

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

VALNEVA AUSTRIA GMBH,
Petitioner,

v.

TAKEDA VACCINES, INC.,
Patent Owner.

Case IPR2024-00776
U.S. Patent No. 11,730,802

DECLARATION OF FARSHAD GUIRAKHOO, PH.D.

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I, Farshad Guirakhoo, Ph.D., hereby declare as follows.

I. INTRODUCTION AND QUALIFICATIONS

A. Introduction

1. I am over the age of eighteen and otherwise am competent to make this declaration.

2. I have been retained as an expert witness on behalf of Petitioner Valneva Austria GMBH. I am being compensated for my time in connection with this Request for Inter Partes Review at my standard consulting rate of \$1,740.00 per hour.

3. I have been asked to offer opinions as an expert regarding patentability or lack of patentability of claims 1-67 of U.S. Patent No. 11,730,802 (“the ‘802 patent”), EX 1001, from the perspective of a person of ordinary skill in the art (“POSA”). Claims 1-67 of the ‘802 patent are directed to methods of vaccinating a human against Zika virus infection or disease using an inactivated whole Zika virus antigen. In rendering my opinions, I have reviewed the ‘802 patent and its prosecution history and the documents listed herein. I understand that my opinions on the claims of the ‘802 patent must be based on what would be known or understood by a POSA at the effective filing date of the ‘802 patent in the field of vaccine development, manufacture and use. My education, experience and knowledge in the field of vaccine development, manufacture and use provide a basis

for what a POSA would know and understand.

4. As detailed further herein, prior art to the '802 patent teaches the use of a purified, inactivated, whole Zika virus antigen vaccine to vaccinate human subjects against Zika virus disease and to generate claimed seroconversion rates before the priority dates of the claims of the '802 patent, along with various commonly known aspects recited in the independent and dependent claims in the '802 patent. In the following table, I have provided the specific reference or combination of references which following the legal principles explained herein, show in my opinion the unpatentability of claims 1-67 of the '802 patent.

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) or, alternatively, obvious under 35 U.S.C. §103 based on Thomas WO2017/210215 ("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 WO2017/109223 ("Barbero")
Ground IV	25	Obviousness under 35 U.S.C. §103 based on Thomas in view of Murata, Vaccines ("Murata")
Ground V	5, 15-18, and 20	Obviousness under 35 U.S.C. §103 based on Thomas in view of Version 8 of NCT02952833

Ground VI	26 and 63	Obviousness under 35 U.S.C. §103 based on Thomas in view of Version 8 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, Human Vaccines & Immunotherapeutics (“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 Version 8 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 Version 8 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. Qualifications and Experience

5. I am a world-renowned virologist and vaccinologist with over 30 years of biotechnology experience, managing the development of vaccines, biologics, and therapeutics from preclinical stages to commercial launches. I was recognized in 2014 as one of the Most Influential People in Vaccines by VaccineNation which can be found at chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://geovax.com/images/pdf/The_Most_Influential_People_In_Vaccines.pdf.

6. In May 1976, I received a B.Sc. in biology from National University of

Iran, Tehran. In May 1979, I received an M.Sc. in genetics from the International Institute for Biophysics & Biochemistry, Tehran University, Tehran, Iran. In June 1987, I received my Ph.D. in virology from the Institute of Virology, Medical University of Vienna, Austria, under Professor Dr. Franz X. Heinz, Director of the Institute of Virology. Thereafter, I was a Post-Doctoral Fellow at the National Centers for Disease Control and Prevention (CDC), Fort Collins, Colorado, with a focus on vector-borne infectious diseases.

7. I have extensive experience in vaccine research and development especially with viruses belonging to the *Flaviviridae* family which includes dengue, TBEV, Zika virus, JEV and WNV. My additional experiences and achievements are summarized in the following:

8. Dengvaxia™: Being the inventor of world's first Dengue tetravalent vaccine, first marketed in 2015, recognized by the World Vaccine Congress as the Best Vaccine in Development in 2011, and licensed by the FDA in 2019.

9. IMOJEV®: Being the co-inventor of world's first recombinant single-dose vaccine for the prevention of Japanese encephalitis (launched 2010 in Australia).

10. PrevNile™: Being the co-inventor of a horse vaccine against West Nile disease (launched 2006), the most advanced human vaccine in development (completed Phase 2a in the elderly).

11. I have been actively working in the vaccinology, virology, and immunology fields since 1982. I have extensive professional experience in vaccine research and development at the following companies.

12. Expres2ion Biotechnology (Dec 2022 – Present) where I am currently Chief Scientific Officer leading R&D activities focusing on oncology and infectious diseases.

13. Vaxxinity (Jun 2022 – Dec 2022) where I was a Senior Advisor, Vaccine R&D, advising the CEO on global vaccine R&D strategies.

14. Vaxxinity (Merger of United Neuroscience & COVAXX) (Apr 2021 – Jun 2022) where I was Chief Scientific Officer leading global R&D for neuro and infectious disease vaccine targets.

15. COVAXX (subsidiary of UNS) (Dec 2020 – Apr 2021) where I was Chief Scientific Officer leading global R&D efforts for infectious disease vaccine development.

16. United Neuroscience (UNS) (Jun 2020 – Dec 2020) where I was Chief Scientific Officer leading global R&D for neuro-targeted vaccines.

17. Responsive BioServices (2017 – 2020) where I was Co-Founder and CEO specializing in CRO for vaccine evaluations, immunology, and regulatory services.

18. GeoVax, Inc. (2015 – 2020) where I was Chief Scientific Officer

leading R&D across infectious diseases and oncology, including the HIV program.

19. Vaxess Technologies (2014 – 2015) where I was Chief Technology Officer (CTO) leading R&D for thermostabilization of vaccines and biologics.

20. Hookipa Biotech (2012 – 2014) where I was Chief Scientific Officer managing preclinical development and GMP manufacturing of CMV vaccine candidates (HB101) and HPV-related head/neck cancer vaccines (HB-201, HB-202).

21. Sanofi Pasteur (2007 – 2012) where I was Executive/Senior Director, External R&D developing expertise in vaccines and therapeutics for infectious diseases and cancer, and contributing to regulatory submissions and product development including IMOJEV™, which is a vaccine for prevention of Japanese encephalitis.

22. Acambis, Inc. (2000 – 2007) where I was Senior Director, Virology leading development of Dengvaxia™, the world's first tetravalent dengue vaccine.

23. Oravax, Inc. (1996 – 1999) where I was Project Leader, ChimeriVax™ leading the development of the ChimeriVax™ vaccine platform, advancing candidates for Japanese encephalitis, Dengue and West Nile vaccines.

24. I have published extensively in peer-reviewed journals and contributed to books, a list of which is provide in my *curriculum vitae* attached as Exhibit A.

25. I have presented over 500 abstracts/talks, and am an invited speaker in

national and international scientific meetings, representative examples of which are listed on my *curriculum vitae* attached as Exhibit A.

26. I am a named inventor on many patents and patent applications directed to vaccines and vaccine development, representative examples of which are listed on my *curriculum vitae* attached as Exhibit A.

27. I maintain my knowledge in the field of virology and vaccine development, manufacture and use by reviewing scientific literature.

28. A true and correct copy of my *curriculum vitae* providing additional information about my background and experience is attached as Exhibit A to this Declaration.

29. In view of my education, experience, and expertise described above and identified on my *curriculum vitae*, I am an expert in the field of vaccine development, manufacture and use. Further, in view of my education, experience, and expertise described above, I understand the perspective of a person of ordinary skill in the art and I am qualified to provide opinions from the perspective of a person of ordinary skill in the art regarding the subject matter disclosed and claimed in the '802 patent.

C. Materials Considered

30. The analysis that I provide in this Declaration is based on my education and over 30 years of experience in the field of vaccine development, manufacture

and use, as well as the documents I have considered including the ‘802 patent which have provided me with a basis of what a POSA would have understood from the prior art documents identified herein. These documents include the materials listed below and which are attached as exhibits to Valneva’s petition. A detailed claim chart comparing each feature of claims 1-67 and where each feature is taught in the prior art is provided in attached Exhibit B.

Exhibit No.	Description
1001	U.S. Patent 11,730,802 (“the ‘802 patent”)
1003	Selected file history of the ‘802 patent
1004	Thomas PCT/US2017/035046 (WO2017/210215) (“Thomas”)
1005	Barbero Calzado PCT/EP2016/082662 (WO2017/109223)
1006	Murata et al, Plaque purification as a method to mitigate the risk of adventitious-agent contamination in influenza vaccine virus seeds, Vaccine, 2011 Apr 12;29(17):3155-61
1007	Faucette et al., Immunization of pregnant women: Future of early infant protection, Human Vaccines & Immunotherapeutics 11:11, 2549-2555; November 2015
1008	PCT/US2018/059233 (published as WO2019/090238)
1009	Provisional application No. 62/592,995
1010	Provisional application No. 62/581,500
1011	Version 8 of Clinical Trial NCT02952833
1012	Liu, et al., Clinical and Vaccine Immunology, Vol. 19, No. 1 (January 2012) pp. 73-78

II. RELEVANT LEGAL STANDARDS

31. I am not a lawyer. In forming my opinions, however, I have been asked

to apply certain standards regarding patentability that were provided to me by counsel for the Petitioner and I have done so. I understand that a claim is unpatentable if it is anticipated or obvious. I understand that, in an inter partes review, Petitioner has the burden of proving that each challenged claim is unpatentable by a preponderance of the evidence. I understand this means Petitioner must show it is more likely than not that each challenged claim is unpatentable. I have been informed that an expert is required to provide their opinions from the perspective of a POSA and may not simply provide his or her own personal conclusions and I have done so with respect to the opinions set forth herein.

A. Anticipation

32. I have been informed that a patent claim is “anticipated” when a single prior art patent or printed publication at the time of the invention describes to a POSA all of the elements of a claim, arranged or combined in the same way as in the claim, either expressly or by inherent disclosure. I further understand that an element of a patent claim is inherently disclosed in a prior art document if it necessarily exists in that disclosure. Regarding claimed ranges, a range is anticipated by a prior art reference if the reference discloses a point within the range.

B. Obviousness

33. I also have been informed by counsel that even if a claim of a patent is not anticipated, that claim can still be obvious. I have been informed that an

obviousness determination includes several factual inquiries, including: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the claimed invention and the prior art; (3) resolving the level of ordinary skill in the pertinent art; and (4) taking into consideration any secondary indicia (objective evidence) of non-obviousness. I am informed that such objective evidence of non-obviousness may include: a long felt but unsolved need that was satisfied by the claimed invention; commercial success attributable to the claimed invention; unexpected results achieved by the claimed invention; praise by experts of the claimed invention with factual support; taking of licenses under the patent by others for reasons related to the alleged non-obviousness of the claimed invention; the failure of others; the teaching away of others; skepticism by experts; and evidence that competitors in the marketplace have copied the invention instead of using the prior art. I further understand based on my review of the prosecution history that the Patentee has not alleged during prosecution of the '802 patent that any secondary considerations are present with respect to the claims of the '802 patent.

34. I have been informed that a claim can be obvious if the differences between the claimed subject matter and either a single prior art reference or a combination of two or more prior art references are such that the subject matter as a whole would have been obvious to a POSA at the time the invention was made. I have been informed that the condition "at the time the invention was made" is

imposed to rule out impermissible hindsight. Accordingly, permissible reasoning takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from the applicant's disclosure. I have been informed by counsel that a claim may be obvious based on a combination of multiple prior art references if a person of ordinary skill in the art would have been motivated to combine elements of the prior art or knowledge within the prior art to achieve the claimed invention and would have had a reasonable expectation of success in doing so. I also understand that the reason to select and combine features, the predictability of the results in doing so, and a reasonable expectation of success of doing so may be found in the teachings of the prior art themselves, in the nature of any need or problem in the field that was addressed by the patent, in the knowledge of persons of ordinary skill in the art at the time, as well as in common sense or the level of creativity exhibited by a person of ordinary skill in the art. There need not be an express or explicit suggestion to combine references. The results of ordinary innovation are not the subject of exclusive rights under the patent laws.

35. I have also been informed by counsel that a patent claim may be considered obvious if, at the time of the invention, combining known elements according to known methods would have yielded no more than predictable results. I have also been informed by counsel that a patent claim may be considered obvious

if there existed at the time of invention a known problem for which there was an obvious solution. The rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art.

36. Further, I understand from counsel that when a patent claims a genus, that claim is obvious if a single embodiment falling within the scope of the claims is obvious. I also understand from counsel that an invention may be obvious to try based on a design need and a finite number of predictable solutions. And I understand from counsel that the optimization of a variable in a known process, or the discovery of an optimum value in a known range of values, is ordinarily obvious, particularly when such optimization may be obtained by routine experimentation (referred to as routine optimization) by a person of ordinary skill in the art.

37. I have been advised that where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. I have been advised that this applies when the variable being optimized is recognized in the art as being a “result-effective variable.” I have been advised that a recognition in the prior art that a property is affected by the variable is sufficient to find the variable result-effective. I have been

advised that no invention is involved in discovering optimum ranges of a process by routine experimentation. I have been advised that the discovery of an optimum value of a result effective variable in a known process is ordinary within the skill of the art. I have been advised that the normal desire of scientists to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges in the optimum combination of percentages. I have been advised that modification of a parameter is not patentable unless it produces a new and unexpected result which is different in kind and not merely in degree from the results of the prior art.

III. THE ‘802 PATENT AND ITS PROSECUTION HISTORY

A. The ‘802 Patent

38. The ‘802 patent (EX 1001) is entitled “Zika Vaccines and Immunogenic Compositions, and Methods of Using the Same.” The ‘802 patent was filed May 4, 2020 and claims the benefit of PCT/US2018/059233 (published as WO2019/090238) (“the ‘233 PCT application”) (EX 1008) filed November 5, 2018. The ‘802 patent also claims the benefit of provisional application No. 62/592,995 (“the ‘995 provisional application”) (EX 1009) filed November 30, 2017 and provisional application No. 62/581,500 (“the ‘500 provisional application”) (EX 1010) filed November 3, 2017. I have reviewed the ‘802 patent, the ‘233 PCT application, the ‘995 provisional application, and the ‘500 provisional application. I

have selected relevant portions of the prosecution history for the ‘802 patent as part of EX 1003.

39. The ‘802 patent is directed to Zika virus vaccines “having one or more antigens from a Zika virus.” EX 1001 1:29-31. The ‘802 patent teaches in the Background that Zika virus is “a flavivirus classified with other mosquito-borne viruses (e.g., yellow fever, dengue, West Nile, and Japanese encephalitis viruses) within the Flaviviridae family . . .” EX 1001 1:41-43. The ‘802 patent identifies the specific known Zika virus strain PRVABC59. EX 1001 1:48. The ‘802 patent teaches that the World Health Organization (WHO) declared Zika virus a “Public Health Emergency of International Concern (PHEIC) (Heymann et al. (2016) Lancet 387(10020):719-21).” EX 1001 2:9-16. The ‘802 patent recognizes as Background that “Zika continues to pose in particular a significant threat for pregnant women and their unborn babies.” EX 1001 2:17-18.

40. The ‘802 patent states “there is a need to develop vaccines and immunogenic compositions for treating and/or preventing Zika virus.” EX 1001 2:38-40. The ‘802 patent further states that “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 (See Examples 1 and 2 below).” EX 1001

3:16-22. The ‘802 patent admits that Yun et al. Genome Announc. 2016 Aug. 18; 4(4) describe that a similar mutation in Zika virus Non-structural protein 1 may have been observed in the genomic sequencing analysis of Zika virus strain PRVABC59. EX 1001 3:23-27. Nevertheless, the inventors of the ‘802 patent state that they “have determined that the adaptation mutation in protein NS1 appeared to enhance genetic stability within the Zika virus, resulting in increased/enhanced replication efficiency.” EX 1001 3:35-39. The inventors further state that the particular Zika strain harboring an adaptive mutation in protein NS1 had the following beneficial aspects: (1) able to be passaged multiple times without developing further mutations; (2) able to be used as a master seed virus for vaccine production; and (3) may also reduce or inhibit the occurrence of undesirable mutations, such as a mutation within the envelope protein E (Env) of the Zika virus strain. EX 1001 3:40-51. However, the inventors never attempted to claim the particular Zika virus strain PRVABC59 with the NS1 mutation during prosecution of the ‘802 patent, which they say provided the beneficial aspects they determined when making a Zika virus vaccine. Instead, the inventors claimed an antigen from any and all Zika viruses.

41. Further, the inventors admit that the techniques and procedures they used to develop a Zika vaccine with the known Zika virus strain PRVABC59 with the NS1 mutation are “generally well understood and commonly employed using conventional methodology by those skilled in the art” EX 1001 17:55-58. The

inventors further admit that the culture conditions they used “are known and described in a variety of publications” or are commercially available. EX 1001 34:23-28. The inventors still further admit that vaccine purification to remove contaminating DNA is “standard practice” “using standard purification procedures e.g. chromatography, etc.” (EX 1001 35:40-45) and that antigens may be isolated using “standard methods” of size exclusion chromatography in particular to obtain purity as a function of main peak to total area under the curve (EX 1001 37:4-27).

42. The ‘802 patent teaches that inactivated whole virus vaccines are old and can be “produced and/or purified or otherwise isolated by any suitable method known in the art.” EX 1001 35:64-36:6. Particular methods of inactivating viruses are known in the art (EX 1001 38:58-60) and include chemical inactivation (EX 1001 39:5-7). The inventors admit that the use of adjuvants with vaccines is well known (EX 1001 42:66-67) and that vaccines may be “conventionally administered” by intramuscular or subcutaneous administration. EX 1001 54:62-65.

43. Accordingly, everything from the need for a Zika virus vaccine, to the particular Zika virus strain PRVABC59 with the NS1 mutation, to the culturing, purifying, inactivating, adjuvant formulating and administering is admitted by the inventors to be in the prior art and conventional. The inventors claim to have discovered the inherent beneficial properties of Zika virus strain PRVABC59 with the NS1 mutation. However, the inventors never claimed a Zika virus vaccine made

from this particular Zika virus strain PRVABC59 with the NS1 mutation. Further, any effect of the vaccine in the human body, such as antibody generation, is an inherent property resulting from practicing the admitted prior art techniques with the admitted prior art Zika virus strain PRVABC59 with the NS1 mutation to make a whole inactivated Zika vaccine. At best, the inventors selected PRVABC59 with the NS1 mutation, manipulated the virus using known methods to make a whole inactivated virus vaccine, and tested the vaccine for inherent properties when administered to a subject.

44. While the '802 patent includes language directed to preventing Zika virus disease in a fetus or newborn by vaccinating a pregnant woman (EX 1001 59:13-22 for example), the '802 patent provides no experiments or data to support safety or efficacy of such a method. However, in my opinion, safety of such a method would be presumed because the prior art recognized the use of inactivated virus vaccines in pregnant women as being safe.

45. Such prior art includes EX 1007 as described herein.

B. Prosecution History of the '802 Patent

46. The application was originally filed with claims 1-54. EX 1003, p. 434-440. A preliminary amendment was filed May 4, 2020 cancelling claims 1-54 and adding new Zika vaccine claims 55-64 and new method claims 65-73 directed to a method for treating or preventing Zika virus infection. EX 1003, p. 269-275.

47. A restriction requirement was issued February 28, 2022 requiring restriction between Group 1 vaccine claims 55-64 and Group 2 method claims 65-73 directed to a method for treating or preventing Zika virus infection. See EX 1003, p. 176-182. In a Response filed June 28, 2022, the applicant selected the Group 2 claims, cancelled claims 55-64 and amended the main independent claim 65 to focus on vaccinating a human with about 1 µg to about 40 µg of inactivated whole Zika virus antigen, as shown below.

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.

See EX 1003, p. 146-156.

48. The applicant also added new claims 74 to 124. Dependent claim 70 directed to a prime and boost administration and new claim 75 directed to seroconversion rate are presented below.

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.

See EX 1003, p. 146-156.

49. The Examiner issued a non-final office action on September 14, 2022. EX 1003, p. 84-91.

50. Claims 91 and 120 were rejected as being indefinite.

51. The Examiner indicated that claims 75 (above), 76, 77, 97-102, 107-119 and 123-124 were objected to but would be allowable if written into independent form including all of the limitations of the base claim and any intervening claims. EX 1003, p. 87.

52. The Examiner rejected claims 65, 66-72, 78, 79, 80-90 and 96 under 35 U.S.C. 102(a)(1) as being anticipated by Barbero WO2017/109223. EX 1003, p. 87. The Examiner noted that Barbero taught “a Zika virus vaccine (abstract), purified (page 7 lines 9-12), that is inactivated by formalin (page 108 lines 1-5). Barbero discloses the antigen doses of 0.012-12 μg and 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 1003, p. 88. The Examiner also noted that “Barbero discloses the administration may be intramuscular or subcutaneous one or more times (page 24 lines 1-7).” Id. The Examiner also note that “Barbero discloses administration and a second administration (boost) 3-4 weeks later (page 115 lines 11-25).” Id. The Examiner also notes that “Barbero discloses administering aluminum hydroxide adjuvant at 500 $\mu\text{g}/\text{ml}$ (page 112 lines 1-5).” Id.

53. I note that the Examiner did not reference Barbero's teaching at page 8 lines 22-25 of "an optimally inactivated or attenuated virus particle, wherein the virus particle in an appropriate dose is able to seroconvert a subject that is administered the virus vaccine with at least a 70% probability, preferably an 80% probability, i.e., is able to confer seroprotection in at least 70% of vaccinated subjects." However, Barbero provides no teaching of seroconversion in a population of at least 20 Zika virus seronegative subjects, as required by claim 1 of the '802 patent. I also note that Barbero does not provide any human clinical trial data. In these aspects, I consider the teachings of Thomas with respect to methods of vaccinating against Zika virus infection in a human subject to be more relevant to patentability than Barbero because Thomas teaches human clinical trials and achieves the claimed seroconversion rate in a population of at least 20 Zika virus seronegative subjects, as I describe herein.

54. The Examiner rejected claims 73-74, 89, 92-93, 94, 95, 103-106, and 121-122 under 35 U.S.C. 103(a) as being obvious in view of Barbero WO2017/109223. EX 1003, p. 89.

55. In a Response filed March 13, 2023 (EX 1003, p. 52-66), the Applicant amended claim 65 to include the subject matter of claim 70 (prime and boost administration) and allowable claim 75 (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).

56. Claim 74 (adoptive transfer between mother and fetus) was amended to include the allowable subject matter of claim 100 (prime and boost administration).

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

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

59. Allowable dependent claim 107 (purified antigen) was amended to include independent claim 74 (adoptive transfer between mother and fetus).

60. Allowable dependent claim 109 (dose between 10 µg to 40 µg) was amended to include independent claim 74 (adoptive transfer between mother and fetus).

61. Allowable dependent claim 115 (aluminum salt adjuvant) was amended to include independent claim 74 (adoptive transfer between mother and fetus).

62. Allowable dependent claim 119 (clonal isolate) was amended to include independent claim 74 (adoptive transfer between mother and fetus).

63. Rejected dependent claim 120 (10 µg virus, 200 µg aluminum hydroxide and buffer) was amended to overcome the indefiniteness rejection and to

include independent claim 74 (adoptive transfer between mother and fetus).

64. Allowable dependent claim 123 (Zika endemic region) was amended to include independent claim 74 (adoptive transfer between mother and fetus).

65. Allowable dependent claim 124 (age between 18-29 or 30-49) was amended to include independent claim 74 (adoptive transfer between mother and fetus).

66. New claims 125 to 133 were added.

67. The Examiner issued a Notice of Allowance dated April 10, 2023 indicating that claims 65-69, 71-99 and 101-133 were allowed. The Examiner did not provide any Statement of Reasons for Allowance. EX 1003, p. 28-33.

C. Technical Considerations Regarding the Claims

68. Independent claim 1 recites a dose range of from about 1 μg to about 40 μg and using a first (prime) and a second (boost) administration. At day 14 and/or 28 after the boost administration, the vaccine achieves a seroconversion rate of at least 80% in a population of at least 20 Zika virus seronegative subjects.

69. Seroconversion is the process by which a person's immune system produces detectable levels of antibodies in response to an infection or vaccination. It marks the transition from being seronegative (no detectable antibodies) to seropositive (detectable antibodies). Seroconversion indicates that the human body has started to recognize and respond to a pathogen, such as a virus or bacteria, and

is actively building immunity against it.

70. Claims dependent from claim 1 recite various aspects such as the human being a woman of childbearing potential or other characteristics of the human, various timings and modes of administration, various dosages within the range of about 1 μg to about 40 μg , various neutralizing antibody titers and seroconversion rates, characteristics of the antigen such as being purified, various adjuvants and amounts of adjuvants within the vaccine.

71. A neutralizing antibody titer, which refers to the level or concentration of neutralizing antibodies, is typically measured by gradually diluting a blood sample (e.g., a serum or a plasma 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 in the blood.

72. Neutralizing antibody titers can be determined by various methods, e.g., a plaque reduction neutralization test (PRNT) or a 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, the plaques formed on the monolayer (clear zones where virus causes a cytopathic effect) 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 the PRNT in which virus neutralization is

assessed in a 96-well format, allowing high-throughput testing. MN assay is adapted to measure viral cytopathic effect by PCR or ELISA. “Geometric mean neutralizing antibody titer” or “GMT” refers to the average level of neutralizing antibodies in a group of individuals, measured using a geometric mean rather than an arithmetic mean. GMTs are commonly used in vaccine and immunology studies to assess immune responses against viruses. Because antibody titers are usually not normally distributed; they tend to follow a log-normal distribution (some people have much higher titers than others). Therefore, the geometric mean (instead of the arithmetic mean) reduces the influence of extremely high or low values, giving a more accurate representation of the central tendency. The titers are typically expressed as the reciprocal of the highest serum dilution that still prevents viral infection (e.g., 1:160, 1:320). A higher GMT suggests a stronger immune response and better protection against infection. A “GMT” is calculated by averaging the logarithms of the observed titers and then converting the arithmetic mean to a real number, as shown below:

$$\log_{10} GMT = \frac{\log_{10} Titer_1 + \log_{10} Titer_2 + \dots + \log_{10} Titer_n}{n}$$

$$GMT = \sqrt[n]{(Titer_1 \times Titer_2 \times \dots \times Titer_n)}$$

73. An adjuvant is a substance that enhances the body's immune response to an antigen. Adjuvants, such as aluminum hydroxide (alum), have long been used in vaccines to improve their effectiveness, such as to increase antibody production

by the body's immune system.

74. Independent claims 9, 41, 43, 49, 53, 54, 57, and 58 are directed to a method of vaccinating against Zika virus disease in a fetus or newborn by administering a Zika virus vaccine to a pregnant woman which results in adoptively transferring neutralizing antibodies from the mother to the fetus or newborn. “Adoptive transfer” as used in the ‘802 patent is generally understood as referring to the production of antibodies in a first subject in response to an antigen (which can be a pregnant woman as recited in the claims), which are then transferred to a second subject (which can be a fetus as recited in the claims). “Passive transfer” described in a prior art document I will rely on herein refers to the similar process of passing antibodies from one person to another, such as from mother to fetus or infant. Independent claims 9, 41, 43, 49, 53, 54, 57, and 58 and their dependent claims recite various aspects in common with claim 1 and its dependent claims.

75. Independent claim 11 is similar to independent claim 1 except that a seroconversion rate of at least 60 % is achieved 14 and/or 28 days after a single dose or prime administration. Claims dependent from claim 11 recite various seroconversion rates.

76. Independent claim 26 is similar to claim 1 except that it recites various components of the vaccine composition, i.e., an aluminum hydroxide adjuvant, a buffer and optionally a sugar. A buffer is generally used in a vaccine composition to

maintain the pH of the vaccine composition. Dependent claim 63 recites that the sugar is sucrose.

77. I note that during prosecution and as described herein, the claims were amended to recite (1) vaccinating a human and (2) achieving a claimed 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. This subject matter was held to be allowable over the art relied on by the Examiner, i.e. Barbero, in rejecting the claims, because Barbero did not teach at least achieving a claimed 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, prior art Thomas expressly teaches an experiment where male and female humans were vaccinated 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. This is the exact subject matter which the Examiner did not believe was taught by the prior art. In my opinion, had the Examiner been aware of this teaching in Thomas whether by reviewing and understanding Thomas or the patentee bringing the teaching of Thomas to the Examiner's attention in view of the claim amendments, the claims would have been rejected based on Thomas.

78. I also acknowledge the '802 patent's admissions that many aspects

recited in the claims are routine in the field of vaccine development, manufacture and use. I have also reviewed prior art which teaches these common and routine aspects. For example, Thomas teaches that administration of purified, whole inactivated Zika virus vaccine induces the body's immune system to produce antibodies to the Zika virus antigen, resulting in seroconversion.

IV. CLAIM CONSTRUCTION UNDER 37 C.F.R. §42.104(b)(3)

79. I understand that, for purposes of my analysis in this *inter partes* review proceeding, the terms appearing in the patent claims “shall be construed using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b), including construing the claim in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” 37 C.F.R. § 42.100(b).

80. At this time, I believe that the claims are understandable to a POSA according to their plain meaning. As provided above, I have explained some of the claim terms as they would be understood by a POSA. However, my explanations should not be interpreted as offering definitions. I reserve the right to respond to any issue of claim construction offered by the Patentee.

V. PERSON OF ORDINARY SKILL IN THE ART

81. A person of ordinary skill in the art 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. One of skill in the art may be part of a multidisciplinary team having experience in one or more of the research, design, development and testing of antiviral vaccines.

VI. THE SCOPE AND CONTENT OF THE PRIOR ART

A. Thomas WO2017/210215

82. Thomas WO 2017/210215 (“Thomas”) (EX 1004) is a PCT Application designating the US that was published December 7, 2017 and has an International Filing Date of May 30, 2017, which is before the earliest provisional application no. 62/581,500 filing date of November 3, 2017 of the ‘802 patent. Accordingly, I understand that Thomas is prior art under 35 U.S.C. §102(a)(2) for claims 1-67 of the ‘802 patent.

83. Thomas teaches that “ZIKV purified inactivated vaccine (PIV) are produced at the Pilot Bioproduction Facility, Walter Reed Army Institute of Research, Silver Spring, MD, USA.” EX 1004 31:27-28. Thomas teaches a method of vaccinating against Zika virus infection in a human in need thereof by administering a 5 µg dose of a purified inactivated whole Zika virus to male and female subjects, using a first (prime) dose and a second (boost) dose, and has demonstrated 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. EX 1004

Abstract, 4:15-18; 6:33 to 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 to 8:2; 6:33 to 7:6; 7:32-33; 9:1-9; 41:9-10; and 42:4-7.

84. Thomas teaches in “Example 5. ZIKV PIV Performance in Human Trials” (EX 1004 40:7 to 43:15) where 5 µg doses of a purified whole inactivated Zika virus adjuvanted with aluminum hydroxide were administered by injection of a prime and boost administration 28 days later to 55 male and female human volunteers with a mean age of 31.5 years. A seroconversion rate of 92% of the 55 male and female volunteers was reported. The generation of neutralizing antibody to Zika virus was characterized, showing a GMT of 983.3 fourteen days after a boost administration and a peak GMT titer of 1061.7. The neutralizing antibody titer post boost being greater than 10 times post prime was reported. No serious adverse events related to vaccination were reported. The disclosure of Example 5. ZIKV PIV Performance in Human Trials is provided below for reference when discussing invalidity of the claims of the ‘802 patent.

