whole virus.
46	The method of claim 9, wherein the vaccine or immunogenic composition comprises a dose of about 10 μg to about 15 μg of purified inactivated whole virus.
47	The method of claim 9, wherein the vaccine or immunogenic composition comprises a dose of about 2 μg, or about 5 μg, or about 10 μg of purified inactivated whole virus.
48	The method of claim 9, wherein the vaccine or immunogenic composition comprises a dose of about 10 μg of purified inactivated whole virus.

Claim Feature	'802 Patent Claims
49	A method of vaccinating against Zika virus disease in a fetus or newborn in need thereof, the method comprising administering to a pregnant human subject a vaccine or immunogenic composition comprising a dose of from about 1 μg to about 40 μg of an antigen from a Zika virus, wherein the antigen is an inactivated whole virus, and wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn, wherein the vaccine or immunogenic composition further comprises an aluminum salt adjuvant.
50	The method of claim 49, wherein the vaccine or immunogenic composition comprises from about 100 μg to about 600 μg or from about 100 μg to about 450 μg or from about from about 100 μg to about 300 μg or from about 150 μg to about 250 μg or from about 100 μg to about 225 μg or about 200 μg of an aluminum salt as adjuvant.
51	The method of claim 49, wherein the adjuvant is aluminum hydroxide.
52	The method of claim 49, wherein at least 75%, or at least 85%, or at least 90%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99%, or 100% of the antigen are adsorbed to the adjuvant.
53A	A method of vaccinating against Zika virus disease in a fetus or newborn in need thereof, the method comprising
53B	administering to a pregnant human subject a vaccine or immunogenic composition comprising a dose of from about 1 μg to about 40 μg of an antigen from a Zika virus,
53C	wherein the antigen is an inactivated whole virus,
53D	and wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn,
53E	wherein the Zika virus is a clonal isolate, in particular from a plaque purified clonal Zika virus isolate.
54A	A method of vaccinating against Zika virus disease in a fetus or newborn in need thereof, the method comprising

Claim Feature	'802 Patent Claims
54B	administering to a pregnant human subject a vaccine or immunogenic composition comprising a dose of from about 1 μg to about 40 μg of an antigen from a Zika virus,
54C	wherein the antigen is an inactivated whole virus,
54D	and wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn,
54E	wherein the vaccine or immunogenic composition comprises a dose of about 10 μg of purified inactivated whole virus, about 200 μg aluminum hydroxide, a buffer; and optionally a sugar.
55	The method of claim 9, wherein administration of the vaccine or immunogenic composition to the pregnant human subject does not result in the pregnant human subject having a severe adverse event as a result of the administration.
56	The method of claim 55, wherein the severe adverse event is a fever of a temperature of 39° C. or higher.
57	A method of vaccinating against Zika virus disease in a fetus or newborn in need thereof, the method comprising administering to a pregnant human subject a vaccine or immunogenic composition comprising a dose of from about 1 μg to about 40 μg of an antigen from a Zika virus, wherein the antigen is an inactivated whole virus, and wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn, wherein the pregnant human subject is from a Zika endemic region or from a Zika non-endemic region travelling to an endemic region.
58	A method of vaccinating against Zika virus disease in a fetus or newborn in need thereof, the method comprising administering to a pregnant human subject a vaccine or immunogenic composition comprising a dose of from about 1 μg to about 40 μg of an antigen from a Zika virus, wherein the antigen is an inactivated whole virus, and wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn, wherein the pregnant human subject is 18 to 29 years of age or 30 to 49 years of age.

Claim Feature	'802 Patent Claims
59	The method of claim 1, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration a seroconversion rate of at least 95% or 100%.
60	The method of claim 11, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the single dose or prime administration a seroconversion rate of 80% in a population of at least 20 Zika virus seronegative subjects.
61	The method of claim 11, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the single dose or prime administration a seroconversion rate of 90% in a population of at least 20 Zika virus seronegative subjects.
62	The method of claim 11, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the single dose or prime administration a seroconversion rate of 95% in a population of at least 20 Zika virus seronegative subjects.
63	The method of claim 26, wherein the sugar is sucrose.
64	The method of claim 54, wherein the sugar is sucrose.
65	The method of claim 39, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the single dose or prime administration a seroconversion rate of 70% in a population of at least 20 Zika virus seronegative subjects.
66	The method of claim 39, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the single dose or prime administration a seroconversion rate of 80% in a population of at least 20 Zika virus seronegative subjects.

Claim Feature	'802 Patent Claims
67	The method of claim 39, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the single dose or prime administration a seroconversion rate of 90% in a population of at least 20 Zika virus seronegative subjects.