Data was reviewed for the ZPIV recipients without known previous exposure through natural infection or vaccination to Zika or other flaviviruses. Two doses were administered at 1 and 28 days, 5 µg per dose, and adjuvanted with alum. Safety and immunogenicity data were collected out to day 57. A total of 67 individuals were in this group, with 55 receiving ZPIV and 12 receiving placebo. Volunteers represent enrollment from Trial Groups 2, 1 and 3 respectively. EX 1004 41:6-11.

A relatively equal number of male and female volunteers were enrolled;

52 and 48%, respectively. The preponderance of volunteers were white (71%) or black (19%). The mean age was 31.5 years with a decline in the mean age from Trial Group 2 (33.3) to Trial Group 1 (30.9) to Trial Group 3 (27.9). EX 1004 41:12-15.

There were no deaths, serious adverse events related to vaccination, or dis-enrollments related to an adverse event. There were no severe local adverse events (pain, redness, swelling at the site of injection). Most local adverse events were infrequent in occurrence and mild in severity. Pain and tenderness at the injection site occurred more frequently and were overwhelmingly mild in severity. Any systemic sign or symptom was reported in a majority of enrolled volunteers with the majority being mild (49.2%) and a smaller proportion being graded as moderate (14.9%) or severe (1.5%). A single (1.5%) volunteer reported nausea and/or vomiting; there were no other severe systemic signs or symptoms. In summary, despite not knowing which local or systemic signs or symptoms were reported by placebo or vaccine recipients, the safety profile in these 67 volunteers is acceptable, comparable to many currently licensed vaccines, and supports advancing clinical development. EX 1004 41:16-27.

Immunogenicity data was generated through the use of microneutralization assay and the titers reported indicating the readout representing the titer at which 50% of the control virus is neutralized (MN50). The cutoff for determining a vaccine take (seroconversion) is a MN titer of 1:10. Titers are measured ~28 days following the second dose of vaccine (study day 57). The MN50 titer found to be protective in mice and non-human primate studies ranges from 1:10 – 1:100, respectively. For context, the neutralizing antibody titers accepted by the regulatory agencies as correlates or surrogates of protection for licensed flavivirus vaccines against yellow fever, Japanese encephalitis (JE), and tick borne encephalitis ranges from 1:5 – 1:10. EX 1004 41:28 to 42:3.

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%. Seroconversion with a titer cutoff of 1:100 (protective titer in non-human primates) was Trial Group 2 65%, Trial Group 1 59%, and Trial

Group 3 100%; overall rate of 69%. EX 1004 42:4-8.

Antibody kinetics based on MN50 titers indicating a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff and then a robust and brisk rise in antibody titer for the Trial Group 2 and Trial Group 3 volunteers following dose two. Peak titers for Trial Group 1 and Trial Group 3 volunteers occur on or about study day 43 (2 weeks post dose two) and are between 500 and 1000. There is a gradual decline in titer between day 43 and day 57 with the final data point indicating titers between ~200-900. The Trial Group 1 volunteers have a distinct kinetic curve following dose two with a gradual rise and no decline in titer peaking at ~100 at day 57. EX 1004 42:9-16.

Detailed antibody data are provided in the table below representing site specific geometric mean titers and the confidence interval around these titers based on the day of collection and the study site where the collection occurred. Peak titers are also represented.

Time Point ^a	Statistic	5 meg ZPIV				Placebo
		16-0033 (N=25)	16-0062 (N=20)	Z0001 (N=10)	All (N=55)	All (N=12)
Day 1	N*	25	20	10	55	12
	GMT	5.0	5.0	5.0	5.0	5.0
	95% CI	-	-	-	-	-
Day 15	N*	25	-	10	35	7
	GMT	5.0	-	8.6	5.8	5.0
	95% CI	-	-	2.5, 28.8	4.3, 8.0	-
Day 29	N*	25	20	10	55	12
	GMT	5.5	8.5	8.7	7.0	5.0
	95% CI	4.5, 6.8	4.7, 15.3	2.5, 30.4	5.2, 9.5	-
Day 43	N*	25	-	10	35	7
	GMT	316.9	-	983.3	437.9	5.0
	95% CI	152.9, 656.6	-	425.4, 2272.5	245.7, 780.6	-
Day 57	N*	25	17	9	51	12
	GMT	142.9	100.8	820.6	173.1	5.0
	95% CI	70.3, 290.4	39.7, 255.7	357.1, 1885.8	104.6, 286.5	-
Peak Titer	N*	25	20	10	55	12
	GMT	345.6	64.2	1061.7	229.8	5.0
	95% CI	166.4, 718.0	25.3, 163.2	452.8, 2489.2	132.6, 398.4	-

EX 1004 42:17-20.

Based on the disclosure and the above data the compositions including inactivated ZIKV demonstrate that the compositions are immunogenic and that vaccines comprising inactivated ZIKV are protective against infection with ZIKV. EX 1004 42:21 to 43:1.

The available immunogenicity data for the ZPIV indicates the candidate is moderate to highly immunogenic following two doses

measured out to study day 57. When aggregated across the sites, titers in the majority of the vaccinated population exceed what is believed to a protective titer based on pre-clinical animal studies. To further support this contention, BIDMC completed a passive transfer study using purified antibody collected from the sera of human vaccine recipients. Nine (9) animals were fully protected by the human antibody following challenge, 1 was partially protected, and 2 were not protected; these data track with the randomization scheme of 10:2 vaccine:placebo. The ZPIV data also tracks with known correlates and surrogates of protection for currently licensed flavivirus vaccines. Completion of the studies is required to further define immune response durability and understand if current variations in response across study sites is maintained when data from all cohorts is collected and flavivirus primed and unprimed subsets are defined. EX 1004 43:2-13.

ZIPV was well tolerated and safe in a small number of volunteers and moderate to highly immunogenic. These data support proceeding to advanced clinical development. EX 1004 43:14-15.

B. Barbero Calzado WO2017/109223

85. Barbero Calzado WO2017/109223 (“Barbero”) was published June 29, 2017 which is before the earliest provisional application no. 62/581,500 filing date of November 3, 2017 of the ‘802 patent. Accordingly, I understand that Barbero is prior art under 35 U.S.C. §102(a)(2) for claims 1-67 of the ‘802 patent.

86. Barbero is a PCT application filed December 23, 2016 and was cited by the Examiner during prosecution of the ‘802 patent. Barbero teaches that “[t]here is a possible association between Zika virus infection during pregnancy and microcephaly in the fetus/neonate. Microcephaly is a rare condition in which a baby’s head circumference is significantly less than expected based on the average for their age, sex, and ethnicity. This is a result of the brain failing to undergo proper

embryonic development, and in 90% of cases is associated with mental retardation (Rocha et al. (2016) *Bull World Health Organ* 8 Feb. 2016).” EX 1005 13:11-16. Barbero teaches that inactivated Zika virus vaccines “are among the safest vaccines and especially preferred for delivery to populations where safety is especially concerning, such as pregnant women” EX 1005 4:8-10; 13:26-28. See also EX 1005 116:17-20. Barbero teaches that its Zika virus vaccine can be administered to a female subject that is pregnant or is planning on becoming pregnant. EX 1005 21:32-33. The subject can be “living in or traveling to an area where Zika virus is present or is thought to be present” or “an area that is experiencing a Zika virus infection outbreak.” EX 1005 21:34-22:1.

87. Barbero teaches that Zika virus can be “inactivated by chemical inactivation, thermal inactivation, pH inactivation, or UV inactivation.” EX 1005 18:30-31. “In a further step, the virus particles of the invention may be optionally inactivated.” EX 1005 11:11-13. Barbero teaches that its inactivated Zika virus vaccine “in an appropriate dose is able to seroconvert a subject that is administered the virus vaccine with at least a 70% probability, preferably an 80% probability, i.e., is able to confer seroprotection in at least 70% of vaccinated subjects.” EX 1005 8:23-25. See also EX 1005 22:12-17 for seroconversion rates of at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or at least 99% probability. Barbero teaches that “seroconversion of a subject is assessed by performing a PRNT.” EX 1005 22:25-

34. Barbero describes the PRNT and results obtained therefrom. EX 1005 114:9-30. Barbero also teaches using the MN described in Larocca, et al. (2016, Nature doi:10.1038/nature18952) to obtain an MN50 titer of 90 at 1µg of inactivated purified virus. EX 1005 114:32-35.

88. Barbero teaches that a physician “can start doses of the inactivated Zika virus vaccine employed in the pharmaceutical composition at levels lower than that required to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect (e.g., production of anti-Zika virus antibodies) is achieved.” 1005 23:29-32. Barbero teaches subcutaneous or intramuscular administration of two doses 7 days apart or 14 days apart or 28 days apart, or a single dose administration. EX 1005 24:1-7.

89. Barbero teaches purified virus, including Zika, for use as an antigen in a vaccine (EX 1005 1:5; 2:19-21; 8:25-28; 10:10-15; 11:20-28) and that the “virus preparation to be purified is provided in a sucrose solution.” EX 1005 10:29-30. “[T]he 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 1005 14:29-31. Barbero teaches that the inactivated Zika virus vaccine can include an adjuvant, such as an “aluminum salt (aluminum hydroxide or aluminum phosphate)” with aluminum hydroxide being preferred. EX

1005 24:20-30. Barbero teaches that aluminum hydroxide adjuvant “was added to a final concentration of 0.5 mg/ml Aluminium (1/20 v/v Alum 2% stock solution added) to prepare ZikaV Drug Product (DP).” EX 1005 112:2-4. 0.5 mg/ml alum equates to 500 µg/ml and 500 µg alum per 1 ml dose. Barbero further teaches that “[t]he DP was gently mixed for 5 min. An aliquot of the DP was removed, Alum sedimented by centrifugation and the clear supernatant analysed by SEC-HPLC. No ZikaV peak was detected in the supernatant indicating complete adsorption (estimated as >95%) of viral particles on the mineral adjuvant.” EX 1005 112:4-7.

90. Barbero teaches that “[a] unique aspect of the current invention is the realization that know-how related to the vaccine design and purification approach used for the Japanese Encephalitis Vaccine (JEV) IXIARO[®] (see Srivastava A.K. et al., 2001, Vaccine 19, 4557-4565, WO99/11762) may be employed and improved upon in order to expedite the development of a Zika” virus vaccine. EX 1005 14:33-15:6. Barbero provides Example 2 where “for the production of a ZikaV the JEV process platform (Srivastava et al., Vaccine 19 (2001) 4557-4565; US 6,309,650B1) was used as a basis.” EX 1005 104:26-31. Barbero teaches that “it is expected that the Zika virus produced by the process of the invention will provide very similar functional read-outs in in vitro, in vivo and finally human trials as the currently licensed JEV vaccine in the EU and US and elsewhere, IXIARO[®]. The dosage may alter but due to the very similar impurity profile and almost identical manufacture, a

very similar efficacy and safety result will be expected as was determined for the currently licensed JEV vaccine (licensed in the EU and US and elsewhere).” EX 1005 115:27-33.

C. Murata, et al., Vaccine 29 (2011) 3155-3161

91. Murata et al., Vaccine 29 (2011) 3155-3161 (“Murata”) was published online February 26, 2011 which is before the earliest provisional application no. 62/581,500 filing date of November 3, 2017 of the ‘802 patent. Accordingly, I understand that Murata is prior art under 35 U.S.C. § 102(a)(2) for claims 1-67 of the ‘802 patent.

92. Murata teaches a plaque purification procedure for influenza virus, in particular to remove contaminating viruses (referred to as “adventitious agents”) from influenza virus. Ex 1006, Abstract. Murata teaches that “[p]laque purification has been used for decades to ensure the homogeneity of virus stocks and to segregate discrete species from mixed virus populations [18-20].” EX 1006 p. 3156. Murata further teaches that “plaque purification may be a rapid and efficient means by which vaccine seed virus purity can be enhanced.” EX 1006 p. 3156. See also EX 1006 p. 3158 (“Our data suggest that plaque purification is a simple and rapid method for removing adventitious viruses.”) Finally, Murata motivates one to use plaque purification because “[p]laque purification is an approach unencumbered by intellectual property constraints.” EX 1006 p. 3159.

93. In particular, Murata used a plaque purification method to remove a nonreplicating virus contaminant from influenza virus. EX 1006 p. 3157 (“The data suggest that, for a non-replicating virus such as SV40, a single round of plaque purification can result in removal of the contaminating virus initially present at a level ~500-fold higher than the influenza virus input level (group C; success rate of 12 out of 20 influenza virus plaque samples, or ~60%).”)

94. Murata also used a plaque purification method to remove a replicating virus contaminant from influenza virus. EX 1006 p. 3158 (“Thus, for an efficiently replicating virus such as CaAdV, a single round of plaque purification can lead to removal of the contaminating virus initially present at a level ~5-fold higher than the influenza virus input level (group A; success rate of 11 out of 20 influenza virus plaque samples, or ~55%).”)

95. Murata also used two rounds of plaque purification to remove a replicating virus contaminant from influenza virus. EX 1006 p. 3158 (“The data suggest that two sequential rounds of plaque purification can efficiently remove CaAdV initially present at a level ~5000-fold higher than the influenza virus input level (group D).”)

96. Murata teaches that “[p]laque purification would mitigate the adventitious-agent risk associated with a virus originally isolated using mammalian cells.” EX 1006 p. 3160. Murata concludes that “our study corroborates the

commonly invoked rule of thumb in virology calling for three rounds of serial plaque purification to ensure homogeneity starting from a mixed population.” EX 1006 p. 3159.

D. Faucette et al., Human Vaccines & Immunotherapeutics 11:11, 2549-2555; November 2015.

97. Faucette et al., Human Vaccines & Immunotherapeutics 11:11, 2549-2555; November 2015 (“Faucette”) was published November 2015 which is before the earliest provisional application no. 62/581,500 filing date of November 3, 2017 of the ‘802 patent. Accordingly, I understand that Faucette is prior art under 35 U.S.C. §102(a)(2) for claims 1-67 of the ‘802 patent.

98. Faucette is directed to immunizing pregnant women with transfer of antibodies to the fetus or newborn. See EX 1007 Abstract (“Immunization during pregnancy can generate maternal immune protection as well as elicit the production and transfer of antibodies cross the placenta and via breastfeeding to provide early infant protection. Several successful vaccines are now recommended to all pregnant women worldwide.”) Immunization of the fetus is based on “the transfer of maternal vaccine-induced humoral immunity to the fetus during gestation”. EX 1007 p. 2549. “Maternal vaccination aims protect the both the mother and neonate.” EX 1007 p. 2550.

99. According to Faucette, vaccine induced antibodies cross the placenta thereby providing fetal and early infant immune protection. EX 1007 p. 2552

(“Underpinning the idea of maternal immunization is that the transport of vaccine-induced maternal immunoglobulin G (IgG) antibody across the placenta by neonatal Fc receptor (FcRn) expressed on trophoblasts across, [citations omitted] confers fetal and early infant immune protection (Fig. 1A).” “IgG transfer from the mother to the fetus can occur as early as gestational week 13, with the largest amount transferred during the third trimester of pregnancy (Fig. 1B). [Citations omitted]. Additional passive immunity in the form of vaccine-induced IgA, IgG and IgM secreted into colostrum and breast milk is transferred during breastfeeding.”) See also EX 1007 p. 2552 (“Maternal immunization presents unique benefits to the mother, fetus and the newborn by inducing active immunity in the mother and the transfer of passive humoral immunity across the placenta to the fetus.”)

100. Faucette teaches that “the vaccines effectiveness is due to both passive antibody transport and reduction of maternal exposure. Therefore, immunizing pregnant women can circumvent the multiple disadvantages of attempting to directly immunize neonates immediately after birth. Another important, albeit less obvious, benefit of maternal vaccination may involve the function of maternal antibodies in promoting the immune maturation and modulation in infants. Animal studies found 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. [Citations omitted.] Maternal antibodies acquired from milk during breastfeeding can provide mucosal protection by neutralizing pathogenic virulence factors in the intestinal lumen and inhibiting the adhesion and invasion of pathogens. [Citations omitted].” EX 1007 p. 2522.

101. Finally, Faucette teaches that “[m]aternal immunization has emerged as a worldwide public health strategy to protect both pregnant women and infants against infections. To date, the ACIP and WHO have specifically recommended immunization of all pregnant women against influenza and pertussis.” However, Faucette recognizes that “pregnant women have been traditionally excluded from many vaccine trials, which have precipitated a lack of long-term safety and efficacy data for pregnant women and the fetus.” EX 1007 p. 2553. Nevertheless, Faucette advocates “that consistent efforts are needed to open well-designed vaccine trials to safely include and monitor pregnant women. As the efficacy of maternal vaccines uniquely relies on the secretion of antibodies at the maternal-fetal interface and in the mammary gland, maternal vaccine development requires a thorough understanding of the mechanisms of mucosal immune regulation and the microbiota influence during pregnancy, [citations omitted] and mucosal immune assessment, in addition to systemic immune assessment, should be incorporated into vaccine trial protocols. Last, we believe that integration of some recent scientific advances in systems vaccinology, which has demonstrated success in systemically profiling and

in certain cases predicting vaccine efficacy, [citations omitted] will improve greatly the speed, accuracy and safety of vaccines development for the pregnant population.” EX 1007 p. 2553-2554.

E. Version 8 of Clinical Trial NCT02952833

102. I understand that Version 8 of Clinical Trial NCT02952833 was publicly available as of July 2, 2017 which is before the earliest provisional application no. 62/581,500 filing date of November 3, 2017. EX 1011. Accordingly, I understand that Version 8 of Clinical Trial NCT02952833 is prior art to claims 1-67 of the ‘802 patent.

103. The study protocol evaluates three dose levels. EX 1011 p. 6. The three dose levels to be evaluated are “5.0 mcg, 2.5 mcg and 10 mcg of ZPIV.” EX 1011 p. 6.

104. The doses are to be administered “by intramuscular (IM) injection on Days 1 and 29. The study will consist of a screening period of up to 28 days, a vaccination period in which subjects will receive a prime dose of vaccine on Day 1 followed by a boost on Day 29, and a follow-up period of 12 months post boost vaccination.” EX 1011 p. 6.

105. “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” EX 1011 p. 6. “The secondary objectives of this study are to 1.

Assess . . . seroconversion rates, and peak GMT” EX 1011 p. 6.

106. Experimental Group 1 will be administered 5.0 mcg ZPIV (aluminum hydroxide adjuvant) in a homologous prime-boost regimen on Day 1 and Day 29. Experimental Group 1 includes 25 subjects of which 5 are given a placebo. EX 1011 p. 8.

107. Experimental Group 2 will be administered 2.5 mcg ZPIV (aluminum hydroxide adjuvant) in a homologous prime-boost regimen on Day 1 and Day 29. Experimental Group 2 includes 25 subjects of which 5 are given a placebo. EX 1011 p. 8.

108. 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 1011 p. 8.

109. The Peak GMT overall and by dosage group is measured by ZIKV ELISA and neutralization assay. 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. 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 neutralization titers in comparison with baseline. EX 1011 p. 10.

110. Eligible study participants included both men and women (nonpregnant) between the ages of 18 and 49. EX 1011 p. 8, 11.

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

111. Liu, et al., Clinical and Vaccine Immunology, Vol. 19, No. 1 (January 2012) pp. 73-78 (“Liu”) was published November 23, 2011 which is before the earliest provisional application no. 62/581,500 filing date of November 3, 2017 of the ‘802 patent. Accordingly, I understand that Liu is prior art under 35 U.S.C. §102(a)(2) for claims 1-67 of the ‘802 patent.

112. Liu is directed to comparing the PRNT with the enzyme-linked immunospot-based MN (ELISPOT-MNT). Liu reports that a good correlation was observed between the two assays. EX 1012 p. 73, 76, 77.

VII. GROUND I: Claims 1-4, 6, 7, 10, 13, 19, 21, 23, 27-31, and 59 are Invalid as Being Anticipated by, or in the Alternative, as Obvious in view of Thomas

A. The Claims are Anticipated by or, in the Alternative, are Obvious Over Thomas

113. A detailed claim chart comparing each feature of claims 1-4, 6, 7, 10, 13, 19, 21, 23, 27-31, and 59 and where each feature is taught in Thomas is provided in Appendix B.

B. Claim by Claim Analysis

1. Claim 1

114. Claim 1 of the ‘802 patent is set forth below.

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

administering to the human subject a vaccine or immunogenic composition comprising a dose of from about 1 μ g to about 40 μ g of an antigen from a Zika virus,

wherein the antigen is an inactivated whole virus, as a first (prime) and a second (boost) administration,

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.

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

115. Thomas teaches vaccines including purified inactivated ZIKV and methods for the prevention and/or treatment of infection by ZIKV. EX 1004, Abstract. Thomas teaches immunizing a human against ZIKV infection. EX 1004 4:15-18; 5:2-6; 6:33-7:2; 5:8-9. Thomas teaches that “anti-Zika antibodies protect against infection in mice and non-human primates. Zika PIV generates robust anti-Zika antibodies in both models. Based on these models, and 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, or a booster dose at 4 weeks as described below).” EX 1004 18:16-20. Thomas concludes from Example 5: ZIKV PIV Performance in Human Trials that “vaccines comprising inactivated ZIKV are protective against infection with ZIKV.” EX 1004 42:21 to 43:1. Accordingly, Thomas teaches this limitation of claim 1.

- b. administering to the human subject a vaccine or immunogenic composition comprising a dose of from about 1 μ g to about 40 μ g of an antigen from a Zika virus**

116. In Example 5: ZIKV PIV Performance in Human Trials, Thomas teaches administering a dose of 5 μ g of an antigen from a Zika virus. EX 1004 41:7-8: “Two doses were administered at 0 and 28 days, 5 μ g per dose, and adjuvanted with alum.” 5 μ g per dose is within the claimed range of about 1 μ g to about 40 μ g. Accordingly, Thomas teaches this limitation of claim 1.

- c. wherein the antigen is an inactivated whole virus, as a first (prime) and a second (boost) administration**

117. Thomas teaches that the antigen is an inactivated whole virus. EX 1004 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”

118. Thomas teaches a first (prime) and a second (boost) administration. EX 1004 4:20-22: “Another example is wherein two doses are administered (e.g., a first dose, followed by a second dose 4 weeks later). A booster dose (second dose or more) may be useful for persons with recurrent infection risk.” EX 1004 7:32-33: “An exemplary dosage schedule entails an initial dose, then a second (booster) dose about 4 weeks later.” EX 1004 41:7-8: “Two doses were administered at 0 and 28 days, 5 μ g per dose, and adjuvanted with alum.” Accordingly, Thomas teaches this limitation of claim 1.

- d. 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**

119. The “at least 20 Zika virus seronegative subjects” refers to human subjects since claim 1 is directed to a method of vaccinating against Zika virus infection in a human subject, and so the claimed seroconversion rate relates to that in human subjects in order to support the claimed objective of vaccinating against Zika virus in a human subject.

120. In Example 5: ZIKV PIV Performance in Human Trials, Thomas teaches a seroconversion rate of 92% for 55 humans at day 57. The Table indicates prime administration at day 1 and boost administration at day 29. Day 57 is 28 days after the boost administration. 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%”. EX 1004 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.

121. As demonstrated above, Thomas teaches each and every limitation of claim 1. Therefore Thomas anticipates claim 1.

122. Alternatively, claim 1 would have been obvious in view of Thomas insofar as Thomas teaches all of the claim limitations including human clinical trials achieving the claimed seroconversion rates. Claim 1 recites a dose range of about 1 μg to about 40 μg of an antigen from a Zika virus and a seroconversion rate of at least 80% in a population of at least 20 Zika virus negative subjects.

123. It is within the level of one of ordinary skill in the art to use Thomas's method for achieving seroconversion after a first (prime) administration or after a second (boost) administration of a purified, inactivated whole Zika virus antigen using a dose range of about 1 μg to about 40 μg in a population of at least 20 Zika virus seronegative subjects to arrive at a seroconversion rate of at least 80% for a population of at least 20 Zika virus seronegative subjects 14 and/or 28 days after a boost dose, as the method of Thomas would require no modification.

124. One would have been motivated to modify the vaccine dose of Thomas exemplified in Example 5. ZIKV PIV Performance in Human Trials within the claimed range by either the amount of antigen and/or adjuvant or the type of adjuvant to induce a seroconversion rate of at least 80% in a population of at least 20 Zika virus seronegative subjects 14 and/or 28 days after a boost administration, because Thomas teaches to do just that. EX 1004 40:19-21 ("ZIPV 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 teaches that a seroconversion rate of 92% can be achieved and is desirable. See Example 5. ZIKV PIV Performance in Human Trials, EX 1004 42:4-8.

125. Based on Thomas, one of skill would have been motivated to explore doses and seroconversion rates with the goal of creating a vaccine with a seroconversion rate of at least 80% in a population of at least 20 Zika virus seronegative subjects 14 and/or 28 days after a boost administration. This is 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 after a first (prime) dose, as well as after a second (boost) dose.

126. One of skill would have had a reasonable expectation of successfully modifying the vaccine dose of Thomas exemplified in Example 5. ZIKV PIV Performance in Human Trials to induce a seroconversion rate of at least 80% in a population of at least 20 Zika virus seronegative subjects 14 and/or 28 days after a boost administration, because Thomas teaches that 5 μ g dose was used to achieve the claimed seroconversion rate and Thomas further teaches that the dose can be optimized. Achieving a seroconversion rate of at least 80% 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.

127. Accordingly, claim 1 is obvious in view of Thomas.

2. Claim 2

128. Claim 2 of the '802 patent depends from claim 1 and is set forth below.

2. The method of claim 1, wherein the subject is pregnant or intends to become pregnant or is a woman of childbearing potential.

129. Thomas teaches use of a purified inactivated whole virus with pregnant women because of a “superior safety profile”. EX 1004 18:28-30. In Example 5: ZIKV PIV Performance in Human Trials, Thomas teaches 55 human volunteers with 52% being male and 48% being female, i.e. women of childbearing potential. EX 1004 41:12-13. Accordingly, Thomas teaches this limitation of claim 2 and all of the limitations of claim 1 and therefore 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 that is well within the skill of a POSA.

3. Claim 3

130. Claim 3 of the '802 patent depends from claim 1 and is set forth below.

3. The method of claim 1, wherein the vaccine or immunogenic composition is administered by intramuscular or subcutaneous administration.

131. Thomas teaches that the vaccine or immunogenic composition is administered by intramuscular injection or subcutaneous injection. EX 1004 7:12-14. Accordingly, Thomas teaches this limitation of claim 3 and all of the limitations of claim 1 and therefore anticipates claim 3. Claim 3 is also obvious in view of

Thomas for the same reasons expressed with respect to claim 1, and further that selecting administration by intramuscular or subcutaneous administration are options expressly taught by Thomas that are well within the skill of a POSA.

4. Claim 4

132. Claim 4 of the '802 patent depends from claim 1 and is set forth below.

4. The method of claim 1, wherein the vaccine or immunogenic composition is administered one or more times.

133. At the outset, I note that claim 1 requires a first (prime) and a second (boost) administration. Accordingly, claim 4 cannot be limited to only a single administration. However, I have analyzed claim 4 from the perspective of the vaccine or immunogenic composition being administered one time or more times. Thomas teaches a single dose in mammals, i.e. humans, can provide 100% protection. EX 1004 4:18-20 (“For example, a single immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against challenge with ZIKV.”) Thomas teaches a single dose is effective, i.e. “[i]deally, only one dose is needed to effect protection against Zika infection for mammals, including humans” and also an initial and booster dose. EX 1004 7:30 to 8:2. In Example 5: ZIKV PIV Performance in Human Trials, Thomas teaches two doses, i.e. one or more times, were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum. EX 1004 41:7-8. Accordingly, Thomas teaches this limitation of claim 4 and all of the limitations of claim 1 and therefore anticipates

claim 4. Claim 4 is also obvious in view of Thomas for the same reasons expressed with respect to claim 1, and further that selecting administration one or more times is an option expressly taught by Thomas that is well within the skill of a POSA.

5. Claim 6

134. Claim 6 of the '802 patent depends from claim 1 and is set forth below.

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.

135. In Example 5: ZIKV PIV Performance in Human Trials, Thomas teaches two doses were administered at 0 and 28 days, i.e. 4 weeks apart. EX 1004 41:7-8. 4 weeks apart (28 days) is within the claimed range of from about 1 to about 16 weeks apart. Accordingly, Thomas teaches this limitation of claim 6 and all of the limitations of claim 1 and therefore anticipates claim 6. Claim 6 is also obvious in view of Thomas for the same reasons expressed with respect to claim 1, and further that selecting timing between prime and boost administrations is an option expressly taught by Thomas that is well within the skill of a POSA. EX 1004 40:23-26 ("ZIPV is explored across a range of schedule 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".)

6. Claim 7

136. Claim 7 of the '802 patent depends from claim 1 and is set forth below.

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.

137. In Example 5: ZIKV PIV Performance in Human Trials, Thomas teaches two doses (prime and boost, respectively) were administered at 0 and 28 days. EX 1004 41:7-8. 28 days is within the claimed range of from about 25 days to about 30 days. Accordingly, Thomas teaches this limitation of claim 7 and all of the limitations of claim 1 and therefore anticipates claim 7. Claim 7 is also obvious in view of Thomas for the same reasons expressed with respect to claim 1, and further that selecting timing between prime and boost administrations is an option expressly taught by Thomas that is well within the skill of a POSA. EX 1004 40:23-26 (“ZIPV is explored across a range of schedule 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”).)

7. Claim 10

138. Claim 10 of the ‘802 patent depends from claim 1 and is set forth below.

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.

139. In Example 5: ZIKV PIV Performance in Human Trials, Thomas teaches a seroconversion rate of 92% for 55 humans at day 57. The Table indicates prime administration at day 1 and boost administration at day 29. Day 57 is 28 days

after the boost administration. 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%.” EX 1004 Table at 42:19 for Trial Group 2 (N=20, 92% seroconversion).

140. Accordingly, Thomas teaches this limitation of claim 10 and all of the limitations of claim 1 and therefore anticipates claim 10. Claim 10 is also obvious in view of Thomas for the same reasons expressed with respect to claim 1, and further that achieving a seroconversion rate and selecting timing after the boost administrations are options expressly taught by Thomas that are well within the skill of a POSA as I have explained with respect to claim 1 and claim 7.

8. Claim 13

141. Claim 13 of the ‘802 patent depends from claim 1 and is set forth below.

13. The method of claim 1, wherein the antigen is purified.

142. Thomas teaches a purified ZIKV antigen in a method of vaccinating a human against ZIKV infection. 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 (e.g., generating an immune response in a subject at risk of infection and/or in need of preventative treatment, or raising antibodies in a subject, or alleviating symptoms of ZIKV in an infected

subject, and the like).” EX 1004 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.” Accordingly, Thomas teaches this limitation of claim 13 and all of the limitations of claim 1 and therefore anticipates claim 13. Claim 13 is also obvious in view of Thomas for the same reasons expressed with respect to claim 1, and further that selecting a purified antigen is an advantageous option expressly taught by Thomas that is well within the skill of a POSA.

9. Claim 19

143. Claim 19 of the ‘802 patent depends from claim 1 and is set forth below.

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.

144. In Example 5: ZIKV PIV Performance in Human Trials, Thomas teaches administering a dose of 5 μg of an antigen from a Zika virus. EX 1004 41:7-8: “Two doses were administered at 0 and 28 days, 5 μg per dose, and adjuvanted with alum.” 5 μg per dose is within about 5 μg . Accordingly, Thomas teaches this limitation of claim 19 and all of the limitations of claim 1 and therefore anticipates claim 19. Claim 19 is also obvious in view of Thomas for the same reasons expressed with respect to claim 1, and further that selecting a dose amount and a dose regimen are options expressly taught by Thomas that are well within the skill of a POSA, as I describe herein.

10. Claim 21

145. Claim 21 of the '802 patent depends from claim 1 and is set forth below.

21. The method of claim 1, wherein the vaccine or immunogenic composition further comprises an aluminum salt adjuvant.

146. In Example 5: ZIKV PIV Performance in Human Trials, Thomas teaches administering a dose of 5 µg of an antigen from a Zika virus, adjuvanted with alum. EX 1004 41:7-8. Thomas teaches that the vaccine compositions can include one or more adjuvants such as an aluminum salt which Thomas teaches is aluminum hydroxide gel otherwise known as “alum”. 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.”)

147. Accordingly, Thomas teaches this limitation of claim 21 and all of the limitations of claim 1 and therefore anticipates claim 21. Claim 21 is also obvious in view of Thomas for the same reasons expressed with respect to claim 1, and further that selecting an aluminum salt adjuvant is an option expressly taught by Thomas that is well within the skill of a POSA.

11. Claim 23

148. Claim 23 of the '802 patent depends from claim 21 which depends from claim 1 and is set forth below.

21. The method of claim 1, wherein the vaccine or immunogenic composition further comprises an aluminum salt adjuvant.

23. The method of claim 21, wherein the adjuvant is aluminum hydroxide.

149. In Example 5: ZIKV PIV Performance in Human Trials, Thomas teaches administering a dose of 5 µg of an antigen from a Zika virus, adjuvanted with alum. EX 1004 41:7-8. Alum is aluminum hydroxide. EX 1004 28:18-24 (“suitable inorganic adjuvants include, but are not limited to, for example, an aluminum salt, such as aluminum hydroxide gel (alum)”). Accordingly, Thomas teaches this limitation of claim 23 and all of the limitations of claims 21 and 1 and therefore anticipates claim 23. Claim 23 is also obvious in view of Thomas for the same reasons expressed with respect to claim 1, and further that selecting an aluminum hydroxide adjuvant is an option expressly taught by Thomas that is well within the skill of a POSA.

12. Claim 27

150. Claim 27 of the ‘802 patent depends from claim 1 and is set forth below.

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.

151. In Example 5: ZIKV PIV Performance in Human Trials, Thomas teaches that there were no “serious adverse events related to vaccination” (EX 1004 41:16) and that “ZPIV was well tolerated and safe in a small number of volunteers”. EX 1004 43:14. Accordingly, Thomas teaches this limitation of claim 27 and all of the limitations of claim 1 and therefore anticipates claim 27. Claim 27 is also obvious

in view of Thomas for the same reasons expressed with respect to claim 1, and further that selecting administration that does not result in the human subject having a severe adverse event as a result of the administration is an advantageous option and objective expressly taught by Thomas that is well within the skill of a POSA.

13. Claim 28

152. Claim 28 of the '802 patent depends from 27 which depends from claim 1 and is set forth below.

28. The method of claim 27, wherein the severe adverse event is a fever of a temperature of 39° C. or higher.

153. In Example 5: ZIKV PIV Performance in Human Trials, since Thomas teaches that there were no “serious adverse events related to vaccination” (EX 1004 41:16) and that “ZPIV was well tolerated and safe in a small number of volunteers” (EX 1004 43:14). Thomas teaches that no serious adverse events related to vaccination were observed and so accordingly teaches that no fever of a temperature of 39° C. or higher resulted from the vaccinations. Accordingly, Thomas teaches this limitation of claim 28 and all of the limitations of claim 27 and claim 1 and therefore anticipates claim 28. Claim 28 is also obvious in view of Thomas for the same reasons expressed with respect to claim 1 and claim 27, and further that selecting the severe adverse event is a fever of a temperature of 39° C. or higher is an adverse event that can occur as a result of vaccination and a POSA would have been motivated to avoid such an adverse event for the health of the human subject.

14. Claim 29

154. Claim 29 of the '802 patent depends from claim 1 and is set forth below.

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.

155. Thomas teaches administering the vaccine to individuals in a region where Zika is potentially endemic. 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 to understand safety and immunogenicity performance in scenarios where dengue and Zika are potentially endemic.”). Thomas, therefore, teaches to administer the vaccine to a subject from a Zika endemic region, i.e. an area having recently experienced a large Zika outbreak. Accordingly, Thomas teaches this limitation of claim 29 and all of the limitations of claim 1 and therefore anticipates claim 29. Claim 29 is also obvious in view of Thomas for the same reasons expressed with respect to claim 1, and further that selecting the subject to be from a Zika endemic region or from a Zika non-endemic region travelling to an endemic region is an option expressly taught by Thomas to address Zika endemics and that is well within the skill of a POSA.

15. Claim 30

156. Claim 30 of the '802 patent depends from claim 1 and is set forth below.

30. The method of claim 1, wherein the subject is 18 to 29 years of age or 30 to 49 years of age.

157. In Example 5: ZIKV PIV Performance in Human Trials, Thomas teaches that the mean age of the volunteers was 31.5 years which teaches individual ages within the range of 30 to 49 years of age. EX 1004 41:13-15. Accordingly, Thomas teaches this limitation of claim 30 and all of the limitations of claim 1 and therefore anticipates claim 30. Claim 30 is also obvious in view of Thomas for the same reasons expressed with respect to claim 1, and further that selecting the subject to be 18 to 29 years of age or 30 to 49 years of age is an option expressly taught by Thomas that is well within the skill of a POSA.

16. Claim 31

158. Claim 31 of the '802 patent depends from claim 1 and is set forth below.

31. The method of claim 1, wherein the subject is a female subject.

159. Thomas teaches use of a purified inactivated whole virus with pregnant women because of a “superior safety profile”. EX 1004 18:28-30. In Example 5: ZIKV PIV Performance in Human Trials, Thomas teaches 55 human volunteers with 52% being male and 48% being female. EX 1004 41:12-13. Accordingly, Thomas teaches this limitation of claim 31 and all of the limitations of claim 1 and therefore anticipates claim 31. Claim 31 is also obvious in view of Thomas for the same reasons expressed with respect to claim 1, and further that selecting the subject to be female is an option expressly taught by Thomas that is well within the skill of a POSA.

17. Claim 59

160. Claim 59 of the '802 patent depends from claim 1 and is set forth below.

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%.

161. In Example 5: ZIKV PIV Performance in Human Trials, Thomas teaches that Trial 2 Group having 20 volunteers exhibited a seroconversion rate of 92% (EX 1004 42:6) meeting the population of at least 20 Zika virus seronegative subjects limitation of claim 1. Thomas further teaches Trial 3 Group having 10 Zika virus seronegative subjects exhibited a seroconversion rate of 100% (EX 1004 42:6-7) meeting the limitation of at least 95% or 100% of claim 59. Accordingly, Thomas teaches this limitation of claim 59 and all of the limitations of claim 1 and therefore anticipates claim 59. Claim 59 is also obvious in view of Thomas for the same reasons expressed with respect to claim 1, and further that achieving a seroconversion rate and selecting timing after the boost administrations are options expressly taught by Thomas that are well within the skill of a POSA.

VIII. GROUND II: Claim 11, 60, 61 and 62 are Invalid as Being Obvious Over Thomas.

A. The Claims are Obvious Over Thomas

162. A detailed claim chart comparing each feature of claims 11, 60, 61 and 62 and where each feature is taught in Thomas is provided in Appendix B.

B. Claim by Claim Analysis

1. Claim 11

163. Claim 11 of the '802 patent is set forth below.

11. A method of vaccinating against Zika virus infection in a human subject in need thereof,

the method comprising administering to the human subject a vaccine or immunogenic composition comprising a dose of from about 1 μ g to about 40 μ g of an antigen from a Zika virus,

wherein the antigen is an inactivated whole virus,

wherein the vaccine or immunogenic composition is administered one or more times,

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.

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

164. This feature of claim 11 is identical to claim 1. As demonstrated in VII(B)(1)(a) incorporated herein by reference, Thomas teaches this aspect of claim 11.

b. administering to the human subject a vaccine or immunogenic composition comprising a dose of from about 1 μ g to about 40 μ g of an antigen from a Zika virus

165. This feature of claim 11 is identical to claim 1. As demonstrated in VII(B)(1)(b) incorporated herein by reference, Thomas teaches this aspect of claim 11.

c. wherein the antigen is an inactivated whole virus,

166. This feature of claim 11 is identical to claim 1. As demonstrated in

VII(B)(1)(c) incorporated herein by reference, Thomas teaches this aspect of claim 11.

d. wherein the vaccine or immunogenic composition is administered one or more times,

167. This feature of claim 11 includes the administration of a first (prime) and a second (boost) administration which is recited in claim 1. As demonstrated in VII(B)(1)(c) incorporated herein by reference, Thomas teaches this aspect of claim 11, i.e. administering one or more times, which includes a first (prime) and a second (boost) administration.

e. 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.

168. The '802 patent provides no data supporting the claimed seroconversion rate of at least of 60% after a single dose or prime administration. The at least 20 Zika virus seronegative subjects in claim 11 refers to human subjects since claim 11 is directed to a method of vaccinating against Zika virus infection in a human subject, and so the claimed seroconversion rate relates to that in human subjects in order to support the claimed objective of vaccinating against Zika virus in a human subject.

169. In Example 5: ZIKV PIV Performance in Human Trials, Thomas teaches a seroconversion rate of 92% for 55 humans at day 57 after a boost

administration. A seroconversion rate of 92% is within the claimed range of at least 60%. The Table indicates prime administration at day 1 and boost administration at day 29. Day 57 is 28 days after the boost administration. 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%”. See also EX 1004 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 a seroconversion rate of at least 60% in a population of at least 20 Zika virus seronegative subjects.

170. Thomas further teaches that “[t]he purified, inactivated ZIKV can be used to immunize mammals (including humans) to elicit high titers of virus neutralizing antibodies and protect the immunized mammal from disease caused by ZIKV. For example, a single immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against challenge with ZIKV. Another example is wherein two doses are administered (e.g., a first dose, followed by a second dose 4 weeks later). A booster dose (second dose or more) may be useful for persons with recurrent infection risk.” EX 1004 4:15-22. “Booster doses may be used, if needed.” EX 1004 7:11. “Ideally, only one dose is needed to effect protection against Zika infection for mammals, including humans.” EX 1004 7:30-

32. “An exemplary dosage schedule entails an initial dose, then a second (booster) dose about 4 weeks later. However, this schedule is exemplary only, and someone skilled in the art would be able to determine without undue experimentation if and when any second dose is needed.” EX 1004 7:32-8:2. “With the information known about the dosing and schedule for other PIV flavivirus vaccines – such as Japanese encephalitis and tick-borne encephalitis – 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 1004 4:24-28. “Based on these models, and 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, or a booster dose at 4 weeks as described below.)” EX 1004 18:17-20.

171. Thomas teaches the use of adjuvants in a vaccine dose and that an adjuvant “is a substance that serves to enhance, accelerate, or prolong the antigen-specific immune response of an antigen when used in combination with specific vaccine antigens but do not stimulate an immune response when used alone.” EX 1004 28:19-22.

172. Thomas teaches in Example 5. ZIKV PIV Performance in Human Trials for a 5 μ g dose that “[a]ntibody kinetics based on MN50 titers indicat[ed] a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff”. EX 1004 42:9-10. See also EX 1004 Table at page 42 Day 1 after

prime administration, GMT of 5.0 for N=55 volunteers. Thomas also teaches that administering a dose of an inactivated, whole Zika virus antigen vaccine effects seroconversion of the human to whom the dose is administered. In particular, seroconversion is increased relative to a human who has not received the vaccine dose after a first (prime) dose and after a second (boost) dose. EX 1004 42:4-23. Accordingly, a vaccine dose including an inactivated, whole Zika virus antigen and an adjuvant which results in seroconversion and, accordingly, a seroconversion rate among study participants, would be recognized by a 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.

173. Thomas does not teach 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.

174. However, Thomas does teach 100% complete protection after a single immunization of the ZIKV vaccine. EX 1004 4:15-22. Thomas teaches a slight rise in antibody after the first (prime) dose of vaccine. 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 1004 7:30-32. Thomas also teaches that a booster dose is not required. EX 1004 4:15-22 and EX 1004 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 1004 42:4-7.

175. It is within the level of one of ordinary skill in the art to use Thomas's method for achieving seroconversion after a first (prime) administration or after a second (boost) administration of a purified, inactivated whole Zika virus antigen in a population of at least 20 Zika virus seronegative subjects 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.

176. One would have been motivated to modify the vaccine dose of Thomas exemplified in Example 5. ZIKV PIV Performance in Human Trials 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 1004 7:30-32. Further, 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. Thomas teaches that based on animal models in the field of flavivirus PIVs, a single dose is a safe and effective dosage. EX 1004 18:17-20. Thomas teaches that a seroconversion rate of 92% can be achieved and is desirable. See Example 5. ZIKV PIV Performance in Human Trials, EX 1004 42:4-8. Thomas teaches that

administering a single dose of its vaccine results in a slight rise in antibody, i.e. seroconversion. EX 1004 42:9-10.

177. Based on Thomas, one of skill 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 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 a single dose is effective and increasing the antibody titer after a single dose or prime 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 vaccine dose affects seroconversion after a first (prime) dose, as well as after a second (boost) dose.

178. One of skill would have had a reasonable expectation of successfully modifying the vaccine dose of Thomas exemplified in Example 5. ZIKV PIV Performance in Human Trials 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 “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 60% 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.

179. Accordingly, claim 11 is obvious in view of Thomas.

2. Claim 60

180. Claim 60 of the '802 patent depends from claim 11 and is set forth below.

60. The method of claim 11, 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 80% in a population of at least 20 Zika virus seronegative subjects.

181. Claim 60 increases the seroconversion rate relative to claim 11 from at least 60% to 80%. The analysis of claim 11 above in VIII(B)(1)(e) is incorporated by reference herein. As detailed above with respect to claim 11, Thomas teaches in Example 5: ZIKV PIV Performance in Human Trials, 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 80%.

182. Thomas does not teach a seroconversion rate of 80% in a population of at least 20 Zika virus seronegative subjects 14 and/or 28 days after a single dose or prime administration.

183. One would have been motivated to modify the vaccine dose of Thomas exemplified in Example 5. ZIKV PIV Performance in Human Trials by either the amount of antigen and/or adjuvant or the type of adjuvant to induce a seroconversion rate of 80% 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 1004 7:30-32. Further, 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. Thomas teaches that based on animal models in the field of flavivirus PIVs, a single dose is a safe and effective dosage. EX 1004 18:17-20. Thomas teaches that a seroconversion rate of 92% can be achieved and is desirable. See Example 5. ZIKV PIV Performance in Human Trials, Ex 1004 42:4-8. Thomas teaches that administering a single dose of its vaccine results in a slight rise in antibody, i.e. seroconversion. EX 1004 42:9-10. Thomas also teaches that administering a dose of an inactivated, whole Zika virus antigen vaccine effects seroconversion of the human to which the dose is administered. In particular, seroconversion is increased relative to a human who has not received the vaccine dose after a first (prime) dose, as well as, after a second (boost) dose. EX 1004 42:4-23. Accordingly, a vaccine dose including an inactivated, whole Zika virus antigen and an adjuvant which

results in seroconversion and, accordingly, a seroconversion rate among study participants, would be recognized by a 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.

184. Based on Thomas, one of skill 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 80% 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 or prime 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 vaccine dose affects seroconversion after a first (prime) dose, as well as after a second (boost) dose.

185. One of skill would have had a reasonable expectation of successfully modifying the vaccine of Thomas exemplified in Example 5. ZIKV PIV Performance in Human Trials to induce a seroconversion rate of 80% 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 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. Further, Thomas demonstrated that a seroconversion rate of 92% was achieved, and so one of skill would reasonably expect that a lower seroconversion rate of 80% could be achieved. Achieving a seroconversion rate of 80% 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.

186. Accordingly, claim 60 is obvious in view of Thomas.

3. Claim 61

187. Claim 61 of the ‘802 patent depends from claim 11 and is set forth below.

61. The method of claim 11, 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 90% in a population of at least 20 Zika virus seronegative subjects.

188. Claim 61 increases the seroconversion rate relative to claim 11 from at least 60% to 90%. The analysis of claim 11 above in VIII(B)(1)(e) is incorporated by reference herein. As detailed above with respect to claim 11, Thomas teaches in Example 5: ZIKV PIV Performance in Human Trials, 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 90%.

189. Thomas does not teach a seroconversion rate of 90% in a population of at least 20 Zika virus seronegative subjects 14 and/or 28 days after a single dose or prime administration.

190. One would have been motivated to modify the vaccine dose of Thomas exemplified in Example 5. ZIKV PIV Performance in Human Trials by either the amount of antigen and/or adjuvant or the type of adjuvant to induce a seroconversion rate of 90% 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 1004 7:30-32. Further, 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. Thomas teaches that based on animal models in the field of flavivirus PIVs, a single dose is a safe and effective dosage. EX 1004 18:17-20. Thomas teaches that a seroconversion rate of 92% can be achieved and is desirable. See Example 5. ZIKV PIV Performance in Human Trials, EX 1004 42:4-8. Thomas teaches that administering a single dose of its vaccine results in a slight rise in antibody, i.e. seroconversion. EX 1004 42:9-10. Thomas also teaches that administering a dose of an inactivated, whole Zika virus antigen vaccine effects seroconversion of the human to which the dose is administered. In particular, seroconversion is increased

relative to a human who has not received the vaccine dose after a first (prime) dose, as well as, after a second (boost) dose. EX 1004 42:4-23. Accordingly, a vaccine dose including an inactivated, whole Zika virus antigen and an adjuvant which results in seroconversion and, accordingly, a seroconversion rate among study participants, would be recognized by a 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.

191. Based on Thomas, one of skill 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 90% 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 or prime 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 vaccine dose affects seroconversion after a first (prime) dose, as well as after a second (boost) dose.

192. One of skill would have had a reasonable expectation of successfully modifying the vaccine of Thomas exemplified in Example 5. ZIKV PIV

Performance in Human Trials to induce a seroconversion rate of 90% 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 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. Further, Thomas demonstrated that a seroconversion rate of 92% was achieved, and so one of skill would reasonably expect that a lower seroconversion rate of 90% could be achieved. Achieving a seroconversion rate of 90% 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.

193. Accordingly, claim 61 is obvious in view of Thomas.

4. Claim 62

194. Claim 62 of the ‘802 patent depends from claim 11 and is set forth below.

62. The method of claim 11, 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 95% in a population of at least 20 Zika virus seronegative subjects.

195. Claim 62 increases the seroconversion rate relative to claim 11 from at least 60% to 95%. The analysis of claim 11 above in VIII(B)(1)(e) is incorporated by reference herein. As detailed above with respect to claim 11, Thomas teaches in

Example 5: ZIKV PIV Performance in Human Trials, a seroconversion rate of 92% for 55 humans at day 57 after a boost administration. A seroconversion rate of 92% is below the claimed value of 95%.

196. Thomas does not teach a seroconversion rate of 95% in a population of at least 20 Zika virus seronegative subjects 14 and/or 28 days after a single dose or prime administration.

197. However, Thomas teaches in Example 5: ZIKV PIV Performance in Human Trials, a seroconversion rate of 100% for Trial Group 3 of 10 individuals after a boost administration. Thomas also teaches that administering a dose of an inactivated, whole Zika virus antigen vaccine effects seroconversion of the human to which the dose is administered. In particular, seroconversion is increased relative to a human who has not received the vaccine dose after a first (prime) dose, as well as, after a second (boost) dose. EX 1004 42:4-23. Accordingly, dosage of an inactivated, whole Zika virus antigen vaccine which results in a seroconversion, would be recognized by a POSA as a result-effective variable.

198. One would have been motivated to modify the vaccine dose of Thomas exemplified in Example 5. ZIKV PIV Performance in Human Trials by either the amount of antigen and/or adjuvant or the type of adjuvant to induce a seroconversion rate of 95% 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 1004 7:30-32. Further, 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. Thomas teaches that based on animal models in the field of flavivirus PIVs, a single dose is a safe and effective dosage. EX 1004 18:17-20. Thomas teaches that a seroconversion rate of 92% can be achieved and is desirable and also that a seroconversion rate of 100% can be achieved and is desirable. See Example 5. ZIKV PIV Performance in Human Trials, EX 1004 42:4-8. Thomas teaches that administering a single dose of its vaccine results in a slight rise in antibody, i.e. seroconversion. EX 1004 42:9-10. Thomas also teaches that administering a dose of an inactivated, whole Zika virus antigen vaccine effects seroconversion of the human to which the dose is administered. In particular, seroconversion is increased relative to a human who has not received the vaccine dose after a first (prime) dose, as well as, after a second (boost) dose. EX 1004 42:4-23. Accordingly, a vaccine dose including an inactivated, whole Zika virus antigen and an adjuvant which results in seroconversion and, accordingly, a seroconversion rate among study participants, would be recognized by a 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.

199. Based on Thomas, one of skill 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 95% 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 or prime 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 vaccine dose affects seroconversion after a first (prime) dose, as well as after a second (boost) dose.

200. One of skill would have had a reasonable expectation of successfully modifying the vaccine of Thomas exemplified in Example 5. ZIKV PIV Performance in Human Trials to induce a seroconversion rate of 95% 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 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. Further, Thomas demonstrated that seroconversion rates of 92% and 100% were achieved, and so one of skill would

reasonably expect that a seroconversion rate of 95% in between 92% and 100% could be achieved. Achieving a seroconversion rate of 95% 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.

201. Accordingly, claim 62 is obvious in view of Thomas.

IX. GROUND III: Claims 8, 12, 14, 22 and 24 are Invalid as Being Obvious Over Thomas and Barbero

A. The Claims are Obvious Over Thomas and Barbero

202. A detailed claim chart comparing each feature of claims 8, 12, 14, 22 and 24 and where each feature is taught in Thomas and Barbero is provided in Appendix B.

B. Claim by Claim Analysis

1. Claim 8

203. Claim 8 of the '802 patent depends from claim 1 and is set forth below.

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).

204. As previously demonstrated at VII(B)(1), Thomas teaches each and every limitation of claim 1. Claim 8 requires generation of neutralizing antibodies titers to Zika virus in a subject of greater than 1000, as determined by the PRNT.

“Neutralizing antibody titer” simply refers to the level or concentration of neutralizing antibodies present in blood that are produced in response to an antigen. The higher the titer, the greater the concentration of neutralizing antibodies in the blood, and the more potent the immune response. One of skill would determine and use neutralizing antibody titer as a measure of the strength of the immune response and immune protection.

205. Thomas 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. One of skill would have looked to the art for examples of determining neutralizing antibody titers to Zika virus as a matter of routine skill and would have been aware of Barbero.

206. Thomas teaches that “[t]here is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.” EX 1004 3:2-5. Thomas teaches to determine generation of neutralizing antibodies titers to Zika virus using a “high-throughput ZIKV MN assay” as described in Larocca et al., “Vaccine protection against Zika virus from Brazil.” *Nature* 536: 474-478 (Jun. 28, 2016). EX 1004 34:26-28. Thomas reports “[p]eak titers for Trial Group 1 and trial Group 3 volunteers occur on or about study day 43 (2 weeks post dose 2) and are between 500 and 1000.” EX 1004 42:12-13. Thomas further teaches with reference to Figure

21 that at day 57 “[a]pproximately 10% of the cohort has titers of 1000.” EX 1004 15:22-27. Thomas provides Figure 20 which demonstrates GMT determined by the MN₅₀ assay based on the trial study groups of human volunteers. EX 1004 15:20-21. Figure 20 shows that members of 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 1004, Fig. 20. Similarly, Figure 21 shows that members of 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 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 MN assay. Additionally, one of skill 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.

207. Thomas does not measure generation of neutralizing antibodies by the PRNT. However, Barbero WO2017/109223 (EX 1005) cited by the Examiner during prosecution and directed to the development and use of a Zika vaccine for vaccinating against Zika virus infection, teaches that “seroconversion of a subject is assessed by performing a PRNT. Briefly, PRNT is used to determine the serum titer

required to reduce the number of Zika virus plaques by 50% (PRNT50) as compared to a control serum antibody. . . . A threshold of neutralizing antibodies of 1:10 dilution of serum in a PRNT50 is generally accepted as evidence of protection (Hombach et al. Vaccine (2005) 23:5205-5211).” EX 1005 22:25-35. See also EX 1005 114:9-30 describing use of the PRNT assay in mice. Seroconversion, which is assessed in Thomas by the MN assay, is the generation of neutralizing antibodies in response to the Zika vaccine.

208. Further, just like Thomas, Barbero teaches use of the same MN assay described in Larocca et al., Nature 536: 474-478 (Jun. 28, 2016) to determine neutralizing antibody titers in mice. EX 1005 114:32-35. Accordingly, Barbero teaches use of both the MN assay and the PRNT to assess neutralizing antibody titer.

209. In my opinion, both the PRNT and MN assays are valid methods of measuring the antibody titer, which reflects seroconversion. As background art, Liu reports that good correlation was observed between the two assays. EX 1012 p. 73, 76, 77. Since Barbero teaches to use both the MN assay and the PRNT assay, a POSA would have understood from Barbero that the methods were interchangeable and would produce similar results regarding antibody titer reflecting seroconversion and a protective immune response.

210. The combination of Thomas and Barbero teaches each element of claim 8 including the elements of claim 1 from which claim 8 depends.

211. It is within the level of skill of one of ordinary skill in the art to use the known method of PRNT of Barbero to determine neutralizing antibody titers because to do so would have only required routine skill insofar as Barbero teaches how to use the PRNT assay to determine neutralizing antibody titers.

212. One would have been motivated to modify the method of Thomas to measure neutralizing antibody titers using PRNT instead of MN50 because Barbero teaches that both PRNT and MN50 are known methods for measuring neutralizing antibody titers, and that each can be used to measure neutralizing antibody titers from a Zika vaccine, as an indication of seroconversion and a protective immune response.

213. One of skill would have had a reasonable expectation of successfully using PRNT instead of MN50 to determine neutralizing antibody titers as an indication of seroconversion and a protective immune response because Barbero teaches successful use of each method to determine neutralizing antibody titers from a Zika vaccine. The substitution of one known method for another known method to achieve the same purpose does not result in patentability absent unexpected results. Each method is known to determine neutralizing antibody titers. PRNT is used for the same objective as MN50, i.e., to measure neutralizing antibody titers, and produces no unexpected result.

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

2. Claim 12

215. Claim 12 of the '802 patent depends from 1 and is set forth below.

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).

216. As previously demonstrated at VII(B)(1), Thomas teaches each and every limitation of claim 1. Claim 12 requires determining 14 and/or 28 days after the boost administration, GMT 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 higher than the GMT induced 28 days after the prime administration, as determined by the PRNT.

217. Thomas 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. One of skill would have looked to the art for examples of determining GMT as a matter of routine skill and would have been aware of Barbero.

218. Thomas teaches that “[t]here is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.” EX 1004 3:2-5. Thomas teaches that

seroconversion is measured by the MN50 assay. EX 1004 42:4. Thomas teaches at the Table (below) at page 42 that GMT 14 or 28 days after the second (boost) administration (Day 43 or day 57) is greater than 10 times higher to that 28 days (day 29) after the first (prime) administration, albeit using the MN50 assay. EX 1004 42:19-20.

Time Point ^a	Statistic	5 meg ZPIV				Placebo
		16-0033 (N=25)	16-0062 (N=20)	Z0001 (N=10)	All (N=55)	All (N=12)
Day 1	N*	25	20	10	55	12
	GMT	5.0	5.0	5.0	5.0	5.0
	95% CI	-	-	-	-	-
Day 15	N*	25	-	10	35	7
	GMT	5.0	-	8.6	5.8	5.0
	95% CI	-	-	2.5, 28.8	4.3, 8.0	-
Day 29	N*	25	20	10	55	12
	GMT	5.5	8.5	8.7	7.0	5.0
	95% CI	4.5, 6.8	4.7, 15.3	2.5, 30.4	5.2, 9.5	-
Day 43	N*	25	-	10	35	7
	GMT	316.9	-	983.3	437.9	5.0
	95% CI	152.9, 656.6	-	425.4, 2272.5	245.7, 780.6	-
Day 57	N*	25	17	9	51	12
	GMT	142.9	100.8	820.6	173.1	5.0
	95% CI	70.3, 290.4	39.7, 255.7	357.1, 1885.8	104.6, 286.5	-
Peak Titer	N*	25	20	10	55	12
	GMT	345.6	64.2	1061.7	229.8	5.0
	95% CI	166.4, 718.0	25.3, 163.2	452.8, 2489.2	132.6, 398.4	-

219. The table shows data for group 16-0033 (N=25), group 16-0062 (N=20); group All (N=55). For each group, the GMT at day 43 or day 57 is more than 10 times the GMT at day 29. See 16-0033 (N=25), Day 29 (5.5), Day 43 (316.9), Day 57 (142.9). See 16-0062 (N=20), Day 29 (8.5), Day 57 (100.8). See All (N=55), Day 29 (7.0), Day 43 (437.9), Day 57 (173.1). EX 1004 42:19-20.

220. Thomas does not determine seroconversion and GMT by the PRNT. However, Barbero WO2017/109223 cited by the Examiner during prosecution and

directed to the development and use of a Zika vaccine for vaccinating against Zika virus infection, teaches that “seroconversion of a subject is assessed by performing a PRNT. Briefly, PRNT is used to determine the serum titer required to reduce the number of Zika virus plaques by 50% (PRNT50) as compared to a control serum antibody. . . . A threshold of neutralizing antibodies of 1:10 dilution of serum in a PRNT50 is generally accepted as evidence of protection (Hombach et al. Vaccine (2005) 23:5205-5211).” EX 1005 22:25-35. See also EX 1005 114:9-30 describing use of the PRNT assay in mice. Seroconversion, which is assessed in Thomas by the MN assay, is the generation of neutralizing antibodies in response to the Zika vaccine.

221. Further, just like Thomas, Barbero teaches use of the same MN assay described in Larocca et al., Nature 536: 474-478 (Jun. 28, 2016) to determine neutralizing antibody titers in mice. EX 1005 114:32-35. Accordingly, Barbero teaches use of both the MN assay and the PRNT to assess neutralizing antibody titer.

222. In my opinion, both the PRNT and MN assays are valid methods of measuring the antibody titer, which reflects seroconversion. As background art, Liu reports that good correlation was observed between the two assays. EX 1012 p. 73, 76, 77. Since Barbero teaches to use both the MN assay and the PRNT assay, a POSA would have understood from Barbero that the methods were interchangeable and would produce similar results regarding antibody titer reflecting seroconversion

and a protective immune response.

223. The combination of Thomas and Barbero teaches each element of claim 12 including the elements of claim 1 from which claim 12 depends.

224. It is within the level of skill of one of ordinary skill in the art to use the known method of PRNT of Barbero to determine neutralizing antibody titers and therefore GMT, because to do so would have only required routine skill insofar as Barbero teaches how to use the PRNT assay to determine neutralizing antibody titers. Additionally, one of skill would have been motivated to achieve a higher neutralizing antibody titer after booster administration, e.g., by adjusting the dosages of antigen at prime administration and/or boost administration, to obtain the desired immune protection.

225. One would have been motivated to modify the method of Thomas to determine GMT using PRNT instead of MN50 because Barbero teaches that both PRNT and MN50 are known methods for measuring neutralizing antibody titers, and that each can be used to measure neutralizing antibody titers from a Zika vaccine, as an indication of seroconversion and a protective immune response.

226. One of skill would have had a reasonable expectation of successfully using PRNT instead of MN50 to determine neutralizing antibody titers and therefore GMT, because Barbero teaches successful use of each method to determine generation of neutralizing antibody titers from a Zika vaccine. The substitution of

one known method for another known method to achieve the same purpose does not result in patentability absent unexpected results. Each method is known to determine neutralizing antibody titers. PRNT is used for the same objective as MN50, i.e., to measure neutralizing antibody titers, and produces no unexpected result.

227. Accordingly claim 12 is obvious in view of Thomas and Barbero.

3. Claim 14

228. Claim 14 of the '802 patent depends from claim 13 which depends from claim 1 and is set forth below.

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.

229. As previously demonstrated at VII(B)(1) and VII(B)(8), Thomas teaches each and every limitation of claims 1 and 13. Claim 14 requires that 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.

230. Thomas 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. One of skill would have looked to the art for examples of ZPIV vaccine purification techniques as a matter of routine skill and would have been aware of Barbero.

231. Thomas teaches that “[t]here is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.” EX 1004 3:2-5. Thomas teaches that ZIKV can be purified and the “level of purity is according to the guidelines of the U.S. Food and Drug Administration (FDA).” EX 1004 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 1004 20:19-24. Size exclusion chromatography is a known method that separates molecules based on their size by filtration through a gel. In my opinion, main peak of the antigen when analyzed by size exclusion chromatography as a percent of the total area under the curve in the size exclusion chromatography would be understood as corresponding to the purity of an antigen preparation. The ‘802 patent admits that “[t]he purity of the purified antigen can be determined by size exclusion chromatography and the %-purity corresponds to the % of the main peak to the total area under the curve.” EX 1001 37:16-19.

232. Thomas teaches purification by size exclusion chromatography, but does not teach that the main peak of the antigen is more than 85% of the total area under the curve when analyzed by size exclusion chromatography. However, 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 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. One of skill would understand that a purity of greater than 90% as determined by size exclusion chromatography is within the claimed more than 85% of the total area under the curve in the size exclusion chromatography.

233. HPLC is a known method that achieves separation by pressure-driven flow of a mobile phase through a column packed with a stationary phase. The mobile phase carries a liquid sample through the column to the detector, and compounds or analytes separate due to varying degrees of interaction with the stationary phase. A detector measures the analytes after elution from the column, and a chromatography data system (CDS) translates the detected signal. The translated data output of an HPLC analysis is a series of peaks called a chromatogram, where the x-axis is a measure of time and the y-axis measures a specific signal generated by the detector.

234. Barbero, therefore, teaches an antigen purity of greater than 90% and an HPLC peak for such a pure antigen analyzed by size exclusion chromatography. Barbero, therefore, teaches a main peak for the antigen which is more than 85% of the total area under the curve in the size exclusion chromatography.

235. The combination of Thomas and Barbero teaches each element of claim 14 including the elements of claim 1 and 13 from which claim 14 depends.

236. It is within the level of skill of one of ordinary skill in the art to utilize the known method, e.g., SEC-HPLC (Size Exclusion Chromatography – HPLC) method of Barbero to evaluate or confirm the desired purity of an antigen preparation of greater than 90% as indicated by an HPLC main peak for the antigen because Thomas teaches to purify ZIKV antigen by size exclusion chromatography and to do so would have only required routine skill insofar as Barbero teaches how to use the known method of SEC-HPLC (Size Exclusion Chromatography – HPLC) to analyze purity.

237. One would have been motivated to obtain a desired purity level for an antigen preparation for vaccination that is more than 85%, as reflected by more than 85% of the total area under the curve determined in the size exclusion chromatography, because Barbero teaches greater than 90% purity as determined by size exclusion chromatography.

238. One of skill would have had a reasonable expectation of successfully using size exclusion chromatography to identify the main peak of the Zika virus antigen being more than 85% of the total area under the curve in the size exclusion chromatography because Barbero teaches successful use of size exclusion chromatography to achieve greater than 90% purity. Where the general conditions

of a claim are disclosed in the prior art, i.e., purity as indicated by area under the curve using size exclusion chromatography, it is not inventive to discover the optimum or workable ranges by routine experimentation. No invention is involved in discovering optimum ranges of a process by routine experimentation.

239. Accordingly, claim 14 is obvious in view of Thomas and Barbero.

4. Claim 22

240. Claim 22 of the '802 patent depends from claim 21 which depends from claim 1 and is set forth below.

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 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.

241. As previously demonstrated at VII(B)(1) and VII(B)(10), Thomas teaches each and every limitation of claims 1 and 21. Claim 22 requires from about 100 μg to about 600 μg , among other narrower ranges, of an aluminum salt as adjuvant.

242. Thomas 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. One of skill would have looked to the art for examples of ZPIV adjuvant amounts as a matter of routine skill and would have been aware of Barbero.

243. Thomas teaches that the vaccine compositions can include one or more adjuvants such as an aluminum salt or aluminum hydroxide gel. EX 1004 28:18-24 (“Suitable inorganic adjuvants include, but are not limited to, for example, an aluminum salt, such as aluminum hydroxide gel (alum) or aluminum phosphate”) Thomas does not teach a specific amount of the adjuvant. However, a POSA would have understood that the amount of adjuvant is a result-effective variable insofar as the amount of adjuvant affects the immune response to the vaccine as taught by Thomas. EX 1004 p. 28:19-22 (“An ‘adjuvant’ is a substance that serves to enhance, accelerate, or prolong the antigen-specific immune response of the antigen when used in combination with specific vaccine antigens but do not stimulate an immune response when used alone.”)

244. Barbero teaches a suitable amount of 500 µg of an aluminum hydroxide adjuvant per ml of ZIKV vaccine. EX 1005 112:2-4 (Aluminum hydroxide adjuvant “was added to a final concentration of 0.5 mg/ml Aluminium (1/20 v/v Alum 2% stock solution added) to prepare ZikaV Drug Product (DP).” One of skill would have understood that one ml is a suitable dose volume for a vaccine. Accordingly, Barbero teaches to a POSA a vaccine dose including 500 µg of an aluminum hydroxide adjuvant. The 500 µg of an aluminum hydroxide adjuvant is within the claimed range of from about 100 µg to about 600 µg.

245. The combination of Thomas and Barbero teaches each element of claim

22 including the elements of claims 1 and 21 from which claim 22 depends.

246. It is within the level of skill of one of ordinary skill in the art to utilize the known amount of 500 μg of an aluminum hydroxide adjuvant of Barbero with the known aluminum salt adjuvant of Thomas because to do so would have only required routine skill to select a specific amount of an aluminum-based adjuvant known in the art as a result-effective variable affecting seroconversion and combine it with an inactivated, purified whole virus antigen.

247. One would have been motivated to modify the method of Thomas to use 500 μg of Barbero for the aluminum salt adjuvant because Thomas teaches to use adjuvants as a component of the ZIKV vaccine “to enhance, accelerate, or prolong the antigen-specific immune response of the antigen when used in combination with specific vaccine antigens.” EX 1004 28:18-22. Thomas teaches to use “a suitable amount of adjuvant.” EX 1004 17:1. Barbero teaches that 500 $\mu\text{g}/\text{ml}$ is a suitable amount for a ZIKV vaccine and a POSA would have recognized that one ml is a suitable dose volume for a vaccine dose.

248. One of skill would have had a reasonable expectation of successfully using a 500 μg amount of adjuvant from Barbero with the aluminum salt of Thomas because both Thomas and Barbero teach to combine inactivated whole virus antigens with an aluminum hydroxide salt adjuvant (alum) when making a vaccine composition. Further, Barbero teaches that 500 μg is a suitable amount for an

aluminum hydroxide salt adjuvant per ml of Zika vaccine. Selecting the 500 µg amount based on Barbero is routine optimization of a result-effective variable affecting seroconversion.

249. Accordingly claim 22 is obvious in view of Thomas and Barbero.

5. Claim 24

250. Claim 24 of the '802 patent depends from claim 21 which depends from claim 1 and is set forth below.

21. The method of claim 1, wherein the vaccine or immunogenic composition further comprises an aluminum salt adjuvant.

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.

251. As previously demonstrated at VII(B)(1) and VII(B)(10), Thomas teaches each and every limitation of claims 1 and 21. Claim 24 requires that at least 75% of the antigen are adsorbed to the aluminum salt adjuvant.

252. Thomas teaches that “[t]here is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.” EX 1004 3:2-5. Thomas teaches that the ZIKV vaccine can be mixed with suitable adjuvants. EX 1004 4:31-5:1. Thomas teaches many adjuvants. EX 1004 28:18-29:31. Thomas teaches that the ZIKV used in Example 5. ZIKV PIV Performance in Human Trials is adjuvanted with alum.

EX 1004 41:6-8. Thomas teaches to use adjuvants as a component of the ZIKV vaccine “to enhance, accelerate, or prolong the antigen-specific immune response of the antigen when used in combination with specific vaccine antigens.” EX 1004 28:18-22. Thomas teaches to use “a suitable amount of adjuvant.” EX 1004 17:1. Thomas teaches that the vaccine compositions can include one or more adjuvants such as an aluminum salt. 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.”)

253. Thomas further teaches that “ZIKV purified inactivated vaccine (PIV) are produced at the Pilot Bioproduction Facility, Walter Reed Army Institute of Research, Silver Spring, MD, USA.” EX 1004 31:27-28. Thomas further teaches that Zika virus is related to “Japanese encephalitis viruses that are also members of the virus family Flaviviridae. Along with other viruses in this family, ZIKV is an enveloped and icosahedral and non-segmented, single stranded, positive sense RNA genome.” EX 1004 1:24-29. Thomas further teaches that Zika virus is a mosquito-borne virus within the same Flaviviridae family as Japanese encephalitis virus. EX 1004 1:24-29.

254. Thomas further teaches to look to Japanese encephalitis virus vaccines for representative neutralizing antibody titers accepted by regulatory agencies to determine neutralizing antibody titers for a Zika virus vaccine. EX 1004 41:28 to

42:3. Thomas further teaches to look to Japanese encephalitis virus vaccines for determining dosing and schedules for a Zika virus vaccine. EX 1004 4:24-28.

255. Thomas does not teach that at least 75% of the antigen are adsorbed to the aluminum salt adjuvant. However, Thomas teaches to use “a suitable amount of adjuvant.” EX 1004 17:1. A POSA would have understood that the Zika virus antigen of Thomas is adsorbed to the aluminum salt adjuvant and that the amount of the adjuvant and the duration of contact between the adjuvant and the Zika virus antigen can be optimized as a matter of routine skill to result in a particular adsorption percentage.

256. Thomas 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. One of skill would have looked to the art for examples of how much antigen to adsorb to an adjuvant as a matter of routine skill because both Thomas and Barbero teach that vaccine compositions are known to include adjuvants and one of skill would have been aware of Barbero.

257. Barbero teaches that aluminum hydroxide adjuvant “was added to a final concentration of 0.5 mg/ml Aluminium (1/20 v/v Alum 2% stock solution added) to prepare ZikaV Drug Product (DP).” EX 1005 112:2-4. 0.5 mg/ml alum equates to 500 µg/ml and 500 µg alum per 1 ml dose. A one ml dose is a common amount for a vaccine dose. Accordingly, Barbero teaches to a POSA a vaccine dose

including 500 µg of alum as adjuvant. Barbero further teaches that “[t]he DP was gently mixed for 5 min. An aliquot of the DP was removed, Alum sedimented by centrifugation and the clear supernatant analysed by SEC-HPLC. No ZikaV peak was detected in the supernatant indicating complete adsorption (estimated as >95%) of viral particles on the mineral adjuvant.” EX 1005 112:4-7.

258. One of skill would have looked to prior art describing Zika vaccines to understand the amount of inactivated whole virus Zika antigen binding to aluminum hydroxide salt adjuvant.

259. It is within the level of skill of one of ordinary skill in the art to utilize known adjuvants because adjuvants were known to be combined with inactivated whole virus for making vaccine compositions. It is within the level of skill of one of ordinary skill in the art to determine the optimized amount of antigen adsorbed to the adjuvant as a matter of routine skill in formulating a ZIKV vaccine, because Thomas teaches to use “a suitable amount of adjuvant” and Barbero teaches how to determine Zika virus antigen adsorbed to alum adjuvant.

260. One of skill would have been motivated to optimize the amount of antigen adsorbed to adjuvant because Thomas teaches to use a “suitable amount” of adjuvant for the benefit “to enhance, accelerate, or prolong the antigen-specific immune response of the antigen”. Barbero teaches that an inactivated whole virus Zika antigen will adsorb to alum in an amount of >95%. EX 1005 112:4-7.

261. One of skill would have had a reasonable expectation of successfully having the amount of ZIKV antigen adsorbed to adjuvant in the amount of at least 75% because Thomas teaches to use “a suitable amount of adjuvant” and Barbero teaches that an inactivated whole virus Zika antigen will adsorb to alum in an amount of >95% which is included within at least 75%. EX 1005 112:4-7.

262. Both Thomas and Barbero teach that it is within routine skill to combine whole inactivated virus antigens with adjuvants. Based on Thomas and Barbero, one of skill would have expected a whole inactivated ZIKA virus antigen to bind to aluminum hydroxide adjuvant in an amount of at least 75%.

263. Accordingly claim 24 is obvious in view of Thomas and Barbero.

X. GROUND IV: Claim 25 is Invalid as Being Obvious Over Thomas and Murata.

A. The Claim is Obvious Over Thomas and Murata

264. A detailed claim chart comparing each feature of claim 25 and where each feature is taught in Thomas and Murata is provided in Appendix B.

B. Claim Analysis

1. Claim 25

265. Claim 25 of the ‘802 patent depends from claim 1 and is set forth below.

25. The method of claim 1, wherein the Zika virus is a clonal isolate, in particular from a plaque purified clonal Zika virus isolate.

266. As previously demonstrated at VII(B)(1), Thomas teaches each and every limitation of claim 1. Claim 25 requires that the Zika virus is a clonal isolate,

in particular from a plaque purified clonal Zika virus isolate.

267. Thomas teaches a method of (i) inoculating a cell culture with a ZIKV strain; (ii) propagating the virus in the inoculated cell culture; (iii) harvesting and isolating virus fluids from the inoculated cell culture to prepare a ZIKV concentrate; and (iv) purifying the ZIKV concentrate. EX 1004 5:25-32. Thomas teaches that Vero cells are a suitable cell line for culturing ZIKV to produce a “Master Seed”. EX 1004 6:4-10. “Specifically, ZIKV is passaged and replication-optimized (e.g., in Vero monkey kidney cells)”. EX 1004 22:21-22. “The Vero cells used for passage and vaccine production were a derivative of a certified cell line manufactured at The Salk Institute, Swiftwater, PA.” EX 1004 32:1-3. “As an example of screening ZIKV isolates for use in our purification-inactivation process, the following passaging protocol can be used. . . . All samples taken can be assayed on Vero-WHO cells using a standard SOP for flavivirus plaque assay (SOP QC-145-xx).” EX 1004 23:10-21.

268. Thomas teaches that “ZIKV can be purified to be free of pathogens and adventitious agents.” EX 1004 3:23. Thomas teaches that “[t]he ZIKV infectious virus particle can be purified away from the host cell proteins (demonstrated by known procedures such as gradient centrifugation and column chromatography).” EX 1004 3:24-26. See also EX 1004 19:15-16 (“A live ZIKV is purified so as to remove all pathogens and adventitious agents.”) 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 1004 20:19-20.

269. Thomas does not teach that the Zika virus clonal isolate is from a plaque purified clonal Zika virus isolate.

270. 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. Based on Thomas teaching 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 1004 20:19-20), one of skill would have looked to the art for examples of isolating and purifying Zika virus as a matter of routine skill and would have been aware of Murata.

271. Thomas teaches that “[t]here is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.” EX 1004 3:2-5. Murata teaches “Plaque purification has been used for decades to ensure the homogeneity of virus stocks and to segregate discrete species from mixed virus populations [18], [19], [20].” “Our data suggest that plaque purification may be a rapid and efficient means by which vaccine seed virus purity can be enhanced.” EX 1006 p. 3156. Murata used plaque purification to purify influenza virus from the adventitious agents of replicating and non-replicating viruses. EX 1006 p. 3157-3158, sections 3.2 and 3.3.

272. Murata teaches that “plaque purification is a simple and rapid method for removing adventitious viruses.” EX 1006 p. 3158. Murata provides motivation to use plaque purification by teaching that “our study corroborates the commonly invoked rule of thumb in virology calling for three rounds of serial plaque purification to ensure homogeneity starting from a mixed population. Plaque purification is an approach unencumbered by intellectual property constraints” EX 1006 p. 3159.

273. It is within the level of skill of one of ordinary skill in the art to utilize plaque purification as a matter of routine skill in purifying a virus because Murata teaches that plaque purification is a well-known process for purifying viruses (“rule of thumb in virology calling for three rounds of serial plaque purification”) and is recommended as “unencumbered by intellectual property constraints.” Further, one of ordinary skill would understand that a virus clonal isolate is obtained using the plaque purification of Murata.

274. One of skill would have been motivated to utilize plaque purification because Thomas teaches that the ZIKV virus is purified using known procedures (EX 1004 3:24-26; EX 1004 20:19-20), and Murata teaches that plaque purification is a well-known and recommended process for purifying viruses. EX 1006 p. 3158-59.

275. One of skill would have had a reasonable expectation of successfully

purifying the ZIKV using plaque purification because Murata teaches successful purification of a virus using plaque purification. The substitution of one known method for purifying the ZIKV (i.e., the physical and/or chemical methods disclosed by Thomas) for another known method for purifying the ZIKV (i.e., plaque purification disclosed by Murata) is well within ordinary skill and does not result in patentability absent unexpected results. Each method is known to purify viruses. The use of the plaque purification of Murata would be expected to purify Zika virus and produces no unexpected result.

276. Accordingly claim 25 is obvious in view of Thomas and Murata.

XI. GROUND V: Claims 5, 15-18, and 20 are Invalid as Being Obvious Over Thomas in view of Version 8 of NCT02952833

A. The Claims are Obvious Over Thomas and Version 8 of NCT02952833

277. A detailed claim chart comparing each feature of claims 5, 15-18, and 20, and where each feature is taught in Thomas and Version 8 of NCT02952833 is provided in Appendix B.

B. Claim by Claim Analysis

1. Claim 5

278. Claim 5 of the '802 patent depends from claim 1 and is set forth below.

5. The method of claim 1, wherein the vaccine or immunogenic composition comprising a dose of 10 µg is administered one time.

279. As previously demonstrated at VII(B)(1), Thomas teaches each and

every limitation of claim 1. Thomas also teaches that administering a dose of an inactivated, whole Zika virus antigen vaccine including an adjuvant effects seroconversion of the human to which the vaccine dose is administered. In particular, Thomas teaches that seroconversion is increased relative to a human who has not received the vaccine dose after a first (prime) dose, as well as, after a second (boost) dose. EX 1004 42:4-23. Thomas teaches that “[w]ith the information known about the dosing and schedule for other PIV flavivirus vaccines – such as Japanese encephalitis and tick-borne encephalitis – 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 1004 4:24-28. “Based on these models, and 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, or a booster dose at 4 weeks as described below.)” EX 1004 18:17-20.

280. Accordingly, a vaccine dose including an inactivated, whole Zika virus antigen and an adjuvant which results in seroconversion and, accordingly, a seroconversion rate among study participants, would be recognized by a 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.

281. Claim 1 requires a first (prime) and second (boost) administration.

Claim 5 requires that a dose of 10 µg is administered one time. Since claim 1 requires both a first (prime) and second (boost) administration, and claim 5 requires that a dose of 10 µg is administered one time, the 10 µg dose may be administered as either the first (prime) or second (boost) but not both.

282. Thomas and Version 8 of NCT02952833 are in the same field of endeavor, i.e. making, testing, and using purified, inactivated whole virus antigen vaccines for use in humans. In fact, both Thomas and Version 8 of NCT02952833 teach use of purified, inactivated, whole Zika virus antigen vaccine. Thomas teaches to determine a “safe and effective dose and schedule for this ZIKV PIV, as needed for persons of any age and size” (EX 1004 4:24-28) and so one of skill would have looked to the art for examples of ZPIV doses as a matter of routine skill and would have been aware of Version 8 of NCT02952833.

283. Thomas teaches that “[t]here is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.” EX 1004 3:2-5. Like Thomas, Version 8 of NCT02952833 teaches a human trial with a Zika vaccine.

284. Version 8 of NCT02952833 evaluates three dose levels of “5.0 mcg, 2.5 mcg and 10mcg of ZPIV.” EX 1011 p. 6. The doses are to be administered “by intramuscular (IM) injection on Days 1 and 29. The study will consist of a screening period of up to 28 days, a vaccination period in which subjects will receive a prime

dose of vaccine on Day 1 followed by a boost on Day 29, and a follow-up period of 12 months post boost vaccination.” 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” EX 1011 p. 6. “The secondary objectives of this study are to 1. Assess . . . seroconversion rates, and peak Geometric Mean Titer (GMT)” EX 1011 p. 6.

285. 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 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 1011 p. 8.

286. The Peak GMT overall and by dosage group is measured by ZIKV ELISA and neutralization assay. 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. 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 neutralization titers in comparison with baseline. EX 1011 p. 10.

287. The 10.0 µg dose of Version 8 of NCT02952833 is identical to the dose

recited in claim 5. Thomas teaches to determine a “safe and effective dose and schedule for this ZIKV PIV, as needed for persons of any age and size” (EX 1004 4:24-28).

288. The combination of Thomas and Version 8 of NCT02952833 teaches each element of claim 5 including the elements of claim 1 from which claim 5 depends.

289. It is within the level of skill of one of ordinary skill in the art to use the 10.0 µg ZIKV dose of Version 8 of NCT02952833 in human trials with the known method of Thomas disclosing a 5 µg ZIKV dose in human trials because to do so would have only required routine skill to change the 5 µg ZIKV dose to a 10.0 µg ZIKV dose.

290. One would have been motivated to modify the method of Thomas to administer the Zika vaccine at a dose of 10.0 µg because Thomas teaches to determine optimal doses of ZIKV antigen based on “dosing and schedule for other PIV flavivirus vaccines – such as Japanese encephalitis and tick-borne encephalitis – 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 1004 4:24-28. 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.” Further, Version 8 of NCT02952833 teaches human studies where both a 5 µg ZIKV dose and a 10 µg ZIKV dose are used to determine safety and immunological response. Further, a POSA would have understood that dosage of antigen is a result-effective variable effecting seroconversion rate. Based on Thomas and Version 8 of NCT02952833, one of skill would have been motivated to explore different dosages, such as a 5 µg ZIKV dose, a 2.5 µg ZIKV dose, and a 10 µg ZIKV dose, in human trials to determine safety and immunological response and to optimize a ZIKV antigen dose, because both Thomas and Version 8 of NCT02952833 teach to do just that, and the ZIKV antigen dose is a result-effective variable affecting seroconversion rate.

291. One of skill would have had a reasonable expectation of successfully using a 10 µg dose from the human vaccination method of Version 8 of NCT02952833 to vaccinate against Zika virus infection in the human vaccination method of Thomas because Thomas demonstrated that two 5 µg doses (a total of 10 µg) were safe and provided significant immune response to provide protection against Zika virus. Thomas demonstrated a greater immunological response and, therefore greater protection, after a second (boost) 5 µg dose. See EX 1004 42:9-11 (“Antibody kinetics based on MN50 titers indicating a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff and then a robust and brisk rise in antibody titer for the Trial Group 2 and Trial Group 3

volunteers following dose two.”) One of skill 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. In general a POSA would understand that a greater amount of antigen exposure leads to a stronger and more rapid immune response.

292. Further, one of skill would have been motivated to modify the method of Thomas to administer a dose of 10 µg ZIKV PIV one time, such as a boost, because Thomas teaches that “[t]he purified, inactivated ZIKV can be used to immunize mammals (including humans) to elicit high titers of virus neutralizing antibodies and protect the immunized mammal from disease caused by ZIKV. For example, a single immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against challenge with ZIKV.” EX 1004 4:15-20. 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.” Version 8 of NCT02952833 teaches to evaluate safety and immunogenicity of three vaccine dosages (5 µg, 2.5 µg, 10 µg) in a prime/boost setting. EX 1011 p. 6. Based on Thomas and Version 8

of NCT02952833, one of skill would have been motivated to explore administering a dose of 10 µg ZIKV one time, such as a boost administration, in human trials to determine safety and immunological response and to optimize a ZIKV antigen dosing schedule, because both Thomas and Version 8 of NCT02952833 teach to do just that.

293. One of skill would have had a reasonable expectation of successfully using a 10 µg dose one time, such as a boost administration, to vaccinate against Zika virus infection because Thomas demonstrated that two 5 µg doses (a total of 10 µg) were safe and provided significant immune response to provide protection against Zika virus. Thomas demonstrated a greater immunological response and, therefore greater protection, after a second (boost) 5 µg dose. One of skill would have reasonably expected that the higher 10 µg dose, such as a boost dose, would provide 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 dose would be expected to elicit a greater immunological response compared to a 5 µg dose. Selecting the 10 µg dose based on Version 8 of NCT02952833 is routine optimization of a result-effective variable.

294. Accordingly claim 5 is obvious in view of Thomas and Version 8 of NCT02952833.

2. Claim 15

295. Claim 15 of the ‘802 patent depends from claim 1 and is set forth below.

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.

296. As previously demonstrated at VII(B)(1) and VII(B)(8), Thomas teaches each and every limitation of claim 1 and claim 13 reciting that the antigen is purified. Thomas also teaches that administering a dose of an inactivated, whole Zika virus antigen vaccine effects seroconversion of the human to which the dose is administered. In particular, Thomas teaches that seroconversion is increased relative to a human who has not received the vaccine dose after a first (prime) dose, as well as, after a second (boost) dose. EX 1004 42:4-23. Thomas teaches that “[w]ith the information known about the dosing and schedule for other PIV flavivirus vaccines – such as Japanese encephalitis and tick-borne encephalitis – 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 1004 4:24-28. “Based on these models, and 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, or a booster dose at 4 weeks as described below.)” EX 1004 18:17-20.

297. Accordingly, a vaccine dose including an inactivated, whole Zika virus antigen and an adjuvant which results in seroconversion and, accordingly, a seroconversion rate among study participants, would be recognized by a 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.

298. Claim 15 requires a dose of from about 10 µg to about 40 µg of purified inactivated whole virus. Claim 15 is similar to claim 5 in that the lower range of claim 15 includes a dose of 10 µg. Accordingly, the analysis of claim 5 at XI(B)(1) is incorporated herein.

299. Thomas and Version 8 of NCT02952833 are in the same field of endeavor, i.e. making, testing, and using purified, inactivated whole virus antigen vaccines for use in humans. In fact, both Thomas and Version 8 of NCT02952833 teach use of purified, inactivated, whole Zika virus antigen vaccine. Thomas teaches to determine a “safe and effective dose and schedule for this ZIKV PIV, as needed for persons of any age and size” (EX 1004 4:24-28) and so one of skill would have looked to the art for examples of ZPIV doses as a matter of routine skill and would have been aware of Version 8 of NCT02952833.

300. Thomas teaches that “[t]here is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.” EX 1004 3:2-5. Like Thomas, Version 8 of NCT02952833 teaches a human trial with a Zika vaccine.

301. Version 8 of NCT02952833 evaluates three dose levels of “5.0 mcg,

2.5 mcg and 10mcg of ZPIV.” EX 1011 p. 6 The doses are to be administered “by intramuscular (IM) injection on Days 1 and 29. The study will consist of a screening period of up to 28 days, a vaccination period in which subjects will receive a prime dose of vaccine on Day 1 followed by a boost on Day 29, and a follow-up period of 12 months post boost vaccination.” 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” EX 1011 p. 6. “The secondary objectives of this study are to 1. Assess . . . seroconversion rates, and peak Geometric Mean Titer (GMT)” EX 1011 p. 6.

302. 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 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 1011 p. 8.

303. The Peak GMT overall and by dosage group is measured by ZIKV ELISA and neutralization assay. 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. 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 neutralization titers in comparison with baseline. EX 1011 p. 10.

304. The 10.0 µg dose of Version 8 of NCT02952833 is within the range of about 10 µg to about 40 µg recited in claim 15. Thomas teaches to determine a “safe and effective dose and schedule for this ZIKV PIV, as needed for persons of any age and size” (EX 1004 4:24-28).

305. The combination of Thomas and Version 8 of NCT02952833 teaches each element of claim 15 including the elements of claim 1 from which claim 15 depends.

306. It is within the level of skill of one of ordinary skill in the art to use the 10.0 µg ZIKV dose of Version 8 of NCT02952833 in human trials with the known method of Thomas disclosing a 5 µg ZIKV dose in human trials because to do so would have only required routine skill to change the 5 µg ZIKV dose to a 10.0 µg ZIKV dose.

307. One would have been motivated to modify the method of Thomas to administer the Zika vaccine at a dose of 10.0 µg because Thomas teaches to determine optimal doses of ZIKV antigen based on “dosing and schedule for other PIV flavivirus vaccines – such as Japanese encephalitis and tick-borne encephalitis – 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 1004 4:24-28.

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.” Further, Version 8 of NCT02952833 teaches human studies where both a 5 μ g ZIKV dose and a 10 μ g ZIKV dose are used to determine safety and immunological response. Further, a POSA would have understood that dosage of antigen is a result-effective variable affecting seroconversion rate. Based on Thomas and Version 8 of NCT02952833, one of skill would have been motivated to explore different dosages, such as a 5 μ g ZIKV dose, a 2.5 μ g ZIKV dose, and a 10 μ g ZIKV dose, in human trials to determine safety and immunological response and to optimize a ZIKV antigen dose, because both Thomas and Version 8 of NCT02952833 teach to do just that, and the ZIKV antigen dose is a result-effective variable affecting seroconversion rate.

308. One of skill would have had a reasonable expectation of successfully using a 10 μ g dose from the human vaccination method of Version 8 of NCT02952833 to vaccinate against Zika virus infection in the human vaccination method of Thomas because Thomas demonstrated that two 5 μ g doses (a total of 10 μ g) were safe and provided significant immune response to provide protection against Zika virus. Thomas demonstrated a greater immunological response and, therefore greater protection, after a second (boost) 5 μ g dose. EX 1004 42:9-11

(“Antibody kinetics based on MN50 titers indicating a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff and then a robust and brisk rise in antibody titer for the Trial Group 2 and Trial Group 3 volunteers following dose two.”). One of skill 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. Selecting the 10 µg dose based on Version 8 of NCT02952833 is routine optimization of a result-effective variable.

309. Accordingly claim 15 is obvious in view of Thomas and Version 8 of NCT02952833.

3. Claim 16

310. Claim 16 of the ‘802 patent depends from claim 1 and is set forth below.

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.

311. As previously demonstrated at VII(B)(1) and VII(B)(8), Thomas teaches each and every limitation of claim 1 and claim 13 reciting that the antigen is purified. Thomas also teaches that administering a dose of an inactivated, whole Zika virus antigen vaccine effects seroconversion of the human to which the dose is

administered. In particular, seroconversion is increased relative to a human who has not received the vaccine dose after a first (prime) dose and after a second (boost) dose. EX 1004 42:4-23. Thomas teaches that “[w]ith the information known about the dosing and schedule for other PIV flavivirus vaccines – such as Japanese encephalitis and tick-borne encephalitis – 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 1004 4:24-28. “Based on these models, and 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, or a booster dose at 4 weeks as described below.)” EX 1004 18:17-20.

312. Accordingly, a vaccine dose including an inactivated, whole Zika virus antigen and an adjuvant which results in seroconversion and, accordingly, a seroconversion rate among study participants, would be recognized by a 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.

313. Claim 16 requires a dose of from about 10 μg to about 30 μg of purified inactivated whole virus. Claim 16 is similar to claim 15 in that the lower range of claim 16 includes a dose of 10 μg . Accordingly, the analysis of claim 15 at XI(B)(2) is incorporated herein.

314. Thomas and Version 8 of NCT02952833 are in the same field of endeavor, i.e. making, testing, and using purified, inactivated whole virus antigen vaccines for use in humans. In fact, both Thomas and Version 8 of NCT02952833 teach use of purified, inactivated, whole Zika virus antigen vaccine. Thomas teaches to determine a “safe and effective dose and schedule for this ZIKV PIV, as needed for persons of any age and size” (EX 1004 4:24-28) and so one of skill would have looked to the art for examples of ZPIV doses as a matter of routine skill and would have been aware of Version 8 of NCT02952833.

315. Thomas teaches that “[t]here is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.” EX 1004 3:2-5. Like Thomas, Version 8 of NCT02952833 teaches a human trial with a Zika vaccine.

316. Version 8 of NCT02952833 evaluates three dose levels of “5.0 mcg, 2.5 mcg and 10mcg of ZPIV.” EX 1011 p. 6. The doses are to be administered “by intramuscular (IM) injection on Days 1 and 29. The study will consist of a screening period of up to 28 days, a vaccination period in which subjects will receive a prime dose of vaccine on Day 1 followed by a boost on Day 29, and a follow-up period of 12 months post boost vaccination.” 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” EX 1011 p. 6. “The

secondary objectives of this study are to 1. Assess . . . seroconversion rates, and peak Geometric Mean Titer (GMT)” EX 1011 p. 6.

317. 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 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 1011 p. 8.

318. The Peak GMT overall and by dosage group is measured by ZIKV ELISA and neutralization assay. 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. 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 neutralization titers in comparison with baseline. EX 1011 p. 10.

319. The 10.0 µg dose of Version 8 of NCT02952833 is within the range of about 10 µg to about 30 µg recited in claim 16. Thomas teaches to determine a “safe and effective dose and schedule for this ZIKV PIV, as needed for persons of any age and size” (EX 1004 4:24-28).

320. The 10.0 µg dose of Version 8 of NCT02952833 is within the range of

about 10 µg to about 30 µg recited in claim 16. Thomas teaches to determine a “safe and effective dose and schedule for this ZIKV PIV, as needed for persons of any age and size” (EX 1004 4:24-28).

321. The combination of Thomas and Version 8 of NCT02952833 teaches each element of claim 16 including the elements of claim 1 from which claim 16 depends.

322. It is within the level of skill of one of ordinary skill in the art to utilize the 10.0 µg ZIKV dose of Version 8 of NCT02952833 in human trials with the known method of Thomas disclosing a 5 µg ZIKV dose in human trials because to do so would have only required routine skill to change the 5 µg ZIKV dose to a 10.0 µg ZIKV dose.

323. One would have been motivated to modify the method of Thomas to administer the Zika vaccine at a dose of 10.0 µg because Thomas teaches to determine optimal doses of ZIKV antigen based on “dosing and schedule for other PIV flavivirus vaccines – such as Japanese encephalitis and tick-borne encephalitis – 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 1004 4:24-28. 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.” Further, Version 8 of NCT02952833 teaches human studies where both a 5µg ZIKV dose and a 10 µg ZIKV dose are used to determine safety and immunological response. Further, a POSA would have understood that dosage of antigen is a result-effective variable affecting seroconversion rate. Based on Thomas and Version 8 of NCT02952833, one of skill would have been motivated to explore different dosages, such as a 5 µg ZIKV dose, a 2.5µg ZIKV dose, and a 10 µg ZIKV dose, in human trials to determine safety and immunological response and to optimize a ZIKV antigen dose, because both Thomas and Version 8 of NCT02952833 teach to do just that, and the ZIKV antigen dose is a result-effective variable affecting seroconversion rate.

324. One of skill would have had a reasonable expectation of successfully using a 10 µg dose from the human vaccination method of Version 8 of NCT02952833 to vaccinate against Zika virus infection in the human vaccination method of Thomas because Thomas demonstrated that two 5 µg doses (a total of 10 µg) were safe and provided significant immune response to provide protection against Zika virus. Thomas demonstrated a greater immunological response and, therefore greater protection, after a second (boost) 5 µg dose. EX 1004 42:9-11 (“Antibody kinetics based on MN50 titers indicating a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff and then a robust and brisk rise in antibody titer for the Trial Group 2 and Trial Group 3

volunteers following dose two.”) One of skill 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. Selecting the 10 µg dose based on Version 8 of NCT02952833 is routine optimization of a result-effective variable.

325. Accordingly claim 16 is obvious in view of Thomas and Version 8 of NCT02952833.

4. Claim 17

326. Claim 17 of the ‘802 patent depends from claim 1 and is set forth below.

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.

327. As previously demonstrated at VII(B)(1) and VII(B)(8), Thomas teaches each and every limitation of claim 1 and claim 13 reciting that the antigen is purified. Thomas also teaches that administering a dose of an inactivated, whole Zika virus antigen vaccine effects seroconversion of the human to which the dose is administered. In particular, Thomas teaches that seroconversion is increased relative to a human who has not received the vaccine dose after a first (prime) dose and after a second (boost) dose. EX 1004 42:4-23. Thomas teaches that “[w]ith the

information known about the dosing and schedule for other PIV flavivirus vaccines – such as Japanese encephalitis and tick-borne encephalitis – 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 1004 4:24-28. “Based on these models, and 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, or a booster dose at 4 weeks as described below.)” EX 1004 18:17-20.

328. Accordingly, a vaccine dose including an inactivated, whole Zika virus antigen and an adjuvant which results in seroconversion and, accordingly, a seroconversion rate among study participants, would be recognized by a 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.

329. Claim 17 requires a dose of from about 10 µg to about 20 µg of purified inactivated whole virus. Claim 17 is similar to claim 15 in that the lower range of claim 17 includes a dose of 10 µg. Accordingly, the analysis of claim 15 at XI(B)(2) is incorporated herein.

330. Thomas and Version 8 of NCT02952833 are in the same field of endeavor, i.e. making, testing, and using purified, inactivated whole virus antigen vaccines for use in humans. In fact, both Thomas and Version 8 of NCT02952833

teach use of purified, inactivated, whole Zika virus antigen vaccine. Thomas teaches to determine a “safe and effective dose and schedule for this ZIKV PIV, as needed for persons of any age and size” (EX 1004 4:24-28) and so one of skill would have looked to the art for examples of ZPIV doses as a matter of routine skill and would have been aware of Version 8 of NCT02952833.

331. Thomas teaches that “[t]here is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.” EX 1004 3:2-5. Like Thomas, Version 8 of NCT02952833 teaches a human trial with a Zika vaccine.

332. Version 8 of NCT02952833 evaluates three dose levels of “5.0 mcg, 2.5 mcg and 10mcg of ZPIV.” EX 1011 p. 6. The doses are to be administered “by intramuscular (IM) injection on Days 1 and 29. The study will consist of a screening period of up to 28 days, a vaccination period in which subjects will receive a prime dose of vaccine on Day 1 followed by a boost on Day 29, and a follow-up period of 12 months post boost vaccination.” 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” EX 1011 p. 6. “The secondary objectives of this study are to 1. Assess . . . seroconversion rates, and peak Geometric Mean Titer (GMT)” EX 1011 p. 6.

333. 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 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 1011 p. 8.

334. The Peak GMT overall and by dosage group is measured by ZIKV ELISA and neutralization assay. 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. 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 neutralization titers in comparison with baseline. EX 1011 p. 10.

335. The 10.0 µg dose of Version 8 of NCT02952833 is within the range of about 10 µg to about 20 µg recited in claim 17. Thomas teaches to determine a “safe and effective dose and schedule for this ZIKV PIV, as needed for persons of any age and size” (EX 1004 4:24-28).

336. The combination of Thomas and Version 8 of NCT02952833 teaches each element of claim 17 including the elements of claim 1 from which claim 17 depends.

337. It is within the level of skill of one of ordinary skill in the art to utilize

the 10.0 µg ZIKV dose of Version 8 of NCT02952833 in human trials with the known method of Thomas disclosing a 5 µg ZIKV dose in human trials because to do so would have only required routine skill to change the 5 µg ZIKV dose to a 10.0 µg ZIKV dose.

338. One would have been motivated to modify the method of Thomas to administer the Zika vaccine at a dose of 10.0 µg because Thomas teaches to determine optimal doses of ZIKV antigen based on “dosing and schedule for other PIV flavivirus vaccines – such as Japanese encephalitis and tick-borne encephalitis – 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 1004 4:24-28. 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.” Further, Version 8 of NCT02952833 teaches human studies where both a 5µg ZIKV dose and a 10 µg ZIKV dose are used to determine safety and immunological response. Further, a POSA would have understood that dosage of antigen is a result-effective variable affecting seroconversion rate. Based on Thomas and Version 8 of NCT02952833, one of skill would have been motivated to explore different dosages, such as a 5 µg ZIKV dose, a 2.5 µg ZIKV dose, and a 10 µg ZIKV dose, in human trials to determine safety and immunological response and to

optimize a ZIKV antigen dose, because both Thomas and Version 8 of NCT02952833 teach to do just that, and the ZIKV antigen dose is a result-effective variable affecting seroconversion rate.

339. One of skill would have had a reasonable expectation of successfully using a 10 μ g dose from the human vaccination method of Version 8 of NCT02952833 to vaccinate against Zika virus infection in the human vaccination method of Thomas because Thomas demonstrated that two 5 μ g doses (a total of 10 μ g) were safe and provided significant immune response to provide protection against Zika virus. Thomas demonstrated a greater immunological response and, therefore greater protection, after a second (boost) 5 μ g dose. EX 1004 42:9-11 (“Antibody kinetics based on MN50 titers indicating a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff and then a robust and brisk rise in antibody titer for the Trial Group 2 and Trial Group 3 volunteers following dose two.”). One of skill would have reasonably expected that the higher 10 μ g 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 μ g boost doses, because the higher antigen content of the 10 μ g boost dose would be expected to elicit a greater immunological response compared to a 5 μ g boost dose. Selecting the 10 μ g dose based on Version 8 of NCT02952833 is routine optimization of a result-effective variable.

340. Accordingly, claim 17 is obvious in view of Thomas and Version 8 of NCT02952833.

5. Claim 18

341. Claim 18 of the '802 patent depends from claim 1 and is set forth below.

18. The method of claim 1, wherein the vaccine or immunogenic composition comprises a dose of from about 10 μg to about 15 μg of purified inactivated whole virus.

342. As previously demonstrated at VII(B)(1) and VII(B)(8), Thomas teaches each and every limitation of claim 1 and claim 13 reciting that the antigen is purified. Thomas also teaches that administering a dose of an inactivated, whole Zika virus antigen vaccine effects seroconversion of the human to which the dose is administered. In particular, Thomas teaches that seroconversion is increased relative to a human who has not received the vaccine dose after a first (prime) dose and after a second (boost) dose. EX 1004 42:4-23. Thomas teaches that “[w]ith the information known about the dosing and schedule for other PIV flavivirus vaccines – such as Japanese encephalitis and tick-borne encephalitis – 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 1004 4:24-28. “Based on these models, and 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, or a booster dose at 4 weeks as described below.)” EX 1004 18:17-20.

343. Accordingly, a vaccine dose including an inactivated, whole Zika virus antigen and an adjuvant which results in seroconversion and, accordingly, a seroconversion rate among study participants, would be recognized by a 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.

344. Claim 18 requires a dose of from about 10 μg to about 15 μg of purified inactivated whole virus. Claim 18 is similar to claim 15 in that the lower range of claim 18 includes a dose of 10 μg . Accordingly, the analysis of claim 15 at XI(B)(2) is incorporated herein.

345. Thomas and Version 8 of NCT02952833 are in the same field of endeavor, i.e. making, testing, and using purified, inactivated whole virus antigen vaccines for use in humans. In fact, both Thomas and Version 8 of NCT02952833 teach use of purified, inactivated, whole Zika virus antigen vaccine. Thomas teaches to determine a “safe and effective dose and schedule for this ZIKV PIV, as needed for persons of any age and size” (EX 1004 4:24-28) and so one of skill would have looked to the art for examples of ZPIV doses as a matter of routine skill and would have been aware of Version 8 of NCT02952833.

346. Thomas teaches that “[t]here is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as

compositions to treat ZIKV post infection.” EX 1004 3:2-5. Like Thomas, Version 8 of NCT02952833 teaches a human trial with a Zika vaccine.

347. Version 8 of NCT02952833 evaluates three dose levels of “5.0 mcg, 2.5 mcg and 10mcg of ZPIV.” EX 1011 p. 6. The doses are to be administered “by intramuscular (IM) injection on Days 1 and 29. The study will consist of a screening period of up to 28 days, a vaccination period in which subjects will receive a prime dose of vaccine on Day 1 followed by a boost on Day 29, and a follow-up period of 12 months post boost vaccination.” 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” EX 1011 p. 6. “The secondary objectives of this study are to 1. Assess . . . seroconversion rates, and peak Geometric Mean Titer (GMT)” EX 1011 p. 6.

348. 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 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 1011 p. 8.

349. The Peak GMT overall and by dosage group is measured by ZIKV ELISA and neutralization assay. 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. 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 neutralization titers in comparison with baseline. EX 1011 p. 10.

350. The 10.0 µg dose of Version 8 of NCT02952833 is within the range of about 10 µg to about 15 µg recited in claim 18. Thomas teaches to determine a “safe and effective dose and schedule for this ZIKV PIV, as needed for persons of any age and size” (EX 1004 4:24-28).

351. The combination of Thomas and Version 8 of NCT02952833 teaches each element of claim 18 including the elements of claim 1 from which claim 18 depends.

352. It is within the level of skill of one of ordinary skill in the art to utilize the 10.0 µg ZIKV dose of Version 8 of NCT02952833 in human trials with the known method of Thomas disclosing a 5 µg ZIKV dose in human trials because to do so would have only required routine skill to change the 5 µg ZIKV dose to a 10.0 µg ZIKV dose.

353. One would have been motivated to modify the method of Thomas to administer the Zika vaccine at a dose of 10.0 µg because Thomas teaches to determine optimal doses of ZIKV antigen based on “dosing and schedule for other

PIV flavivirus vaccines – such as Japanese encephalitis and tick-borne encephalitis – 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 1004 4:24-28. 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.” Further, Version 8 of NCT02952833 teaches human studies where both a 5 µg ZIKV dose and a 10 µg ZIKV dose are used to determine safety and immunological response. Further, a POSA would have understood that dosage of antigen is a result-effective variable affecting seroconversion rate. Based on Thomas and Version 8 of NCT02952833, one of skill would have been motivated to explore different dosages, such as a 5 µg ZIKV dose, a 2.5 µg ZIKV dose, and a 10 µg ZIKV dose, in human trials to determine safety and immunological response and to optimize a ZIKV antigen dose, because both Thomas and Version 8 of NCT02952833 teach to do just that, and the ZIKV antigen dose is a result-effective variable affecting seroconversion rate.

354. One of skill would have had a reasonable expectation of successfully using a 10 µg dose from the human vaccination method of Version 8 of NCT02952833 to vaccinate against Zika virus infection in the human vaccination method of Thomas because Thomas demonstrated that two 5 µg doses (a total of 10

µg) were safe and provided significant immune response to provide protection against Zika virus. Thomas demonstrated a greater immunological response and, therefore greater protection, after a second (boost) 5 µg dose. EX 1004 42:9-11 (“Antibody kinetics based on MN50 titers indicating a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff and then a robust and brisk rise in antibody titer for the Trial Group 2 and Trial Group 3 volunteers following dose two.”) One of skill 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 doses, 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. Selecting the 10 µg dose based on Version 8 of NCT02952833 is routine optimization of a result-effective variable.

355. Accordingly claim 18 is obvious in view of Thomas and Version 8 of NCT02952833.

6. Claim 20

356. Claim 20 of the ‘802 patent depends from claim 1 and is set forth below.

20. The method of claim 1, wherein the vaccine or immunogenic composition comprises a dose of about 10 µg of purified inactivated whole virus.

357. As previously demonstrated at VII(B)(1) and VII(B)(8), Thomas

teaches each and every limitation of claim 1 and claim 13 reciting that the antigen is purified. Thomas also teaches that administering a dose of an inactivated, whole Zika virus antigen vaccine effects seroconversion of the human to which the dose is administered. In particular, Thomas teaches that seroconversion is increased relative to a human who has not received the vaccine dose after a first (prime) dose and after a second (boost) dose. EX 1004 42:4-23. Thomas teaches that “[w]ith the information known about the dosing and schedule for other PIV flavivirus vaccines – such as Japanese encephalitis and tick-borne encephalitis – 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 1004 4:24-28. “Based on these models, and 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, or a booster dose at 4 weeks as described below.)” EX 1004 18:17-20.

358. Accordingly, a vaccine dose including an inactivated, whole Zika virus antigen and an adjuvant which results in seroconversion and, accordingly, a seroconversion rate among study participants, would be recognized by a 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.

359. Claim 20 requires a dose of about 10 μ g of purified inactivated whole

virus. Claim 20 is similar to claim 15 in that claim 20 includes a dose of about 10 µg. Accordingly, the analysis of claim 15 at XI(B)(2) is incorporated herein.

360. Thomas and Version 8 of NCT02952833 are in the same field of endeavor, i.e. making, testing, and using purified, inactivated whole virus antigen vaccines for use in humans. In fact, both Thomas and Version 8 of NCT02952833 teach use of purified, inactivated, whole Zika virus antigen vaccine. Thomas teaches to determine a “safe and effective dose and schedule for this ZIKV PIV, as needed for persons of any age and size” (EX 1004 4:24-28) and so one of skill would have looked to the art for examples of ZPIV doses as a matter of routine skill and would have been aware of Version 8 of NCT02952833.

361. Thomas teaches that “[t]here is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.” EX 1004 3:2-5. Like Thomas, Version 8 of NCT02952833 teaches a human trial with a Zika vaccine.

362. Version 8 of NCT02952833 evaluates three dose levels of “5.0 mcg, 2.5 mcg and 10 mcg of ZPIV.” EX 1011 p. 6. The doses are to be administered “by intramuscular (IM) injection on Days 1 and 29. The study will consist of a screening period of up to 28 days, a vaccination period in which subjects will receive a prime dose of vaccine on Day 1 followed by a boost on Day 29, and a follow-up period of 12 months post boost vaccination.” 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” EX 1011 p. 6. “The secondary objectives of this study are to 1. Assess . . . seroconversion rates, and peak Geometric Mean Titer (GMT)” EX 1011 p. 6.

363. 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 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 1011 p. 8.

364. The Peak GMT overall and by dosage group is measured by ZIKV ELISA and neutralization assay. 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. 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 neutralization titers in comparison with baseline. EX 1011 p. 10.

365. The 10.0 µg dose of Version 8 of NCT02952833 is within the about 10 µg recited in claim 20. Thomas teaches to determine a “safe and effective dose and schedule for this ZIKV PIV, as needed for persons of any age and size” (EX 1004

4:24-28).

366. The combination of Thomas and Version 8 of NCT02952833 teaches each element of claim 20 including the elements of claim 1 from which claim 20 depends.

367. It is within the level of skill of one of ordinary skill in the art to utilize the 10.0 µg ZIKV dose of Version 8 of NCT02952833 in human trials with the known method of Thomas disclosing a 5 µg ZIKV dose in human trials because to do so would have only required routine skill to change the 5 µg ZIKV dose to a 10.0 µg ZIKV dose.

368. One would have been motivated to modify the method of Thomas to administer the Zika vaccine at a dose of 10.0 µg because Thomas teaches to determine optimal doses of ZIKV antigen based on “dosing and schedule for other PIV flavivirus vaccines – such as Japanese encephalitis and tick-borne encephalitis – 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 1004 4:24-28. 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.” Further, Version 8 of NCT02952833 teaches human studies where both a 5 µg ZIKV dose and a 10 µg ZIKV dose are used to determine safety and

immunological response. Further, a POSA would have understood that dosage of antigen is a result-effective variable affecting seroconversion rate. Based on Thomas and Version 8 of NCT02952833, one of skill would have been motivated to explore different dosages, such as a 5 µg ZIKV dose, a 2.5 µg ZIKV dose, and a 10 µg ZIKV dose, in human trials to determine safety and immunological response and to optimize a ZIKV antigen dose, because both Thomas and Version 8 of NCT02952833 teach to do just that, and the ZIKV antigen dose is a result-effective variable affecting seroconversion rate.

369. One of skill would have had a reasonable expectation of successfully using a 10 µg dose from the human vaccination method of Version 8 of NCT02952833 to vaccinate against Zika virus infection in the human vaccination method of Thomas because Thomas demonstrated that two 5 µg doses (a total of 10 µg) were safe and provided significant immune response to provide protection against Zika virus. Thomas demonstrated a greater immunological response and, therefore greater protection, after a second (boost) 5 µg dose. EX 1004 42:9-11 (“Antibody kinetics based on MN50 titers indicating a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff and then a robust and brisk rise in antibody titer for the Trial Group 2 and Trial Group 3 volunteers following dose two.”) One of skill would have reasonably expected that the higher 10 µg dose would provide similar if not greater immunological response

and protection against Zika virus compared to a single 5 µg dose or two 5 µg doses, because the higher antigen content of the 10 µg dose would be expected to elicit a greater immunological response compared to a 5 µg dose, whether the 10 µg dose was used as a first (prime) or a (second) boost) or as a single dose only. Selecting the 10 µg dose based on Version 8 of NCT02952833 is routine optimization of a result-effective variable.

370. Accordingly claim 20 is obvious in view of Thomas and Version 8 of NCT02952833.

XII. GROUND VI: Claims 26 and 63 are Invalid as Being Obvious Over Thomas and Version 8 of NCT02952833 and further in view of Barbero

A. The Claims are Obvious Over Thomas, Version 8 of NCT02952833 and Barbero

371. A detailed claim chart comparing each feature of claims 26 and 63 and where each feature is taught in Thomas, Version 8 of NCT02952833 and Barbero is provided in Appendix B.

B. Claim by Claim Analysis

1. Claim 26

372. Claim 26 of the '802 patent is an independent claim and is presented below.

26. A method of vaccinating against Zika virus infection in a human subject in need thereof, the method comprising
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,

wherein the antigen is an inactivated whole virus,
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.

373. Claim 26 is similar to claim 1 except that claim 26 does not recite a first (prime) and a second (boost) administration and requires 10 µg of purified inactivated whole virus, about 200 µg aluminum hydroxide, a buffer; and optionally a sugar.

374. As previously demonstrated at VII(B)(1), Thomas teaches each and every limitation of claim 1. Thomas further teaches an 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”) Thomas teaches the use of a sugar. EX 1004 28:27 (“acylated sugars”) and EX 1004 30:20 (a “sucrose solution”). Thomas teaches use of a buffer. EX 1004 30:18-21 (“pharmaceutically acceptable buffer solutions.”)

375. Thomas does not teach 10 µg of ZIKV. A POSA would have understood that the amount of a Zika virus vaccine is a result-effective variable affecting seroconversion as previously discussed. One of skill would have looked to the art for examples of ZPIV doses as a matter of routine skill and would have been aware of Version 8 of NCT02952833.

376. Thomas teaches that “[t]here is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as

compositions to treat ZIKV post infection.” EX 1004 3:2-5. Version 8 of NCT02952833 evaluates three dose levels of “5.0 mcg, 2.5 mcg and 10mcg of ZPIV.” EX 1011 p. 6. The doses are to be administered “by intramuscular (IM) injection on Days 1 and 29. The study will consist of a screening period of up to 28 days, a vaccination period in which subjects will receive a prime dose of vaccine on Day 1 followed by a boost on Day 29, and a follow-up period of 12 months post boost vaccination.” 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” EX 1011 p. 6. “The secondary objectives of this study are to 1. Assess . . . seroconversion rates, and peak Geometric Mean Titer (GMT)” EX 1011 p. 6.

377. 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 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 1011 p. 8.

378. The Peak GMT overall and by dosage group is measured by ZIKV ELISA and neutralization assay. 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. 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 neutralization titers in comparison with baseline. EX 1011 p. 10.

379. The 10.0 µg dose of Version 8 of NCT02952833 is within the range of about 10 µg as recited in claim 26. Thomas teaches to determine a “safe and effective dose and schedule for this ZIKV PIV, as needed for persons of any age and size” (EX 1004 4:24-28).

380. It is within the level of skill of one of ordinary skill in the art to utilize the 10.0 µg ZIKV dose of Version 8 of NCT02952833 in human trials with the known method of Thomas disclosing a 5 µg ZIKV dose in human trials because to do so would have only required routine skill to change the 5 µg ZIKV dose to a 10.0 µg ZIKV dose.

381. One would have been motivated to modify the method of Thomas to administer the Zika vaccine at a dose of 10.0 µg because Thomas teaches to determine optimal doses of ZIKV antigen based on “dosing and schedule for other PIV flavivirus vaccines – such as Japanese encephalitis and tick-borne encephalitis – 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 1004 4:24-28. 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.” Further, Version 8 of NCT02952833 teaches human studies where both a 5 μ g ZIKV dose and a 10 μ g ZIKV dose are used to determine safety and immunological response. Further, a POSA would have understood that dosage of antigen is a result-effective variable affecting seroconversion rate. Based on Thomas and Version 8 of NCT02952833, one of skill would have been motivated to explore different dosages, such as a 5 μ g ZIKV dose, a 2.5 μ g ZIKV dose, and a 10 μ g ZIKV dose, in human trials to determine safety and immunological response and to optimize a ZIKV antigen dose, because both Thomas and Version 8 of NCT02952833 teach to do just that, and ZIKV antigen dose is a result-effective variable affecting seroconversion rate.

382. One of skill would have had a reasonable expectation of successfully using a 10 μ g dose from the human vaccination method of Version 8 of NCT02952833 to vaccinate against Zika virus infection in the human vaccination method of Thomas because Thomas demonstrated that two 5 μ g doses (a total of 10 μ g) were safe and provided significant immune response to provide protection against Zika virus. Thomas demonstrated a greater immunological response and, therefore greater protection, after a second (boost) 5 μ g dose. EX 1004 42:9-11 (“Antibody kinetics based on MN50 titers indicating a slight rise in antibody after

the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff and then a robust and brisk rise in antibody titer for the Trial Group 2 and Trial Group 3 volunteers following dose two.”) One of skill would have reasonably expected that the higher 10 µg dose would provide a similar if not greater immunological response and protection against Zika virus compared to a single 5 µg dose or two 5 µg doses, because the higher antigen content of the 10 µg dose would be expected to elicit a greater immunological response compared to a 5 µg dose, whether the 10 µg dose was used as a first (prime) or a (second) boost) or as a single dose only. Selecting the 10 µg dose based on Version 8 of NCT02952833 is routine optimization of a result-effective variable.

383. Thomas does not teach a 200 µg amount of aluminum hydroxide.

384. Thomas 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. One of skill would have looked to the art for examples of ZPIV adjuvant amounts as a matter of routine skill and would have been aware of Barbero.

385. Thomas teaches that the vaccine compositions can include an aluminum hydroxide gel. 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”) As previously discussed, a POSA would have understood that the amount of an adjuvant is a result-effective variable

affecting antigen-specific immune response, i.e., seroconversion.

386. Barbero teaches a suitable amount of 500 µg of an aluminum hydroxide adjuvant per ml of ZIKV vaccine. EX 1005 112:2-4 (Aluminum hydroxide adjuvant “was added to a final concentration of 0.5 mg/ml Aluminium (1/20 v/v Alum 2% stock solution added) to prepare ZikaV Drug Product (DP).” One of skill would have understood that one ml is a suitable dose volume for a vaccine. Accordingly, Barbero teaches to a POSA a vaccine dose including 500 µg of an aluminum hydroxide adjuvant.

387. It is within the level of ordinary skill to use the known amount of 500 µg of an aluminum hydroxide adjuvant of Barbero with the known aluminum hydroxide adjuvant of Thomas because to do so would have only required routine skill to select a specific amount of an aluminum-based adjuvant known in the art.

388. One would then have been motivated to modify the 500 µg amount of the aluminum hydroxide adjuvant of Barbero to 200 µg because Thomas teaches to use adjuvants as a component of the ZIKV vaccine “to enhance, accelerate, or prolong the antigen-specific immune response of the antigen when used in combination with specific vaccine antigens.” EX 1004 28:18-22. Thomas teaches to use “a suitable amount of adjuvant.” EX 1004 17:1.

389. The amount of adjuvant is a routine design parameter for vaccines and is a result-effective variable affecting seroconversion. One of skill would have been

able to 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.

390. A POSA would have had a reasonable expectation of successfully using a Zika vaccine with about 200 µg aluminum hydroxide as adjuvant 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. A POSA would have understood that the inactivated Zika virus antigen adsorbed to 200 µg aluminum hydroxide would affect seroconversion rate, and therefore result in vaccination. Where the general conditions of a claim are disclosed in the prior art, i.e., an amount of aluminum hydroxide adjuvant in a vaccine dose, it is not inventive to discover the optimum or workable ranges by routine experimentation. No invention is involved in discovering optimum ranges of a process by routine experimentation. The discovery of an optimum value for the amount of aluminum hydroxide adjuvant in a vaccine dose, which is a result effective variable affecting seroconversion in a known process, is ordinary within the skill of the art.

391. Accordingly claim 26 is obvious in view of Thomas and Barbero.

2. Claim 63

392. Claim 63 of the ‘802 patent depends from claim 26 and is presented

below.

63. The method of claim 26, wherein the sugar is sucrose.

393. As previously demonstrated at XII(B)(1), the combination of Thomas, Version 8 of NCT02952833 and Barbero teaches each and every limitation of claim 26 and renders claim 26 obvious. The analysis of claim 26 is incorporated by reference herein.

394. Claim 63 further requires that the sugar is sucrose.

395. Thomas teaches use of sucrose. EX 1004 30:20 (a “sucrose solution”). Accordingly, the combination of Thomas, Version 8 of NCT02952833 and Barbero teaches each and every limitation of claim 63 and for the same reasons as claim 26, claim 63 is obvious in view of Thomas, Version 8 of NCT02952833 and Barbero.

396. Accordingly, claim 63 is obvious in view of Thomas, Version 8 of NCT02952833 and Barbero.

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

A. The Claims are Obvious Over Thomas and Faucette

397. A detailed claim chart comparing each feature of claims 9, 32, 33, 35, 36, 38, 39, 41, 47, 49, 51, 55-58, and 65-67 and where each feature is taught in Thomas and Faucette is provided in Appendix B.

B. Claim by Claim Analysis

1. Claim 9

398. Claim 9 of the '802 patent is set forth below.

9. 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,
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 is administered as a first (prime) and a second (boost) administration.

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

399. Thomas teaches vaccines including purified inactivated ZIKV and methods for the prevention and/or treatment of infection by ZIKV. EX 1004 Abstract. Thomas teaches immunizing a human against ZIKV infection. EX 1004 4:15-18; 5:2-6; 6:33-7:2; 5:8-9. Thomas teaches that “anti-Zika antibodies protect against infection in mice and non-human primates. Zika PIV generates robust anti-Zika antibodies in both models. Based on these models, and 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, or a booster dose at 4 weeks as described below).” EX 1004 18:16-20. Thomas concludes from Example 5: ZIKV PIV Performance in Human Trials that “vaccines comprising inactivated ZIKV are protective against infection with ZIKV.” EX 1004 42:21 to 43:1.

400. Thomas teaches that “[r]esearchers estimate between 1-13% of ZIKV infections during the first trimester of pregnancy will result in microcephaly. In addition ZIKV has been causally associated with intrauterine growth retardation, and other congenital malformations in both humans (15-18) and mice (19-21). Several reports have shown that ZIKV can infect placental and fetal tissues, leading to prolonged viremia in pregnant women (23) and nonhuman primates (24). ZIKV also appears to target cortical neural progenitor cells (19-21, 25 and 26), which likely contributes to neuropathology. The increased incidence of microcephaly temporally related to the introduction of ZIKV in the Americas resulted in the World Health Organization establishing a Public Health Emergency of International Concern (PHEIC). It is also because of these severe outcomes that a protective vaccine is required.” EX 1004 2:13-24. “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post-infection. Mechanisms of action of a prophylactic vaccine 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.

401. Thomas teaches that the “purified, inactivated ZIKV, when used in immunogenic compositions and vaccines, has a major advantage over attenuated virus vaccines and immunogenic compositions in that inactivated vaccines are not

infectious and therefore, cannot revert to virulence or cause disease. This is important when considering vaccination in known or potentially special populations such as those with immunodeficiencies (e.g., HIV) or those who are pregnant.” EX 1004 4:2-7. “Zika is unique in that there are congenital and neurological outcomes believed to result from autoimmune versus direct viral effects, and additionally, a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.” EX 1004 18:26-30.

402. Thomas teaches a need for a Zika virus vaccine that protects pregnant women and fetuses. EX 1004 2:13-24. Thomas teaches that a purified inactivated whole Zika virus vaccine is advantageous for pregnant women (EX 1004 4:2-7; EX 1004 18:26-30) and that 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.

403. Accordingly, Thomas teaches this limitation of claim 9 of a method of vaccinating against Zika virus disease in a fetus or newborn in need thereof.

b. 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

404. As indicated above, Thomas teaches administering a vaccine to a

pregnant human subject. In Example 5: ZIKV PIV Performance in Human Trials, Thomas teaches administering a dose of 5 μ g of an antigen from a Zika virus. EX 1004 41:7-8: “Two doses were administered at 0 and 28 days, 5 μ g per dose, and adjuvanted with alum.” 5 μ g per dose is within the claimed range of about 1 μ g to about 40 μ g. Accordingly, Thomas teaches this limitation of claim 9.

c. wherein the antigen is an inactivated whole virus,

405. Thomas teaches that the antigen is an inactivated whole virus. EX 1004 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”

406. Accordingly, Thomas teaches this limitation of claim 9.

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

407. The '802 patent provides no human experimental data supporting that its Zika vaccine when administered to a pregnant woman results in the adoptive transfer of an effective amount of neutralizing antibodies against Zika virus to the fetus or newborn. The '802 patent provides a study of the transfer of neutralizing antibodies from vaccinated mice to unvaccinated mice which were then challenged with the Zika virus. The '802 patent teaches that neutralizing antibodies from vaccinated mice can be transferred to unvaccinated mice and such neutralizing antibodies can delay the onset of disease when the unvaccinated mice were

challenged with ZIKV PRVABC59. For example, pooled serum from vaccinated and challenged AG129 mice was injected into 5-6 week old AG129 mice. “Following passive transfer (~16-19 hours later), whole blood was collected and serum was separated by centrifugation from each mouse prior to virus challenge for determination of circulating neutralizing antibody titer (Fig. 17). Just prior to virus challenge, groups of mice . . . had mean log 10 neutralizing antibody titers Twenty four hours following passive transfer of ZIKV nAbs, mice were intraperitoneally challenged with 104 pfu of ZIKV PRVABC59. . . . These results suggested that detectable levels ($\geq 1.30 \log 10$) of ZIKV neutralizing antibodies delayed onset of disease in a dose-dependent manner.” Ex 1001 77:10-78:50.

408. Thomas does not expressly teach that the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn, as recited in claim 9. However, Thomas does teach that 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.

409. Thomas further teaches an adoptive transfer study in mice similar to that described in the ‘802 patent. 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. “For adoptive transfer studies, Balb/c mice are infused i.v. with IgG purified from PIV vaccinated monkeys at week 8 and were challenged by the i.v. route with 10^5 VP (10^2 PFU) ZIKV-BR. Rhesus monkeys are infused i.v. with IgG purified from PIV vaccinated monkeys at week 8 and were challenged by the s.c. (SQ) route with 10^6 VP (10^3 PFU) ZIKV-BR.” EX 1004 33:21-25. Thomas explored “the observed protection by adoptive transfer studies.” In mice infused with vaccine-elicited, ZIKV-specific IgG and then challenged with ZIKV-BR, “[t]he higher two doses of purified IgG provides complete protection following ZIKV challenge” EX 1004 38:5-16. In rhesus monkeys infused with vaccine-elicited, ZIKV-specific IgG and then challenged with ZIKV-BR, “one animal is completely protected and the other showed a blip of viremia on days 3-5 (Fig. 12B).” EX 1004 38:17-22. 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 to

39:2.

410. Thomas teaches that neutralizing antibodies generated in one animal can be adoptively transferred to another animal, and that such neutralizing antibodies provide a vaccine effective amount to the recipient animal. EX 1004 38:5-16; 38:17-22; 8:24-26; 38:30 to 39:2.

411. Thomas does not provide human experimental data supporting adoptive transfer from a pregnant mother to the fetus. However, Thomas teaches that “if vaccination does not cause any adverse events in the animal and induces an effective immune response (neutralizing antibodies) which protects against a live virus challenge in comparison to a placebo or another control this is typically supportive data to advance to human trials.” EX 1004 26:26-30. 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.

412. 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. One of skill 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.

413. Thomas teaches a need for a Zika virus vaccine that protects pregnant

women and fetuses. EX 1004 2:13-24. Thomas teaches that a purified inactivated whole Zika virus vaccine is advantageous for pregnant women (EX 1004 4:2-7; EX 1004 18:26-30) and that 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.

414. Faucette is directed to immunization during pregnancy and teaches adoptive transfer of antibodies from a mother to a fetus or newborn. Faucette teaches that “[i]mmunization during pregnancy can generate maternal immune protection as well as elicit the production and transfer of antibodies cross the placenta . . . to provide early infant protection. Several successful vaccines are now recommended to all pregnant women worldwide.” EX 1007 p. 2549. “[I]mmunization of pregnant women has emerged as an alternative strategy to combat neonatal infection. It relies on the transfer of maternal vaccine-induced humoral immunity to the fetus during gestation . . . to confer early immune protection until routine vaccination of the child is initiated.” EX 1007 p. 2549. “Several successful maternal vaccines, such as Tetanus-Diphtheria-Pertussis (Tdap) vaccine and inactivated influenza vaccine (IIV), are now universally recommended by the Center for Disease Control and prevention (CDC) to all pregnant women.” EX 1007 p. 2549. “Maternal vaccination aims protect the both the mother and neonate.” EX 1007 p. 2550. “Underpinning

the idea of maternal immunization is that the transport of vaccine-induced maternal immunoglobulin G (IgG) antibody across the placenta by neonatal Fc receptor (FcRn) expressed on trophoblasts across [citations omitted], confers fetal and early infant immune protection (Fig. 1A). The amount of IgG transferred across the placenta to the fetus correlates with IgG concentration in the maternal circulation . . .” EX 1007 p. 2552. “IgG transfer from the mother to the fetus can occur as early as gestational week 13, with the largest amount transferred during the third trimester of pregnancy (Fig. 1B). [Citations omitted.] Additional passive immunity in the form of vaccine-induced IgA, IgG and IgM secreted into colostrum and breast milk is transferred during breastfeeding.” EX 1007 p. 2552. “Maternal immunization presents unique benefits to the mother, fetus and the newborn by inducing active immunity in the mother and the transfer of passive humoral immunity across the placenta to the fetus.” EX 1007 p. 2552. Faucette further teaches that “the vaccines effectiveness is due to both passive antibody transport and reduction of maternal exposure. Therefore, immunizing pregnant women can circumvent the multiple disadvantages of attempting to directly immunize neonates immediately after birth.” EX 1007 p. 2552. “Another important, albeit less obvious, benefit of maternal vaccination may involve the function of maternal antibodies in promoting the immune maturation and modulation in infants. Animal studies found 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.

415. Thomas teaches a need for a vaccine to protect both a pregnant woman and the fetus. EX 1004 2:13-24; EX 1004 4:2-7; EX 1004 18:26-30. Thomas teaches adoptive transfer of neutralizing antibodies in mice and rhesus monkeys and that “taken together, these data are reasonably predictive for how ZIKV vaccines will perform in humans.” EX 1004 39:15-16. Thomas teaches the mechanism of action of vaccinating the pregnant woman is vaccine induced immunity that prevents fetal infection from taking hold. EX 1004 3:2-12. Faucette teaches that immunizing pregnant women can generate maternal immune protection and “elicit the production and transfer of antibodies cross the placenta . . . to provide early infant protection.” EX 1007 Abstract, p. 2549.

416. Thomas and Faucette teach administering a vaccine to a pregnant woman and adoptively transferring a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus in the pregnant woman or the newborn by breastfeeding. Accordingly, Thomas and Faucette teach this limitation of claim 9.

417. It is within the level of skill of one of ordinary skill in the art to administer a Zika virus vaccine to a pregnant woman, as Thomas teaches to do just that, and Faucette teach vaccinating pregnant women with respect to inactivated

virus vaccines.

418. One of skill 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 because to do so provides protection of the fetus and newborn to Zika virus infection. Thomas teaches a need for a vaccine to protect both a pregnant woman and the fetus. EX 1004 2:13-24; EX 1004 4:2-7; EX 1004 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. Faucette teaches the benefit of maternally derived antibodies in providing profound and long-lasting effects in promoting development of infant B cells and antibody diversification and production. Based on Thomas and Faucette, one of skill would have been motivated to vaccinate a pregnant woman with an inactivated whole Zika virus antigen to adoptively transfer a vaccine effective amount of neutralizing antibodies because Thomas and Faucette teach that it is beneficial to immunize a fetus or provide antibodies via breastfeeding, rather than attempting to immunize the neonate immediately after birth, and that maternally derived antibodies have beneficial effects.

419. One of skill 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 because Thomas provides animal studies of successful adoptive transfer. EX 1004 38:5-16; EX 1004 38:17-22; EX 1004 38:24-26; EX 1004 38:30 to 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.

420. Accordingly, Thomas and Faucette teach this limitation of claim 9.

e. wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration.

421. Thomas teaches a first (prime) and a second (boost) administration. EX 1004 4:20-22: “Another example is wherein two doses are administered (e.g., a first dose, followed by a second dose 4 weeks later). A booster dose (second dose or more) may be useful for persons with recurrent infection risk.” EX 1004 7:32-33: “An exemplary dosage schedule entails an initial dose, then a second (booster) dose about 4 weeks later.” EX 1004 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”

422. Accordingly, Thomas teaches this limitation of claim 9.

423. Based on the above, Claim 9 is obvious in view of Thomas and

Faucette.

2. Claim 32

424. Claim 32 of the '802 patent depends from claim 9 and is set forth below.

32. The method of claim 9, wherein the vaccine or immunogenic composition is administered by intramuscular or subcutaneous administration.

425. As previously demonstrated at XIII(B)(1), claim 9 from which claim 32 depends is obvious over Thomas and Faucette. Claim 32 recites the same limitation as claim 3. As previously demonstrated at VII(B)(3), Thomas teaches this limitation. Accordingly, claim 32 is obvious over Thomas and Faucette.

3. Claim 33

426. Claim 33 of the '802 patent depends from claim 9 and is set forth below.

33. The method of claim 9, wherein the vaccine or immunogenic composition is administered one or more times.

427. I note that claim 9 requires a first (prime) and a second (boost) administration. Accordingly, claim 9 cannot include a single administration. In any event, as previously demonstrated at XIII(B)(1), claim 9 from which claim 33 depends is obvious over Thomas and Faucette. Claim 33 recites the same limitation as claim 4. As previously demonstrated at VII(B)(4), Thomas teaches this limitation. Accordingly, claim 33 is obvious over Thomas and Faucette.

4. Claim 35

428. Claim 35 of the '802 patent depends from claim 9 and is set forth below.

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.

429. As previously demonstrated at XIII(B)(1), claim 9 from which claim 35 depends is obvious over Thomas and Faucette. Claim 35 recites the same limitation as claim 6. As previously demonstrated at VII(B)(5), Thomas teaches this limitation. Accordingly, claim 35 is obvious over Thomas and Faucette.

5. Claim 36

430. Claim 36 of the '802 patent depends from claim 9 and is set forth below.

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.

431. As previously demonstrated at XIII(B)(1), claim 9 from which claim 36 depends is obvious over Thomas and Faucette. Claim 36 recites the same limitation as claim 7. As previously demonstrated at VII(B)(6), Thomas teaches this limitation. Accordingly, claim 36 is obvious over Thomas and Faucette.

6. Claim 38

432. Claim 38 of the '802 patent depends from claim 9 and is set forth below.

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.

433. As previously demonstrated at XIII(B)(1), claim 9 from which claim

38 depends is obvious over Thomas and Faucette. Claim 38 recites the same limitation as claim 1, i.e., a seroconversion rate of at least 80% in a population of at least 20 Zika virus seronegative subjects. As previously demonstrated at VII(B)(1)(d), Thomas teaches this limitation. Accordingly, claim 38 is obvious over Thomas and Faucette.

7. Claim 39

434. Claim 39 of the '802 patent depends from claim 9 and is set forth below.

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.

435. As previously demonstrated at XIII(B)(1), claim 9 from which claim 39 depends is obvious over Thomas and Faucette. Claim 39 recites the same limitation as claim 11, i.e., a seroconversion rate after a single dose or prime administration of at least 60% in a population of at least 20 Zika virus seronegative subjects. As previously demonstrated at VIII(B)(1)(e) with respect to claim 11, Thomas renders this limitation obvious. Accordingly, claim 39 is obvious over Thomas and Faucette.

8. Claim 41

436. Claim 41 of the '802 patent is set forth below.

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,
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.

437. With the exception of the antigen being purified, all of the limitations of claim 41 are found in claim 9. As previously demonstrated at XIII(B)(1), claim 9 is obvious over Thomas and Faucette. Claim 13 recites the limitation of claim 41 where the antigen is purified. As previously demonstrated at VII(B)(8), Thomas teaches this limitation. Accordingly, claim 41 is obvious over Thomas and Faucette.

9. Claim 47

438. Claim 47 of the '802 patent depends from claim 9 and is set forth below.

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.

439. As previously demonstrated at XIII(B)(1), claim 9 from which claim 47 depends is obvious over Thomas and Faucette. Claim 13 recites the limitation of claim 47 where the inactivated whole virus is purified. As previously demonstrated at VII(B)(8), Thomas teaches this limitation. As previously demonstrated at VII(B)(1)(b), Thomas teaches a dose of about 5 µg. Accordingly, claim 47 is obvious over Thomas and Faucette.

10. Claim 49

440. Claim 49 of the '802 patent is set forth below.

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,
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.

441. With the exception of the vaccine or immunogenic composition further comprising an aluminum salt adjuvant, all of the limitations of claim 49 are found in claim 9. As previously demonstrated at XIII(B)(1), claim 9 is obvious over Thomas and Faucette. Claim 21 recites the limitation wherein the vaccine or immunogenic composition further comprises an aluminum salt adjuvant. As previously demonstrated in VII(B)(10), Thomas teaches this limitation. Accordingly, claim 49 is obvious over Thomas and Faucette.

11. Claim 51

442. Claim 51 of the '802 patent depends from claim 49 and is set forth below.

51. The method of claim 49, wherein the adjuvant is aluminum hydroxide.

443. As previously demonstrated at XIII(B)(10), claim 49 from which claim 51 depends is obvious over Thomas and Faucette. Claim 51 recites the same

limitation as claim 23. As previously demonstrated at VII(B)(11), Thomas teaches this limitation. Accordingly, claim 51 is obvious over Thomas and Faucette.

12. Claim 55

444. Claim 55 of the '802 patent depends from claim 9 and is set forth below.

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.

445. As previously demonstrated at XIII(B)(1), claim 9 from which claim 55 depends is obvious over Thomas and Faucette. Claim 27 recites the limitation wherein administration of the vaccine or immunogenic composition to the human subject does not result in the human subject having a severe adverse event as a result of the administration. As previously demonstrated in VII(B)(12), Thomas teaches this limitation. Accordingly, claim 55 is obvious over Thomas and Faucette.

13. Claim 56

446. Claim 56 of the '802 patent depends from claim 55 and is set forth below.

56. The method of claim 55, wherein the severe adverse event is a fever of a temperature of 39° C. or higher.

447. As previously demonstrated at XIII(B)(12), claim 55 from which claim 56 depends is obvious over Thomas and Faucette. Claim 28 recites the limitation wherein the severe adverse event is a fever of a temperature of 39° C. or higher. As

previously demonstrated in VII(B)(13), Thomas teaches this limitation. Accordingly, claim 56 is obvious over Thomas and Faucette.

14. Claim 57

448. Claim 57 of the '802 patent is set forth below.

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.

449. With the exception of the pregnant human subject being from a Zika endemic region or from a Zika non-endemic region travelling to an endemic region, all of the limitations of claim 57 are found in claim 9. As previously demonstrated at XIII(B)(1), claim 9 is obvious over Thomas and Faucette. Claim 29 recites the limitation wherein the pregnant human subject is from a Zika endemic region or from a Zika non-endemic region travelling to an endemic region. As previously demonstrated in VII(B)(14), Thomas teaches this limitation. Accordingly, claim 57 is obvious over Thomas and Faucette.

15. Claim 58

450. Claim 58 of the '802 patent is set forth below.

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.

451. With the exception of the pregnant human subject being 18 to 29 years of age or 30 to 49 years of age, all of the limitations of claim 58 are found in claim 9. As previously demonstrated at XIII(B)(1), claim 9 is obvious over Thomas and Faucette. Claim 30 recites the limitation wherein the pregnant human subject is 18 to 29 years of age or 30 to 49 years of age. As previously demonstrated in VII(B)(15), Thomas teaches this limitation. Accordingly, claim 58 is obvious over Thomas and Faucette.

16. Claim 65

452. Claim 65 of the '802 patent depends from claim 39 which depends from claim 9 and is set forth below.

65. The method of claim 39, 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 70% in a population of at least 20 Zika virus seronegative subjects.

453. As previously demonstrated at XIII(B)(1), claim 9 from which claim 39 depends is obvious over Thomas and Faucette. As previously demonstrated at

XIII(B)(7), claim 39 from which claim 65 depends is obvious over Thomas and Faucette. Claim 65 increases the seroconversion rate relative to claim 39 from at least 60% to 70%. The analysis of claim 39 and claim 11 at VIII(B)(1)(e) with respect to this feature is therefore incorporated by reference herein. In sum, Thomas renders this feature obvious on the same basis as provided for with respect to claim 11 and claim 39. In sum, Thomas teaches in Example 5: ZIKV PIV Performance in Human Trials, 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%. Thomas also teaches that administering a dose of an inactivated, whole Zika virus antigen vaccine affects seroconversion of the human to which the dose is administered. In particular, seroconversion is increased relative to a human who has not received the vaccine dose after a first (prime) dose, as well as, after a second (boost) dose. EX 1004 42:4-23. Accordingly, a vaccine dose including an inactivated, whole Zika virus antigen and an adjuvant which results in seroconversion and, accordingly, a seroconversion rate among study participants, would be recognized by a 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.

454. 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.

455. However, Thomas does teach 100% protection after a single immunization of the ZIKV vaccine. EX 1004 4:15-22. Thomas teaches a slight rise in antibody after the first (prime) dose of vaccine. 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 1004 7:30-32. Thomas also teaches that a booster dose is not required. EX 1004 4:15-22 and EX 1004 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 1004 42:4-7.

456. It is within the level of one of ordinary skill in the art to use Thomas’s method for achieving seroconversion after a first (prime) administration or after a second (boost) administration of a purified, inactivated whole Zika virus antigen in a population of at least 20 Zika virus seronegative subjects 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.

457. One would have been motivated to modify the vaccine of Thomas exemplified in Example 5. ZIKV PIV Performance in Human Trials by either the amount of antigen and/or adjuvant or the type of adjuvant to induce 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

“[i]deally, only one dose is needed to effect protection against Zika infection for mammals, including humans.” EX 1004 7:30-32. Further, Thomas teaches that “a single immunization of the vaccine can be shown to provide 100% protection in susceptible mammals against challenge with ZIKV.” EX 1004 4:15-22. Thomas teaches that based on animal models in the field of flavivirus PIVs, a single dose is a safe and effective dosage. EX 1004 18:17-20. Thomas teaches that a seroconversion rate of 92% can be achieved and is desirable. See Example 5. ZIKV PIV Performance in Human Trials, EX 1004 42:4-8. Thomas teaches that administering a single dose of its vaccine results in a slight rise in antibody, i.e. seroconversion. EX 1004 42:9-10.

458. Based on Thomas, one of skill 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 or prime 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 vaccine dose affects seroconversion after a first (prime) dose, as well as after a

second (boost) dose.

459. One of skill would have had a reasonable expectation of successfully modifying the vaccine of Thomas exemplified in Example 5. ZIKV PIV Performance in Human Trials to induce 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 immunization of the vaccine can be shown to provide 100% 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. Further, Thomas demonstrated that a seroconversion rate of 92% was achieved, and so one of skill would reasonably expect that a lower seroconversion rate of 70% could be achieved. Achieving a seroconversion rate of at least 60% 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.

460. Accordingly, claim 65 is obvious in view of Thomas and Faucette.

17. Claim 66

461. Claim 66 of the ‘802 patent depends from claim 39 which depends from claim 9 and is set forth below.

66. The method of claim 39, 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 80% in a population of at least 20 Zika virus seronegative subjects.

462. As previously demonstrated at XIII(B)(1), claim 9 from which claim 39 depends is obvious over Thomas and Faucette. As previously demonstrated at XIII(B)(7), claim 39 from which claim 65 depends is obvious over Thomas and Faucette. Claim 66 recites the limitation 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 80% in a population of at least 20 Zika virus seronegative subjects. This is the same limitation recited in claim 60 which depends from claim 11. As previously demonstrated in VIII(B)(2) for claim 60, Thomas renders this limitation obvious. Accordingly, claim 66 is obvious over Thomas and Faucette.

18. Claim 67

463. Claim 67 of the '802 patent depends from claim 39 which depends from claim 9 and is set forth below.

67. The method of claim 39, 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 90% in a population of at least 20 Zika virus seronegative subjects.

464. As previously demonstrated at XIII(B)(1), claim 9 from which claim 39 depends is obvious over Thomas and Faucette. As previously demonstrated at XIII(B)(7), claim 39 from which claim 65 depends is obvious over Thomas and

Faucette. Claim 67 recites the limitation 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 90% in a population of at least 20 Zika virus seronegative subjects. This is the same limitation recited in claim 61 which depends from claim 11. As previously demonstrated in VIII(B)(3) for claim 61, Thomas teaches this limitation. Accordingly, claim 66 is obvious over Thomas and Faucette.

XIV. GROUND VIII: Claims 34, 43-46 and 48 are Invalid as Being Obvious Over Thomas in view of Faucette and further in view of Version 8 of NCT02952833

A. The Claims are Obvious Over Thomas and Faucette and further in view of Version 8 of NCT02952833

465. A detailed claim chart comparing each feature of claims 34, 43-46 and 48 and where each feature is taught in Thomas and Faucette and Version 8 of NCT02952833 is provided in Appendix B.

B. Claim by Claim Analysis

1. Claim 34

466. Claim 34 of the '802 patent depends from claim 9 and is set forth below.

34. The method of claim 9, wherein the vaccine or immunogenic composition comprising a dose of 10µg is administered one time.

467. As previously demonstrated at XIII(B)(1), claim 9 from which claim 34 depends is obvious over Thomas and Faucette. Claim 34 recites the same 10 µg dose administered one time as claim 5. As previously demonstrated at XI(B)(1), Version 8 of NCT02952833 teaches use of a 10 µg dose in humans clinical trials

including women A POSA would have been aware of the vaccination of pregnant women and adoptive transfer to a fetus from Thomas and Faucette and would have looked to the art for examples of ZPIV doses for use with women, and further for use with pregnant women, as a matter of routine skill and would have been aware of Version 8 of NCT02952833.

468. The 10.0 µg dose of Version 8 of NCT02952833 is the same as the 10 µg dose recited in claim 34. Thomas teaches to determine a “safe and effective dose and schedule for this ZIKV PIV, as needed for persons of any age and size” (EX 1004 4:24-28).

469. It is within the level of skill of one of ordinary skill in the art to use the 10.0 µg ZIKV dose of Version 8 of NCT02952833 in human trials with the known method of Thomas disclosing a 5 µg ZIKV dose in human trials and in a method of vaccinating pregnant women as disclosed in Thomas and Faucette because to do so would have only required routine skill to change the 5 µg ZIKV dose to a 10.0 µg ZIKV dose.

470. One would have been motivated to modify the method of Thomas to administer the Zika vaccine at a dose of 10.0 µg because Thomas teaches to determine optimal doses of ZIKV antigen based on “dosing and schedule for other PIV flavivirus vaccines – such as Japanese encephalitis and tick-borne encephalitis – 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 1004 4:24-28. 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.” Further, Version 8 of NCT02952833 teaches human studies where both a 5µg ZIKV dose and a 10 µg ZIKV dose are used to determine safety and immunological response. EX 1011 p. 6. Further, a POSA would have understood that dosage of antigen is a result-effective variable affecting seroconversion rate. Based on Thomas, Faucette and Version 8 of NCT02952833, one of skill would have been motivated to explore different dosages for a pregnant woman, such as a 5 µg ZIKV dose, a 2.5 µg ZIKV dose, and a 10 µg ZIKV dose, to determine safety and immunological response and to optimize a ZIKV antigen dose, because both Thomas and Version 8 of NCT02952833 teach to do just that, and the ZIKV antigen dose is a result-effective variable affecting seroconversion rate.

471. One of skill would have had a reasonable expectation of successfully using a 10 µg dose one time (i.e., as the boost dose for example) from the human vaccination method of Version 8 of NCT02952833 to vaccinate against Zika virus infection in the human vaccination method of Thomas (which also teaches vaccinating pregnant women) and in the vaccination method of Faucette with adoptive transfer to a fetus because Thomas demonstrated that two 5 µg doses (a

total of 10 µg) were safe and provided significant immune response to provide protection against Zika virus. Faucette teaches that vaccinating a pregnant woman will adoptively transfer to the fetus. Thomas demonstrated a greater immunological response and, therefore greater protection, after a second (boost) 5 µg dose. EX 1004 42:9-11 (“Antibody kinetics based on MN50 titers indicating a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff and then a robust and brisk rise in antibody titer for the Trial Group 2 and Trial Group 3 volunteers following dose two.”). One of skill 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. Selecting the 10 µg dose based on Version 8 of NCT02952833 is routine optimization of a result-effective variable.

472. Accordingly, claim 34 is obvious over Thomas and Faucette and further in view of Version 8 of NCT02952833.

2. Claim 43

473. Claim 43 of the ‘802 patent is set forth below.

43. 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,
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 comprises a
dose of from about 10 µg to about 40 µg of purified inactivated whole
virus.

474. With the exception of the vaccine or immunogenic composition comprising a dose of from about 10 µg to about 40 µg of purified inactivated whole virus, all of the limitations of claim 43 are found in claim 9. As previously demonstrated at XIII(B)(1), claim 9 is obvious over Thomas and Faucette. Claim 13 recites the limitation of claim 43 where the inactivated whole virus is purified. As previously demonstrated at VII(B)(8) with respect to claim 13, Thomas teaches this limitation. Claim 15 recites the limitation wherein the vaccine or immunogenic composition comprises a dose of from about 10 µg to about 40 µg of purified inactivated whole virus. As previously demonstrated in XI(B)(2) with respect to claim 15, Version 8 of NCT02952833 teaches use of a 10 µg dose in human clinical trials including women. Based on Thomas and Faucette teaching vaccinating the mother to result in adoptive transfer to the fetus, one of skill would have been motivated to use a 10 µg dose with a pregnant woman with a reasonable expectation of successfully vaccinating the mother and with adoptive transfer to the fetus. Further, based on the analysis of claim 34 set forth above in XIV(B)(1), one of skill would have been motivated by Thomas, Faucette and Version 8 of NCT02952833

to use a 10 µg dose with a pregnant woman with a reasonable expectation of successfully vaccinating the mother and with adoptive transfer to the fetus. Accordingly, claim 43 is obvious over Thomas and Faucette, and further in view of Version 8 of NCT02952833.

3. Claim 44

475. Claim 44 of the '802 patent depends from claim 9 and is set forth below.

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.

476. As previously demonstrated at XIII(B)(1), claim 9 from which claim 44 depends is obvious over Thomas and Faucette. Claim 13 recites the limitation of claim 44 where the inactivated whole virus is purified. As previously demonstrated at VII(B)(8) with respect to claim 13, Thomas teaches this limitation. Claim 16 recites the limitation wherein the vaccine or immunogenic composition comprises a dose of from about 10 µg to about 30 µg of purified inactivated whole virus. As previously demonstrated in XI(B)(3) with respect to claim 16, Version 8 of NCT02952833 teaches use of a 10 µg dose in human clinical trials including women. Based on Thomas and Faucette teaching vaccinating the mother to result in adoptive transfer to the fetus, one of skill would have been motivated to use a 10 µg dose with a pregnant woman with a reasonable expectation of successfully vaccinating the mother and with adoptive transfer to the fetus. Further, based on the analysis of claim

34 set forth above in XIV(B)(1), one of skill would have been motivated by Thomas, Faucette and Version 8 of NCT02952833 to use a 10 µg dose with a pregnant woman with a reasonable expectation of successfully vaccinating the mother and with adoptive transfer to the fetus. Accordingly, claim 44 is obvious over Thomas and Faucette and further in view of Version 8 of NCT02952833.

4. Claim 45

477. Claim 45 of the '802 patent depends from claim 9 and is set forth below.

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.

478. As previously demonstrated at XIII(B)(1), claim 9 from which claim 45 depends is obvious over Thomas and Faucette. Claim 13 recites the limitation of claim 45 where the inactivated whole virus is purified. As previously demonstrated at VII(B)(8) with respect to claim 13, Thomas teaches this limitation. Claim 17 recites the limitation wherein the vaccine or immunogenic composition comprises a dose of from about 10 µg to about 20 µg of purified inactivated whole virus. As previously demonstrated in XI(B)(4) with respect to claim 17, Version 8 of NCT02952833 teaches use of a 10 µg dose in human clinical trials including women. Based on Thomas and Faucette teaching vaccinating the mother to result in adoptive transfer to the fetus, one of skill would have been motivated to use a 10 µg dose with a pregnant woman with a reasonable expectation of successfully vaccinating the

mother and with adoptive transfer to the fetus. Further, based on the analysis of claim 34 set forth above in XIV(B)(1), one of skill would have been motivated by Thomas, Faucette and Version 8 of NCT02952833 to use a 10 µg dose with a pregnant woman with a reasonable expectation of successfully vaccinating the mother and with adoptive transfer to the fetus. Accordingly, claim 45 is obvious over Thomas and Faucette, and further in view of Version 8 of NCT02952833.

5. Claim 46

479. Claim 46 of the '802 patent depends from claim 9 and is set forth below.

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.

480. As previously demonstrated at XIII(B)(1), claim 9 from which claim 46 depends is obvious over Thomas and Faucette. Claim 13 recites the limitation of claim 46 where the inactivated whole virus is purified. As previously demonstrated at VII(B)(8) with respect to claim 13, Thomas teaches this limitation. Claim 18 recites the limitation wherein the vaccine or immunogenic composition comprises a dose of from about 10 µg to about 15 µg of purified inactivated whole virus. As previously demonstrated in XI(B)(5) with respect to claim 18, Version 8 of NCT02952833 teaches use of a 10 µg dose in human clinical trials including women. Based on Thomas and Faucette teaching vaccinating the mother to result in adoptive transfer to the fetus, one of skill would have been motivated to use a 10 µg dose with

a pregnant woman with a reasonable expectation of successfully vaccinating the mother and with adoptive transfer to the fetus. Further, based on the analysis of claim 34 set forth above in XIV(B)(1), one of skill would have been motivated by Thomas, Faucette and Version 8 of NCT02952833 to use a 10 µg dose with a pregnant woman with a reasonable expectation of successfully vaccinating the mother and with adoptive transfer to the fetus. Accordingly, claim 46 is obvious over Thomas and Faucette, and further in view of Version 8 of NCT02952833.

6. Claim 48

481. Claim 48 of the '802 patent depends from claim 9 and is set forth below.

48. The method of claim 9, wherein the vaccine or immunogenic composition comprises a dose of about 10 µg of purified inactivated whole virus.

482. As previously demonstrated at XIII(B)(1), claim 9 from which claim 48 depends is obvious over Thomas and Faucette. Claim 13 recites the limitation of claim 48 where the inactivated whole virus is purified. As previously demonstrated at VII(B)(8) with respect to claim 13, Thomas teaches this limitation. Claim 20 recites the limitation wherein the vaccine or immunogenic composition comprises a dose of about 10 µg. As previously demonstrated in XI(B)(6) with respect to claim 20, Version 8 of NCT02952833 teaches use of a 10 µg dose in human clinical trials including women. Based on Thomas and Faucette teaching vaccinating the mother to result in adoptive transfer to the fetus, one of skill would have been motivated to

use a 10 µg dose with a pregnant woman with a reasonable expectation of successfully vaccinating the mother and with adoptive transfer to the fetus. Further, based on the analysis of claim 34 set forth above in XIV(B)(1), one of skill would have been motivated by Thomas, Faucette and Version 8 of NCT02952833 to use a 10 µg dose with a pregnant woman with a reasonable expectation of successfully vaccinating the mother and with adoptive transfer to the fetus. Accordingly, claim 48 is obvious over Thomas and Faucette and further in view of Version 8 of NCT02952833.

XV. 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

A. The Claims are Obvious Over Thomas and Faucette and further in view of Barbero

483. A detailed claim chart comparing each feature of claims 37, 40, 42, 50 and 52 and where each feature is taught in Thomas and Faucette and further in view of Barbero is provided in Appendix B.

B. Claim by Claim Analysis

1. Claim 37

484. Claim 37 of the '802 patent depends from claim 9 and is set forth below.

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).

485. As previously demonstrated at XIII(B)(1), claim 9 from which claim 37 depends is obvious over Thomas and Faucette. Claim 37 recites the same limitation as claim 8. As previously demonstrated at IX(B)(1) with respect to claim 8 incorporated herein, Thomas teaches neutralizing antibodies titers to Zika virus in the human subject of greater than 1000 and Barbero teaches use of the PRNT. A POSA would have been aware of the vaccination of pregnant women and adoptive transfer to a fetus from Thomas and Faucette and would have looked to the art for examples of methods of characterizing neutralizing antibody titers as a matter of routine skill and would have been aware of Barbero. One of skill would determine and use neutralizing antibody titer on a pregnant woman as a measure of the strength of the immune response and immune protection.

486. Following the analysis of claim 8 and applying that analysis to claim 37, one of skill would have been aware of the interchangeability of the MN assay of Thomas with the PRNT of Barbero to produce similar results regarding antibody titer reflecting seroconversion and a protective immune response. As background art, Liu reports that good correlation was observed between the two assays. EX 1012 p. 73, 76, 77.

487. One would have been motivated to modify the method of Thomas to measure neutralizing antibody titers using PRNT instead of MN50 because Barbero teaches that both PRNT and MN50 are known methods for measuring neutralizing

antibody titers, and that each can be used to measure neutralizing antibody titers from a Zika vaccine, as an indication of seroconversion and a protective immune response. One of skill would have been motivated to apply these teachings to a pregnant woman because Thomas and Faucette teach vaccination of pregnant women and adoptive transfer to a fetus.

488. One of skill would have had a reasonable expectation of successfully using PRNT instead of MN50 to determine neutralizing antibody titers as an indication of seroconversion and a protective immune response in a pregnant woman because Barbero teaches successful use of each method to determine neutralizing antibody titers from a Zika vaccine. The substitution of one known method for another known method to achieve the same purpose does not result in patentability absent unexpected results. Each method is known to determine neutralizing antibody titers in women in general and would be expected to perform similarly in a pregnant woman. PRNT is used for the same objective as MN50, i.e., to measure neutralizing antibody titers, and produces no unexpected result.

489. Accordingly, claim 37 is obvious over Thomas and Faucette and further in view of Barbero.

2. Claim 40

490. Claim 40 of the '802 patent depends from claim 9 and is set forth below.

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).

491. As previously demonstrated at XIII(B)(1), claim 9 from which claim 40 depends is obvious over Thomas and Faucette. Claim 40 recites the same limitation as claim 12. As previously demonstrated at IX(B)(2) with respect to claim 12, Thomas teaches GMT 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 higher than the GMT induced 28 days after the prime administration and Barbero teaches use of the PRNT. A POSA would have been aware of the vaccination of pregnant women and adoptive transfer to a fetus from Thomas and Faucette and would have looked to the art for examples of methods of characterizing neutralizing antibody titers, such as GMT, as a matter of routine skill and would have been aware of Barbero. One of skill would determine and use neutralizing antibody titer on a pregnant woman as a measure of the strength of the immune response and immune protection.

492. Following the analysis of claim 12 and applying that analysis to claim 40, one of skill would have been aware of the interchangeability of the MN assay of Thomas with the PRNT of Barbero to produce similar results regarding antibody

titer reflecting seroconversion and a protective immune response. As background art, Liu reports that good correlation was observed between the two assays. EX 1012 p. 73, 76, 77.

493. Following the analysis of claim 12 and applying that analysis to claim 40, it is within the level of skill of one of ordinary skill in the art to use the known method of PRNT of Barbero to determine neutralizing antibody titers and therefore GMT, because to do so would have only required routine skill insofar as Barbero teaches how to use the PRNT assay to determine neutralizing antibody titers. Additionally, one of skill would have been motivated to achieve a higher neutralizing antibody titer after booster administration, e.g., by adjusting the dosages of antigen at primer administration and/or boost administration, to obtain the desired immune protection.

494. One would have been motivated to modify the method of Thomas to determine GMT using PRNT instead of MN50 because Barbero teaches that both PRNT and MN50 are known methods for measuring neutralizing antibody titers, and that each can be used to measure neutralizing antibody titers from a Zika vaccine, as an indication of seroconversion and a protective immune response. One of skill would have been motivated to apply these teachings to a pregnant woman because Thomas and Faucette teach vaccination of pregnant women and adoptive transfer to a fetus.

495. One of skill would have had a reasonable expectation of successfully using PRNT instead of MN50 to determine neutralizing antibody titers and therefore GMT as an indication of seroconversion and a protective immune response in a pregnant woman, because Barbero teaches successful use of each method to determine generation of neutralizing antibody titers from a Zika vaccine. The substitution of one known method for another known method to achieve the same purpose does not result in patentability absent unexpected results. Each method is known to determine neutralizing antibody titers in women in general and would be expected to perform similarly in a pregnant woman. PRNT is used for the same objective as MN50, i.e., to measure neutralizing antibody titers, and produces no unexpected result.

496. Accordingly, claim 40 is obvious over Thomas and Faucette and further in view of Barbero.

3. Claim 42

497. Claim 42 of the '802 patent depends from claim 41 and is set forth below.

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.

498. As previously demonstrated at XIII(B)(8), claim 41 from which claim 42 depends is obvious over Thomas and Faucette. Claim 42 recites the same

limitation as claim 14. As previously demonstrated at IX(B)(3) with respect to claim 14, Thomas teaches purification using size -exclusion chromatography and Barbero teaches a purity of greater than 90% as determined by size exclusion chromatography.

499. Following the analysis of claim 14 and applying that analysis to claim 42, it is within the level of skill of one of ordinary skill in the art to utilize size-exclusion chromatography as a purification method because both Thomas and Barbero teach to do so. One would have been motivated to obtain a desired purity level for an antigen preparation for vaccination that is more than 85%, as reflected by more than 85% of the total area under the curve determined in the size exclusion chromatography, because Barbero teaches greater than 90% purity as determined by size exclusion chromatography. One of skill would have been motivated to apply these teachings to a pregnant woman because Thomas and Faucette teach vaccination of pregnant women and adoptive transfer to a fetus.

500. One of skill would have had a reasonable expectation of successfully using size exclusion chromatography to identify the main peak of the Zika virus antigen being more than 85% of the total area under the curve in the size exclusion chromatography because Barbero teaches successful use of size exclusion chromatography to achieve greater than 90% purity. Where the general conditions of a claim are disclosed in the prior art, i.e., purity as indicated by area under the

curve using size exclusion chromatography, it is not inventive to discover the optimum or workable ranges by routine experimentation. No invention is involved in discovering optimum ranges of a process by routine experimentation.

501. Accordingly, claim 42 is obvious over Thomas and Faucette and further in view of Barbero.

4. Claim 50

502. Claim 50 of the '802 patent depends from claim 49 and is set forth below.

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.

503. As previously demonstrated at XIII(B)(10), claim 49 from which claim 50 depends is obvious over Thomas and Faucette. Claim 50 recites the same limitation as claim 22. As previously demonstrated at IX(B)(4), Barbero teaches 500 μg of an aluminum hydroxide adjuvant.

504. Following the analysis of claim 22 and applying that analysis to claim 50, it is within the level of skill of one of ordinary skill in the art to utilize the known amount of 500 μg of an aluminum hydroxide adjuvant of Barbero with the known aluminum salt adjuvant of Thomas because to do so would have only required routine skill to select a specific amount of an aluminum-based adjuvant known in

the art as a result-effective variable affecting seroconversion and combine it with an inactivated, purified whole virus antigen.

505. Following the analysis of claim 22 and applying that analysis to claim 50, one would have been motivated to modify the method of Thomas to use 500 µg of Barbero for the aluminum salt adjuvant because Thomas teaches to use adjuvants as a component of the ZIKV vaccine Barbero teaches that 500 µg is a suitable amount for a ZIKV vaccine. One of skill would have been motivated to apply these teachings to a pregnant woman because Thomas and Faucette teach vaccination of pregnant women and adoptive transfer to a fetus.

506. Following the analysis of claim 22 and applying that analysis to claim 50, one of skill would have had a reasonable expectation of successfully using a 500 µg amount of adjuvant from Barbero with the aluminum salt of Thomas because both Thomas and Barbero teach to combine inactivated whole virus antigens with an aluminum hydroxide salt adjuvant (alum) when making a vaccine composition. Further, Barbero teaches that 500 µg is a suitable amount for an aluminum hydroxide salt adjuvant. Selecting the 500 µg amount based on Barbero is routine optimization of a result-effective variable affecting seroconversion.

507. Accordingly, claim 50 is obvious over Thomas and Faucette, and further in view of Barbero.

5. Claim 52

508. Claim 52 of the '802 patent depends from claim 49 and is set forth below.

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.

509. As previously demonstrated at XIII(B)(10), claim 49 from which claim 52 depends is obvious over Thomas and Faucette. Claim 52 recites the same limitation as claim 24. As previously demonstrated at IX(B)(5) with respect to claim 24, Thomas teaches to use suitable amounts of adjuvants as a component of the ZIKV vaccine and Barbero teaches greater than 95% adsorption of Zika virus particles on aluminum hydroxide adjuvant

510. Following the analysis of claim 24 and applying that analysis to claim 52, one of skill would have been motivated to optimize the amount of antigen adsorbed to adjuvant because Thomas teaches to use a suitable amount of adjuvant and Barbero teaches that an inactivated whole virus Zika antigen will adsorb to alum in an amount of >95%. One of skill would have been motivated to apply these teachings to a pregnant woman because Thomas and Faucette teach vaccination of pregnant women and adoptive transfer to a fetus.

511. Following the analysis of claim 24 and applying that analysis to claim 52, one of skill would have had a reasonable expectation of successfully having the amount of ZIKV antigen adsorbed to adjuvant in the amount of at least 75% because

Thomas teaches to use a suitable amount of adjuvant and Barbero teaches that an inactivated whole virus Zika antigen will adsorb to alum in an amount of >95% which is included within at least 75%.

512. Accordingly, claim 52 is obvious over Thomas and Faucette, and further in view of Barbero.

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

A. The Claims are Obvious Over Thomas and Faucette and further in view of Version 8 of NCT02952833 and Barbero

513. A detailed claim chart comparing each feature of claims 54 and 64 and where each feature is taught in Thomas and Faucette and further in view of Version 8 of NCT02952833 and Barbero is provided in Appendix B.

B. Claim by Claim Analysis

1. Claim 54

514. Claim 54 of the '802 patent is set forth below.

54. 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,

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 comprises a dose of about 10 µg of purified inactivated whole virus, about 200 µg aluminum hydroxide, a buffer, and optionally a sugar.

515. With the exception of the vaccine or immunogenic composition comprising a dose of about 10 µg of purified inactivated whole virus, about 200 µg aluminum hydroxide, a buffer, and optionally a sugar, all of the limitations of claim 54 are found in claim 9. As previously demonstrated at XIII(B)(1), claim 9 is obvious over Thomas and Faucette. Claim 26 recites the limitation 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. As previously demonstrated in XII(B)(1) with respect to claim 26, Thomas teaches an aluminum hydroxide adjuvant, use of a sugar and use of a buffer, Version 8 of NCT02952833 teaches a 10 µg dose and Barbero teaches 500 µg of an aluminum hydroxide adjuvant.

516. Following the analysis of claim 26 and applying that analysis to claim 54, a POSA would have understood that the amount of a Zika virus vaccine is a result-effective variable affecting seroconversion as previously discussed. One of skill would have looked to the art for examples of ZPIV doses as a matter of routine skill and would have been aware of Version 8 of NCT02952833. One of skill would have been motivated to use a 10.0 µg dose of Version 8 of NCT02952833 because Thomas teaches to determine optimal doses of ZIKV antigen. One of skill would have been motivated to apply these teachings to a pregnant woman because Thomas and Faucette teach vaccination of pregnant women and adoptive transfer to a fetus.

One of skill would have had a reasonable expectation of successfully using a 10 µg dose because Thomas demonstrated that two 5 µg doses (a total of 10 µg) were safe and provided significant immune response to provide protection against Zika virus. Thomas demonstrated a greater immunological response and, therefore greater protection, after a second (boost) 5 µg dose. One of skill would have reasonably expected that the higher 10 µg dose would provide a similar if not greater immunological response and protection against Zika virus compared to a single 5 µg dose or two 5 µg doses, because the higher antigen content of the 10 µg dose would be expected to elicit a greater immunological response compared to a 5 µg dose, whether the 10 µg dose was used as a first (prime) or a (second) boost) or as a single dose only. Selecting the 10 µg dose based on Version 8 of NCT02952833 is routine optimization of a result-effective variable.

517. Following the analysis of claim 26 and applying that analysis to claim 54, a POSA would have understood that the amount of adjuvant is a result-effective variable affecting seroconversion as previously discussed. Barbero teaches to a POSA a vaccine dose including 500 µg of an aluminum hydroxide adjuvant. A POSA would have been motivated to modify the 500 µg amount of the aluminum hydroxide adjuvant of Barbero to 200 µg because Thomas teaches to use a suitable amount of an adjuvant. The amount of adjuvant is a routine design parameter for vaccines and is a result-effective variable affecting seroconversion. One of skill

would have been able to 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.

518. Following the analysis of claim 26 and applying that analysis to claim 54, a POSA would have had a reasonable expectation of successfully using a Zika vaccine with about 200 µg aluminum hydroxide as adjuvant because Thomas teaches to use a suitable amount of adjuvant and Barbero teaches that inactivated Zika virus will adsorb to aluminum hydroxide so as to function as an adjuvant. A POSA would have understood that the inactivated Zika virus antigen adsorbed to 200 µg aluminum hydroxide would affect seroconversion rate, and therefore result in vaccination. Where the general conditions of a claim are disclosed in the prior art, i.e., an amount of aluminum hydroxide adjuvant in a vaccine dose, it is not inventive to discover the optimum or workable ranges by routine experimentation. No invention is involved in discovering optimum ranges of a process by routine experimentation. The discovery of an optimum value for the amount of aluminum hydroxide adjuvant in a vaccine dose, which is a result effective variable affecting seroconversion in a known process, is ordinary within the skill of the art.

519. Accordingly, claim 54 is obvious over Thomas and Faucette, and further in view of Version 8 of NCT02952833 and Barbero.

2. Claim 64

520. Claim 64 of the '802 patent depends from claim 54 and is set forth below.

64. The method of claim 54, wherein the sugar is sucrose.

521. As previously demonstrated at XVI(B)(1), claim 54 from which claim 64 depends is obvious over Thomas and Faucette and further in view of Version 8 of NCT02952833 and Barbero. Claim 63 recites the limitation wherein the sugar is sucrose. As previously demonstrated in XII(B)(2) with respect to claim 63, Thomas teaches this limitation. Accordingly, claim 64 is obvious over Thomas and Faucette, and further in view of Version 8 of NCT02952833 and Barbero.

XVII.GROUND XI: Claim 53 is Invalid as Being Obvious Over Thomas in view of Faucette, and further in view of Murata

A. The Claim is Obvious Over Thomas and Faucette and further in view of Murata

522. A detailed claim chart comparing each feature of claim 53 and where each feature is taught in Thomas and Faucette and further in view of Murata is provided in Appendix B.

B. Claim Analysis

1. Claim 53

523. Claim 53 of the '802 patent is set forth below.

53. 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,
wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn,
wherein the Zika virus is a clonal isolate, in particular from a plaque purified clonal Zika virus isolate.

524. With the exception of the Zika virus being a clonal isolate, in particular from a plaque purified clonal Zika virus isolate, all of the limitations of claim 53 are found in claim 9. As previously demonstrated at XIII(B)(1), claim 9 is obvious over Thomas and Faucette. Claim 25 recites the limitation wherein the Zika virus is a clonal isolate, in particular from a plaque purified clonal Zika virus isolate. As previously demonstrated in X(B)(1) with respect to claim 25, Murata teaches plaque purification and one of ordinary skill would understand that a virus clonal isolate is obtained using the plaque purification of Murata.

525. Following the analysis of claim 25 and applying that analysis to claim 53, it is within the level of skill of one of ordinary skill in the art to utilize plaque purification as a matter of routine skill in purifying a virus because Murata which teaches that plaque purification is a well-known process for purifying viruses (“rule of thumb in virology calling for three rounds of serial plaque purification”) and is recommended as “unencumbered by intellectual property constraints.”

526. Following the analysis of claim 25 and applying that analysis to claim 53, one of skill would have been motivated to utilize plaque purification because Thomas teaches that the ZIKV virus is purified using known procedures and Murata

teaches that plaque purification is a well-known and recommended process for purifying viruses. One of skill would have been motivated to apply these teachings to a method of vaccinating a pregnant woman because Thomas and Faucette teach vaccination of pregnant women and adoptive transfer to a fetus.

527. One of skill would have had a reasonable expectation of successfully purifying the ZIKV using plaque purification because Murata teaches successful purification of a virus using plaque purification. The substitution of one known method for purifying the ZIKV (i.e., the physical and/or chemical methods disclosed by Thomas) for another known method for purifying the ZIKV (i.e., plaque purification disclosed by Murata) is well within ordinary skill and does not result in patentability absent unexpected results. Each method is known to purify viruses. The use of the plaque purification of Murata would be expected to purify Zika virus and produces no unexpected result.

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

XVIII. NO SECONDARY CONSIDERATIONS OF NON OBVIOUSNESS EXIST

529. As part of my obviousness analysis, I have considered whether there is any secondary consideration in favor of the non-obviousness of the claims. My review of the prosecution history did not reveal any objective evidence of non-obviousness, such as failure of others, unexpected results, praise in the industry,

long-felt, but unmet need, copying or commercial success. Accordingly, I am unaware of any such evidence.

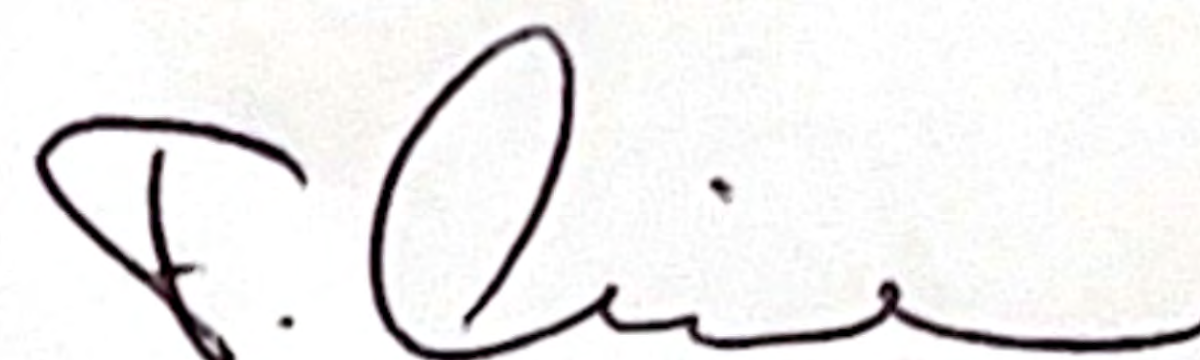
XIX. CONCLUSION

530. In view of the discussion above and my understanding of the law of anticipation and obviousness, the claims of the '802 patent are either anticipated by or obvious in view of prior art, in light of common general knowledge.

531. In signing this Declaration, I recognize that the Declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also recognize that I may be subject to cross-examination in this proceeding. If required, I will appear for cross-examination at the appropriate time. I reserve the right to offer opinions relevant to the invalidity of the '802 patent claims at issue and/or offer testimony in support of this Declaration.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: 30/03/2025



Farshad Guirakhoo, Ph.D.

Exhibit A

FARSHAD GUIRAKHOO, PH.D.**Curriculum Vitae****Residence:**

Chemin de Jalliet 28
1277 Borex, Switzerland

Email: farshad.guirakhoo@gmail.com

Cell: +41 (0) 76 476 2153 / +1 781 827 1176

SUMMARY

- **World-renowned virologist and vaccinologist** with over **30 years** of biotechnology experience, managing the development of vaccines, biologics, and therapeutics from preclinical stages to commercial launches.
 - Expertise spans across **infectious diseases, neurodegenerative diseases, chronic diseases, and cancer**, with a focus on building innovative pipelines, evaluating new technologies, and leading external R&D collaborations.
 - High success rate in carrying projects from invention/conception and early stages of R&D through IND to clinical phases and regulatory submissions, as demonstrated by the successful development of multiple products and the **invention** of:
 - **Dengvaxia™**: World's first Dengue tetravalent vaccine, first marketed in 2015, recognized by the World Vaccine Congress as the **Best Vaccine** in Development in 2011, and licensed by the FDA in 2019.
 - **IMOJEV®**: World's first recombinant single-dose vaccine for the prevention of Japanese encephalitis (launched 2010).
 - **PrevNile™**: Horse vaccine against West Nile disease (launched 2006).
 - **West Nile human vaccine**: The most advanced human vaccine in development (completed Phase 2a in the elderly).
 - Proven leader with skills in managing and directing research projects, building innovative pipelines, and leading diverse groups of scientists.
 - Recognized in **2014** as one of the **Most Influential People in Vaccines** (#22) by VaccineNation (Cameron Bisset, "The Most Influential People in Vaccines." *Vaccine Nation*, Sept. 9, 2014. *Internet Archive*, [web.archive.org/web/20140909091357/http://www.vaccinationation.org/2014/09/03/influential-people-vaccines-2014/](http://www.vaccinationation.org/2014/09/03/influential-people-vaccines-2014/)) (https://geovax.com/images/pdf/The_Most_Influential_People_In_Vaccines.pdf).
-

EDUCATION

Ph.D. in Virology

Institute of Virology, Medical University of Vienna, Vienna, Austria

Thesis: Immunological and protein chemical analysis of Tick-borne encephalitis virus proteins (June 1987)

Mentor: Professor Dr. Franz X. Heinz, Director of the Institute of Virology

M.Sc. in Genetics

International Institute for Biophysics & Biochemistry, Tehran University, Tehran, Iran

Thesis: Difference in DNA excision repair between hetero- and euchromatin chromosomes of mealy bug insects (May 1979)

B.Sc. in Biology

National University of Iran, Tehran, Iran (May 1976)

POST-DOCTORAL TRAINING**Post-Doctoral Fellow**

National Centers for Disease Control and Prevention (CDC), Fort Collins, CO

- Focus: Vector-borne infectious diseases
- Supervisor: Dr. John Roehrig, Branch Chief, CDC

Post-Doctoral Research Scientist

Institute of Virology, Medical University of Vienna, Vienna, Austria

- Supervisor: Professor Dr. Franz X. Heinz, Director of the Inst. of Virology

PROFESSIONAL EXPERIENCE**Expres2ion Biotechnology**

Chief Scientific Officer (Dec 2022 – Present)

- Leading R&D activities, focusing on oncology, infectious diseases, neurodegenerative diseases, and chronic conditions.
- Driving lead candidate for HER2+ breast cancer into clinical stages.

Vaxxinity

Senior Advisor, Vaccine R&D (Jun 2022 – Dec 2022)

- Advisor to the CEO on global vaccine R&D strategies.

Vaxxinity (Merger of United Neuroscience & COVAXX)

Chief Scientific Officer (Apr 2021 – Jun 2022)

- Led global R&D for neuro and infectious disease vaccine targets.

COVAXX (subsidiary of UNS)

Chief Scientific Officer (Dec 2020 – Apr 2021)

- Led global R&D efforts for infectious disease vaccine development.

United Neuroscience (UNS)

Chief Scientific Officer (Jun 2020 – Dec 2020)

- Led global R&D for neuro-targeted vaccines.

Responsive BioServices

Co-Founder and CEO (2017 – 2020)

- Specialized CRO for vaccine evaluations, immunology, and regulatory services.

GeoVax, Inc.

Chief Scientific Officer (2015 – 2020)

- Led R&D across infectious diseases and oncology, including the HIV program.
- Secured government funding and built strategic external collaborations.

Vaxess Technologies

Chief Technology Officer (CTO) (2014 – 2015)

- Led R&D for thermostabilization of vaccines and biologics.

Hookipa Biotech

Chief Scientific Officer (2012 – 2014)

- Managed preclinical development and GMP manufacturing of CMV vaccine candidates (HB101) and HPV-related head/neck cancer vaccines (HB-201, HB-202).

SANOFI PASTEUR

Executive/Senior Director, External R&D (2007 – 2012)

- Evaluated biotech partnerships and in-licensed technologies.
- Developed expertise in vaccine and therapeutic development for infectious diseases and cancer.
- Contributed to regulatory submissions and product development (IMOJEV™, Dengue vaccine).

ACAMBIS, INC.

Senior Director, Virology (2000 – 2007)

- Led development of **Dengvaxia™**, the world's first tetravalent dengue vaccine.
- Managed research teams and collaborated with Sanofi Pasteur.
- Supervised IND preparation and contributed to BLA filings for vaccines.

ORAVAX, INC.

Project Leader, ChimeriVax™ (1996 – 1999)

- Led the development of the **ChimeriVax™** vaccine platform, advancing candidates for **Japanese encephalitis**, RSV, and more.

PUBLICATIONS, PRESENTATIONS & PATENTS

- Published extensively in **peer-reviewed journals** and contributed to books.
- Presented over **500 abstracts/talks**, including invited speaker in national and international scientific meetings.
- Filed **over 100 patents** to enhance platform technology and vaccine development.
<https://patents.justia.com/search?q=guirakhoo>

LEADERSHIP & SKILLS

- Strong track record in **scientific leadership, cross-functional team management, and external collaborations**.
- Expertise in **vaccine development, biologics, regulatory affairs, product innovation, and strategic partnerships**.

Languages: English (Fluent), German (Fluent), Farsi (Native), French (Basic).

PUBLICATIONS/BOOK CHAPTERS

1. HEINZ, F.X., WINKLER, G., MANDL, C., GUIRAKHOO, F., TUMA, W., and KUNZ, C.: Epitope mapping of a flavivirus glycoprotein. In: Positive strand RNA viruses. UCLA Symposia on Molecular and Cellular Biology, New Series, Vol. 54 (M. Brinton, R. Rueckert, eds.), Alan R. Liss, Inc., New York, 1987.
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Aedes aegypti by real-time reverse transcriptase-polymerase chain reaction. *Am J. Trop. Med. Hyg.* 70(1):89-97 (2004).

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SELECTED INVITED SPEAKER PRESENTATIONS IN RECENT YEARS

91. The 5th International CMV Conference April 20-24, 2015 in Brisbane, Australia.
92. EMORY CONFERENCE CENTER, Atlanta, Georgia, May1-3, 2016.
93. USARMY MEDCOM USAMRIID, WDC, May 16, 2016
94. Presentation for DTRA, WDC, May 21, 2016
95. Presentation for JVAP. WDC, June 15, 2016
96. Presentation to BARDA, TechWatch, WDC, July 19, 2016
97. 10TH ISV ANNUAL VACCINE CONGRESS. Boston, MA, Oct 2-4, 2016.
98. INTERNATIONAL MEETING ON EMERGING DISEASES AND SURVEILLANCE, Vienna, Austria, November 4–7, 2016.
99. INTERNATIONAL CONFERENCE ON VACCINE RESEARCH AND DEVELOPMENT. Cartagena, Colombia November 10-12, 2016.
100. KEYSTONE SYMPOSIA. HEMORRHAGIC FEVER VIRUSES (S3). Hilton Santa Fe Historic Plaza Hotel, Santa Fe, New Mexico, December 4-8, 2016.
101. 35TH ANNUAL JP MORGAN HEALTHCARE CONFERENCE. San Francisco, January 9-12, 2017.
102. EMORY UNIVERSITY SPORE PROGRAM, February 16, 2017.
103. HIV VACCINE TRIAL NETWORK, HVTN, SPRING MEETING, WDC, May 23-25, 2017.
104. ASM MICROBE, 2017. ASM/ICAAC, New Orleans, June 1-5, 2017

105. BIO-2017 INTERNATIONAL CONFERENCE, San Diego, June 19-22, 2017.
106. CAMBRIDGE HEALTH INSTITUTE 5TH ANNUAL IMMUNO-ONCOLOGY SUMMIT, POWERING NEXT GENERATION TARGETED IMMUNOTHERAPIES. Boston MA, Aug 28-Sep 1, 2017.
107. 11TH VACCINE CONGRESS, Paradis Point, San Diego, CA 17-20 September 2017.
108. EMERGENT BIO, WDC, Sep 26, 2017.
109. 2017 INTERNATIONAL SOCIETY OF VACCINES ANNUAL CONGRESS, Paris, France, Oct 5-17, 2017.
110. WORLD VACCINE CONGRESS EUROPE Barcelona, October 10-12, 2017. 22.
111. HIV VACCINE TRIAL NETWORK, HVTN, FALL MEETING, Seattle, WA, Oct 23-25, 2017.
112. III INTERNATIONAL CONFERENCE ON VACCINES RESEARCH AND DEVELOPMENT (VACCINE R&D 2017). WDC, Nov-13-15, 2017.
113. JP MORGAN ANNUAL HEALTH CARE CONFERENCES, San Diego, CA, Jan 8-11, 2018.
114. WHO R&D ROADMAP / EBOLA/MARBURG & LASSA, London, Jan 17-19, 2018.
115. ASM BIOTHRREATS. Baltimore MD, Feb 12-14, 2018.
116. IMPACT, THE INTEGRATED MCM PLATFORM ACCELERATION TEAM. Collaborative Partners Leveraging Complementary Platforms in a Coordinated Model to Create a Pipeline of Critical MCMs and Provide DoD with the Capability to Respond Rapidly to New Threats, WDC, March 08, 2018.
117. WORLD VACCINE CONGRESS, 2018 WDC, Apr 3-5.
118. NFID 2018 ANNUAL CONFERENCE ON VACCINOLOGY RESEARCH (ACVR), Bethesda MD, Apr 23-25, 2018.
119. ASM MICROBE 2018, June 7-11, Atlanta, GA.
120. VACCINE AND VACCINATIONS, Barcelona, Spain, Jun 14-16, 2018.
121. INTERNATIONAL CONFERENCE OF HIV/AIDS, STD AND STI'S. Valencia, Spain, Apr 23-25, 2018.
122. WORLD VACCINE CONGRESS, Europe, Lisbon, Portugal, Oct 29-31– 2018.
123. VACCINE R&D 2018, Baltimore, MD, Nov 12-14, 2018.
124. WORLD VACCINE AND IMMUNOTHERAPY CONGRESS, San Diego, CA, Nov 28-30.
125. JP MORGAN HEALTHCARE CONFERENCE, San Francisco, CA, Jan 07-10, 2019.
126. BIO 2019, Philadelphia, PA, Jun 3-6, 2019.
127. FESTIVAL OF BIOLOGICS, Basel, Switzerland, Oct 15-17, 2019.
128. 2019 ISV ANNUAL CONGRESS, Ghent, Belgium, Oct 27-29.
129. WORLD VACCINE CONGRESS EUROPE 2019, Barcelona, Catalonia, Spain, Oct 29-31, 2019.

130. VACCINE R&D-2019, Boston, MA, Nov 18-20.
131. WORLD VACCINE & IMMUNOTHERAPY CONGRESS, 2019, SF, CA 02-05 Dec.
132. 38TH ANNUAL J.P. MORGAN HEALTHCARE CONFERENCE, 2020, SF, CA 13-16 Jan.
133. FESTIVAL OF BIOLOGICS, 2020, SD, CA 02-04 Mar.
134. NFID ANNUAL CONFERENCE ON VACCINOLOGY RESEARCH, 2020, WD, USA 23-25 Mar.
135. CANCER BIOLOGY, IMMUNOTHERAPY CONGRESS, SAVANNAH, GA, March 31-Apr 01 2020.
136. DISEASE PREVENTION AND CONTROL, SUMMIT-AMERICA, July 28th, 2020.
137. VACCINE SUMMIT 2020, VIRTUAL CONFERENCE, 14-Aug-20.
138. WORLD VACCINE CONGRESS EUROPE October 19-21, 2020.
139. 20TH WVC, VIRTUAL, PANEL DISCUSSIONS, Sep 28 – Oct 1, 2020.
140. FESTIVAL OF BIOLOGICS, WORLD IMMUNOTHERAPY CONGRESS 2020, Closing keynote panel discussion, 1/3/2020.
141. PROGRESS ON COVID-19 VACCINE DEVELOPMENT PROGRAMS 11/2/2020.
142. VACCINE SUMMIT OHIO March 1-3, 2021.
143. CAMBRIDGE HEALTH INSTITUTE'S INAUGURAL, THERAPEUTIC INTERVENTIONS FOR COVID-19, THE RACE TO A CURE, May 12-13, 2021.
144. WORLD VACCINE CONGRESS, USA, May 4-6, 2021, virtual.
145. 11TH ANNUAL VACCINES WORLD SUMMIT 2021, 19-20 May 2021, virtual.
146. VACCINE SUMMIT 2021, Sep 20-21, 2021, WDC FESTIVAL OF BIOLOGICS, WORLD IMMUNOTHERAPY, Basel 9-11 Nov 2021.
147. WORLD VACCINE CONGRESS WEST COAST, 30th Nov – 2nd December 2021 in San Diego.
148. World VACCINE CONFERENCE APR17-21, 2021 WDC.
149. World VACCINE CONFERENCE APR18-21, 2022 WDC.
150. IMPAC, VACCINE< WORLD SUMMIT, 5-6 May 2022, India.
151. World VACCINE CONFERENCE EU, Barcelona, Spain Oct 11-13, 2022.
152. FESTIVAL OF BIOLOGICS, 2-4 November 2022, Basel, Switzerland.
153. VACCINES EU, OXFORD GLOBAL, 29-30 November, 2022 Berlin, Germany.
154. World Vaccine Conference Barcelona, Oct 17-19, 2023.
155. Vaccine RD Baltimore MD, November 6-8, 2023.

156. Vaccines Summit, Boston USA, November 13-15, 2023.
157. World Vaccine Congress, 1-4 April 2024, Walter E. Washington Convention Center, Washington, DC, USA.
158. Immuno-Oncology Summit Europe 2024. 23 - 25 April 2024. London, UK.
159. Vaccines Summit 2024, November 13-15, 2024, Hilton Woburn, Boston, MA, USA.

NOTABLE PATENTS AND PATENT APPLICATIONS

1. U.S. Patent No. 7,459,160 (entitled "Chimeric Flaviviruses")
2. U.S. Published Patent Application No. 2009/0191240 (entitled "Flavivirus Vaccines")
3. U.S. Published Patent Application No. 2010/0158938 (entitled "Tetravalent Dengue Vaccines")
4. U.S. Published Patent Application No. 2010/0278773 (entitled "Chimeric flavivirus vaccines")
5. U.S. Patent No. 8,691,550 (entitled "Vaccines Against Japanese Encephalitis Virus and West Nile Virus")
6. U.S. Patent No. 8,871,222 (entitled "Recombinant Flavivirus Vaccines")
7. U.S. Published Patent Application No. 2013/0095136 (entitled "Tetravalent Dengue Vaccines")
8. U.S. Patent No. 8,852,914 (entitled "Flavivirus Vaccines")
9. U.S. Patent No. 9,228,203 (entitled "Recombinant Bicistronic Flavivirus Vectors")
10. U.S. Patent No. 10,172,929 (entitled "Flavivirus Vaccines")
11. U.S. Patent No. 8,486,417 (entitled "Recombinant Bicistronic Flavivirus Vectors")
12. U.S. Patent No. 8,591,916 (entitled "Flavivirus Vaccine Vector Against Influenza Virus")

Exhibit B

Claim US 11,730,802	Thomas WO2017/210215 (EX 1004)	Secondary Reference
<p>1. A method of vaccinating against Zika virus infection in a human subject in need thereof, the method comprising</p>	<p>EX 1004: Abstract: “The invention generally relates to a purified inactivated Zika virus (ZIKV), methods for producing the purified inactivated ZIKV, immunogenic compositions and vaccines comprising the purified inactivated ZIKV and methods for the prevention and/or treatment of infection by ZIKV.”</p> <p>EX 1004: 4:15-20: “The purified, inactivated ZIKV can be used to immunize mammals (including humans) to elicit high titers of virus neutralizing antibodies and protect the immunized mammal from disease caused by ZIKV. For example, a single immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against challenge with ZIKV.”</p> <p>EX 1004: 6:33-7:2: “Also contemplated are methods and kits to induce immune responses to ZIKV, or raise antibodies that recognize ZIKV, in a mammal (especially humans).”</p> <p>EX 1004: 7:8-9: “Specifically, methods are provided for immunizing a mammal (especially a human) against ZIKV infection”.</p> <p>EX 1004: 42:20-43: 1: “Based on the disclosure and the above data the compositions including inactivated ZIKV demonstrate that the compositions are immunogenic and that vaccines comprising inactivated ZIKV are protective against infection with ZIKV.”</p>	

	<p>See also EX 1004 4:15-18; 5:2-6; 6:33-7:2; 5:8-9.</p> <p>EX 1004 18:16-20: Thomas teaches that “anti-Zika antibodies protect against infection in mice and non-human primates. ZIKV PIV generates robust anti-Zika antibodies in both models. Based on these models, and 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, or a booster dose at 4 weeks as described below).”</p>	
<p>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,</p>	<p>EX 1004: 7:2-6: “The method comprises administering to a subject a composition comprising, including or consisting essentially of, one or more of the purified inactivated ZIKV as described herein, in a pharmaceutically acceptable adjuvant, in an amount effective to cause an immune response (including raising antibodies that recognize ZIKV) in the subject.”</p> <p>EX 1004: Page 7, lines 8-11: “Specifically, methods are provided for immunizing a mammal (especially a human) against ZIKV infection, which comprises administering to the mammal an amount of one or more of the vaccines disclosed herein to achieve effective immunization against ZIKV.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p> <p>EX 1004: 4:20-28: “Another example is wherein two doses are administered (e.g., a</p>	

	<p>first dose, followed by a second dose 4 weeks later). A booster dose (second dose or more) may be useful for persons with recurrent infection risk. This is similar to the booster dose regimen associated with the PIV for the flavivirus, Japanese encephalitis (JEV). With the information known about the dosing and schedule for other PIV flavivirus vaccines - such as Japanese encephalitis and tick-borne encephalitis - 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.”</p> <p>EX 1004: 40:18-26:</p> <p>“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</p> <p>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”</p>	
wherein the antigen is an inactivated whole virus	<p>EX 1004: 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p> <p>EX 1004: Abstract: “The invention generally relates to a purified inactivated Zika virus (ZIKV), methods for producing the purified inactivated ZIKV, immunogenic compositions and vaccines comprising the</p>	

	<p>purified inactivated ZIKV and methods for the prevention and/or treatment of infection by ZIKV.”</p> <p>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 (e.g., generating an immune response in a subject at risk of infection and/or in need of preventative treatment, or raising antibodies in a subject, or alleviating symptoms of ZIKV in an infected subject, and the like).”</p>	
as a first (prime) and a second (boost) administration,	<p>EX 1004: 4:20-22: “Another example is wherein two doses are administered (e.g., a first dose, followed by a second dose 4 weeks later). A booster dose (second dose or more) may be useful for persons with recurrent infection risk.”</p> <p>EX 1004: 7:32-33: “An exemplary dosage schedule entails an initial dose, then a second (booster) dose about 4 weeks later.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p>	
wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration	<p>EX 1004: 7:30-8:2: “Ideally, only one dose is needed to effect protection against Zika infection for mammals, including humans. An exemplary dosage schedule entails an initial dose, then a second (booster) dose about 4 weeks later. However, this schedule</p>	

	<p>is exemplary only, and someone skilled in this art would be able to determine without undue experimentation if and when any second dose is needed.”</p> <p>EX 1004: 6:33-7:6: Also contemplated are methods and kits to induce immune responses to ZIKV, or raise antibodies that recognize ZIKV, in a mammal (especially humans). The method comprises administering to a subject a composition comprising, including or consisting essentially of, one or more of the purified inactivated ZIKV as described herein, in a pharmaceutically acceptable adjuvant, in an amount effective to cause an immune response (including raising antibodies that recognize ZIKV) in the subject.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p>	
<p>a seroconversion rate of at least 80% in a population of at least 20 Zika virus seronegative subjects.</p>	<p>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%.”</p> <p>EX 1004 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.</p> <p>EX 1004: 41:9-10: A total of 67 individuals were in this group, with 55 receiving ZPIV and 12 receiving placebo.</p>	

<p>2. The method of claim 1, wherein the subject is pregnant or intends to become pregnant or is a woman of childbearing potential.</p>	<p>EX 1004: 4:2-7: “The purified, inactivated ZIKV, when used in immunogenic compositions and vaccines, has a major advantage over attenuated virus vaccines and immunogenic compositions in that inactivated viruses are not infectious and therefore, cannot revert to virulence or cause disease. This is important when considering vaccination in known or potentially special populations such as those with immunodeficiencies (e.g., HIV) or those who are pregnant.”</p> <p>EX 1004: 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p> <p>EX 1004 41:12-15: In Example 5: ZIKV PIV Performance in Human Trials, Thomas teaches 55 human volunteers with mean age of 31.5 years with 52% being male and 48% being female, i.e. women of childbearing potential.</p>	
<p>3. The method of claim 1, wherein the vaccine or immunogenic composition is administered by intramuscular or subcutaneous administration.</p>	<p>EX 1004: 9:10-12: “18. The method of any of claims 16 or 17, wherein the administering is via intramuscular injection, intradermal injection, subcutaneous injection, intravenous injection, oral administering, or intranasal administering.”</p> <p>EX 1004: 7:12-14: “Administration may be by any known route, such as transcutaneous injection, intramuscular injection, intradermal injection, subcutaneous injection, intravenous injection, oral, or intranasal inoculation.”</p>	

<p>4. The method of claim 1, wherein the vaccine or immunogenic composition is administered one or more times.</p>	<p>EX 1004: 7:32-33: “An exemplary dosage schedule entails an initial dose, then a second (booster) dose about 4 weeks later.”</p> <p>EX 1004 4:18-20: “For example, a single immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against challenge with ZIKV.”</p> <p>EX 1004 7:30-8:2. “Ideally, only one dose is needed to effect protection against Zika infection for mammals, including humans. An exemplary dosage schedule entails an initial dose, then a second (booster) dose about 4 weeks later. However, this schedule is exemplary only, and someone skilled in this art would be able to determine without undue experimentation if and when any second dose is needed.”</p> <p>EX 1004 41:7-8: Example 5: ZIKV PIV Performance in Human Trials, Thomas teaches two doses, i.e. one or more times, were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.</p>	
<p>5. The method of claim 1, wherein the vaccine or immunogenic composition comprising a dose of 10 µg is administered one time.</p>	<p>EX 1004 3:2-5: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p> <p>EX 1004: 4:24-28: “With the information known about the dosing and schedule for other PIV flavivirus vaccines - such as</p>	<p>EX 1011 p. 6: Version 8 of NCT0292833 evaluates three dose levels of “5.0 mcg, 2.5 mcg and 10mcg of ZPIV.”</p> <p>EX 1011 p. 6: The doses are to be administered “by intramuscular (IM) injection on Days 1 and 29. The study will consist of a screening period of up to 28 days, a vaccination period in which subjects will receive a prime dose of vaccine on Day 1 followed by a boost on Day 29, and a follow-up period of 12 months post boost vaccination.”</p>

	<p>Japanese encephalitis and tick-borne encephalitis - 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.”</p> <p>EX 1004: 40:18-26: “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</p> <p>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”</p> <p>EX 1004 18:17-20: “Based on these models, and 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, or a booster dose at 4 weeks as described below.)”</p> <p>EX 1004 42:9-11: “Antibody kinetics based on MN50 titers indicating a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff and then a robust and brisk rise in antibody titer for the Trial Group 2 and Trial Group 3 volunteers following dose 2.”</p>	<p>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”</p> <p>EX 1011 p. 6: “The secondary objectives of this study are to 1. Assess . . . seroconversion rates, and peak Geometric Mean Titer (GMT)”</p> <p>EX 1011 p. 8, 11: 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.</p> <p>EX 1011 p. 8: 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.</p> <p>EX 1011 p. 10: The Peak GMT overall and by dosage group is measured by ZIKV ELISA and neutralization assay.</p> <p>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.</p> <p>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 neutralization titers in comparison with baseline.</p>
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<p>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.</p>	<p>EX 1004: 7:32-8:2: “An exemplary dosage schedule entails an initial dose, then a second (booster) dose about 4 weeks later. However, this schedule is exemplary only, and someone skilled in this art would be able to determine without undue experimentation if and when any second dose is needed.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p>	
<p>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.</p>	<p>EX 1004: 7:32-8:2: “An exemplary dosage schedule entails an initial dose, then a second (booster) dose about 4 weeks later. However, this schedule is exemplary only, and someone skilled in this art would be able to determine without undue experimentation if and when any second dose is needed.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p>	
<p>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).</p>	<p>EX 1004 34:26-28: Thomas teaches to determine generation of neutralizing antibodies titers to Zika virus using a “high-throughput ZIKV microneutralization (MN) assay” as described in Larocca et al., Vaccine protection against Zika virus from Brazil. Nature 536: 474-478 (Jun. 28, 2016).</p> <p>EX 1004 42:12-13: Thomas reports “[p]eak titers for Trial Group 1 and trial Group 3 volunteers occur on or about study day 43 (2 weeks post dose two) and are between 500 and 1000.”</p> <p>EX 1004 15:22-27: Thomas further teaches with reference to Figure 21 that at day 57</p>	<p>EX 1005 22:25-35: “seroconversion of a subject is assessed by performing a plaque reduction neutralization test (PRNT). Briefly, PRNT is used to determine the serum titer required to reduce the number of Zika virus plaques by 50% (PRNT50) as compared to a control serum antibody. . . . A threshold of neutralizing antibodies of 1:10 dilution of serum in a PRNT50 is generally accepted as evidence of protection (Hombach et al. Vaccine (2005) 23:5205-5211).”</p> <p>See also EX 1005 114:9-30 describing use of the PRNT assay in mice.</p>

	<p>“[a]pproximately 10% of the cohort has titers of 1000 at this same time point.”</p> <p>EX 1004 15:20-21: Thomas provides Figure 20 which demonstrates geometric mean antibody titers determined by the MN₅₀ assay based on the trial study groups of human volunteers.</p> <p>Ex 1004, Fig. 20: Figure 20 shows that members of group Z0001 5 mcg ZPIV generated neutralizing antibodies greater than 1000, as demonstrated by the error bars at around day 43 and day 57.</p> <p>EX 1004, Fig. 21: Figure 21 shows that members of 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).</p>	<p>EX 1005 114:32-35: Barbero teaches use of the same microneutralization assay described in Larocca et al., Nature 536: 474-478 (Jun. 28, 2016) to determine neutralizing antibody titers in mice.</p> <p>As background art, Liu (EX 1012) reports that good correlation was observed between the microneutralization assay and the PRNT assay.</p> <p>EX 1012 p. 73: “A good correlation . . . was observed between the two assays.”</p> <p>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”</p> <p>EX 1012 p. 77: “The results of our comparison of PRNT and ELISPOT-MNT show that there was significant agreement . . . between the two methods.”</p>
9. A method of vaccinating against Zika virus disease in a fetus or newborn in need thereof,	<p>EX 1004 2:13-24: “Researchers estimate between 1-13% of ZIKV infections during the first trimester of pregnancy will result in microcephaly. In addition ZIKV has been causally associated with intrauterine growth retardation, and other congenital malformations in both humans (15-18) and mice (19-21). Several reports have shown that ZIKV can infect placental and fetal tissues, leading to prolonged viremia in pregnant women (23) and nonhuman primates (24). ZIKV also appears to target cortical neural progenitor cells (19-21, 25 and 26), which likely contributes to neuropathology. The increased incidence of microcephaly temporally related to the</p>	

	<p>introduction of ZIKV in the Americas resulted in the World Health Organization establishing a Public Health Emergency of International Concern (PHEIC). It is also because of these severe outcomes that a protective vaccine is required.”</p> <p>EX 1004 3:2-12: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post-infection. Mechanisms of action of a prophylactic vaccine could include . . . protecting the fetus during maternal infection (infection during pregnancy occurs but vaccine induced immunity prevents fetal infection from taking hold).”</p> <p>EX 1004: 4:2-7: “The purified, inactivated ZIKV, when used in immunogenic compositions and vaccines, has a major advantage over attenuated virus vaccines and immunogenic compositions in that inactivated viruses are not infectious and therefore, cannot revert to virulence or cause disease. This is important when considering vaccination in known or potentially special populations such as those with immunodeficiencies (e.g., HIV) or those who are pregnant.”</p> <p>EX 1004 18:26-30: “Zika is unique in that there are congenital and neurologic outcomes believed to result from autoimmune versus direct viral effects, and additionally, a purified inactivated whole virus is advantageous because of its potential for a</p>	
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	<p>superior safety profile in special populations like pregnant women.”</p> <p>EX 1004: 38:30-39:2: “The 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.”</p>	
<p>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,</p>	<p>EX 1004: 4:2-7: “The purified, inactivated ZIKV, when used in immunogenic compositions and vaccines, has a major advantage over attenuated virus vaccines and immunogenic compositions in that inactivated viruses are not infectious and therefore, cannot revert to virulence or cause disease. This is important when considering vaccination in known or potentially special populations such as those with immunodeficiencies (e.g., HIV) or those who are pregnant.”</p> <p>EX 1004: 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p>	

<p>wherein the antigen is an inactivated whole virus, and</p>	<p>EX 1004: 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p> <p>EX 1004: Abstract: “The invention generally relates to a purified inactivated Zika virus (ZIKV), methods for producing the purified inactivated ZIKV, immunogenic compositions and vaccines comprising the purified inactivated ZIKV and methods for the prevention and/or treatment of infection by ZIKV.”</p> <p>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 (e.g., generating an immune response in a subject at risk of infection and/or in need of preventative treatment, or raising antibodies in a subject, or alleviating symptoms of ZIKV in an infected subject, and the like).”</p>	
<p>wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn,</p>	<p>EX 1004: 3:2-12: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV,... and/or protecting the fetus during maternal infection (infection during pregnancy occurs but vaccine induced immunity prevents fetal infection from taking hold).”</p> <p>EX 1004 26:26-30: “Therefore, if vaccination does not cause any adverse events in the animal and induces an effective immune response (neutralizing antibodies) which protects against a live virus challenge</p>	<p>EX 1007 p. 2549: Faucette teaches that “[i]mmunization during pregnancy can generate maternal immune protection as well as elicit the production and transfer of antibodies cross the placenta . . . to provide early infant protection. Several successful vaccines are now recommended to all pregnant women worldwide.”</p> <p>EX 1007 p. 2549: “[I]mmunization of pregnant women has emerged as an alternative strategy to combat neonatal infection. It relies on the transfer of maternal vaccine-induced humoral immunity to the fetus during gestation . . . to</p>

	<p>in comparison to a placebo or another control this is typically supportive data to advance to human trials.”</p> <p>EX 1004 33:8-10: “Adoptive transfer studies are conducted demonstrating that the ZIKV PIV created antibodies and these antibodies protect against infection.”</p> <p>EX 1004 33:21-25. “For adoptive transfer studies, Balb/c mice are infused i.v. with IgG purified from PIV vaccinated monkeys at week 8 and were challenged by the i.v. route with 10^5 VP (10^2 PFU) ZIKV-BR. Rhesus monkeys are infused i.v. with IgG purified from PIV vaccinated monkeys at week 8 and were challenged by the s.c. (SQ) route with 10^6 VP (10^3 PFU) ZIKV-BR.”</p> <p>EX 1004 38:5-15: Thomas explored “the observed protection by adoptive transfer studies.” In mice infused with vaccine-elicited, ZIKV-specific IgG and then challenged with ZIKV-BR, “[t]he higher two doses of purified IgG provides complete protection following ZIKV challenge”</p> <p>EX 1004 38:17-22. In rhesus monkeys infused with vaccine-elicited, ZIKV-specific IgG and then challenged with ZIKV-BR, “one animal is completely protected and the other showed a blip of viremia on days 3-5 (Fig. 12B).”</p> <p>EX 1004 38:24-26: “Taken together, these data demonstrate that purified IgG from ZIKV PIV vaccinated rhesus monkeys provided passive protection following</p>	<p>confer early immune protection until routine vaccination of the child is initiated.”</p> <p>EX 1007 p. 2549: “Several successful maternal vaccines, such as Tetanus-Diphtheria-Pertussis (Tdap) vaccine and inactivated influenza vaccine (IIV), are now universally recommended by the Center for Disease Control and prevention (CDC) to all pregnant women.”</p> <p>EX 1007 p. 2550: “Maternal vaccination aims protect the both the mother and neonate.”</p> <p>EX 1007 p. 2552: “Underpinning the idea of maternal immunization is that the transport of vaccine-induced maternal immunoglobulin G (IgG) antibody across the placenta by neonatal Fc receptor (FcRn) expressed on trophoblasts across [citations omitted], confers fetal and early infant immune protection (Fig. 1A). The amount of IgG transferred across the placenta to the fetus correlates with IgG concentration in the maternal circulation”</p> <p>EX 1007 p. 2552: “IgG transfer from the mother to the fetus can occur as early as gestational week 13, with the largest amount transferred during the third trimester of pregnancy (Fig. 1B). [Citations omitted.] Additional passive immunity in the form of vaccine-induced IgA, IgG and IgM secreted into colostrum and breast milk is transferred during breastfeeding.”</p> <p>EX 1007 p. 2552: “Maternal immunization presents unique benefits to the mother, fetus and the newborn by inducing active immunity in the mother and the transfer of passive humoral immunity across the placenta to the fetus.”</p>
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	<p>adoptive transfer in both rodents and primates.”</p> <p>EX 1004 38:30-39:2: “The 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.”</p> <p>EX 1004 38:5-16; 38:17-22; 8:24-26; 38:30 to 39:2: Thomas teaches that neutralizing antibodies generated in one animal can be adoptively transferred to another animal, and that such neutralizing antibodies provide a vaccine effective amount to the recipient animal.</p> <p>EX 1004 39:15-16: “Taken together, these data are reasonably predictive for how ZIKV vaccines will perform in humans.”</p>	<p>EX 1007 p. 2552: “the vaccines effectiveness is due to both passive antibody transport and reduction of maternal exposure. Therefore, immunizing pregnant women can circumvent the multiple disadvantages of attempting to directly immunize neonates immediately after birth.”</p> <p>EX 1007 p. 2552: “Another important, albeit less obvious, benefit of maternal vaccination may involve the function of maternal antibodies in promoting the immune maturation and modulation in infants. Animal studies found 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.”</p>
wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration.	<p>EX 1004 4:20-22: “Another example is wherein two doses are administered (e.g., a first dose, followed by a second dose 4 weeks later). A booster dose (second dose or more) may be useful for persons with recurrent infection risk.”</p> <p>EX 1004 7:32-33: “An exemplary dosage schedule entails an initial dose, then a second (booster) dose about 4 weeks later.”</p>	

	EX 1004 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”	
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.	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%.” EX 1004 Table at 42:19 for Trial Group 2 (N=20, 92% seroconversion).	
11. A method of vaccinating against Zika virus infection in a human subject in need thereof, the method comprising	EX 1004: Abstract: “The invention generally relates to a purified inactivated Zika virus (ZIKV), methods for producing the purified inactivated ZIKV, immunogenic compositions and vaccines comprising the purified inactivated ZIKV and methods for the prevention and/or treatment of infection by ZIKV.” EX 1004: 4:15-20: “The purified, inactivated ZIKV can be used to immunize mammals (including humans) to elicit high titers of virus neutralizing antibodies and protect the immunized mammal from disease caused by ZIKV. For example, a single immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against challenge with ZIKV.” EX 1004: 6:33;7:2: “Also contemplated are methods and kits to induce immune responses to ZIKV, or raise antibodies that recognize ZIKV, in a mammal (especially humans).”	

	<p>EX 1004: 7:8-9: “Specifically, methods are provided for immunizing a mammal (especially a human) against ZIKV infection”.</p> <p>EX 1004: 42:20-43:1: “Based on the disclosure and the above data the compositions including inactivated ZIKV demonstrate that the compositions are immunogenic and that vaccines comprising inactivated ZIKV are protective against infection with ZIKV.”</p> <p>See also EX 1004 4:15-18; 5:2-6; 6:33-7:2; 5:8-9.</p> <p>EX 1004 18:16-20: “anti-Zika antibodies protect against infection in mice and non-human primates. ZIKV PIV generates robust anti-Zika antibodies in both models. Based on these models, and 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, or a booster dose at 4 weeks as described below).”</p>	
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,	<p>EX 1004: 7:2-6: “The method comprises administering to a subject a composition comprising, including or consisting essentially of, one or more of the purified inactivated ZIKV as described herein, in a pharmaceutically acceptable adjuvant, in an amount effective to cause an immune response (including raising antibodies that recognize ZIKV) in the subject.”</p> <p>EX 1004: 7:8-11: “Specifically, methods are provided for immunizing a mammal</p>	

	<p>(especially a human) against ZIKV infection, which comprises administering to the mammal an amount of one or more of the vaccines disclosed herein to achieve effective immunization against ZIKV.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p> <p>EX 1004: 4:20-28: “Another example is wherein two doses are administered (e.g., a first dose, followed by a second dose 4 weeks later). A booster dose (second dose or more) may be useful for persons with recurrent infection risk. This is similar to the booster dose regimen associated with the PIV for the flavivirus, Japanese encephalitis (JEV). With the information known about the dosing and schedule for other PIV flavivirus vaccines - such as Japanese encephalitis and tick-borne encephalitis - 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.”</p> <p>EX 1004: 40:18-26:</p> <p>“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</p> <p>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</p>	
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	booster doses to create durable immune responses”	
wherein the antigen is an inactivated whole virus,	<p>EX 1004: 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p> <p>EX 1004: Abstract: “The invention generally relates to a purified inactivated Zika virus (ZIKV), methods for producing the purified inactivated ZIKV, immunogenic compositions and vaccines comprising the purified inactivated ZIKV and methods for the prevention and/or treatment of infection by ZIKV.”</p> <p>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 (e.g., generating an immune response in a subject at risk of infection and/or in need of preventative treatment, or raising antibodies in a subject, or alleviating symptoms of ZIKV in an infected subject, and the like).”</p>	
wherein the vaccine or immunogenic composition is administered one or more times,	<p>EX 1004: 7:32-33: “An exemplary dosage schedule entails an initial dose, then a second (booster) dose about 4 weeks later.”</p> <p>EX 1004 4:18-20: “For example, a single immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against challenge with ZIKV.”</p> <p>EX 1004 7:30-8:2. “Ideally, only one dose is needed to effect protection against Zika</p>	

	<p>infection for mammals, including humans. An exemplary dosage schedule entails an initial dose, then a second (booster) dose about 4 weeks later. However, this schedule is exemplary only, and someone skilled in this art would be able to determine without undue experimentation if and when any second dose is needed.”</p> <p>EX 1004 41:7-8: Example 5: ZIKV PIV Performance in Human Trials, Thomas teaches two doses, i.e. one or more times, were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.</p>	
<p>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.</p>	<p>EX 1004: In Example 5: ZIKV PIV Performance in Human Trials, Thomas teaches a seroconversion rate of 92% for 55 humans at day 57 after a boost administration. A seroconversion rate of 92% is within the claimed range of at least 60%. The Table indicates prime administration at day 1 and boost administration at day 29. Day 57 is 28 days after the boost administration.</p> <p>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%”.</p> <p>See also EX 1004 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.</p>	

	<p>EX 1004 4:15-22: “The purified, inactivated ZIKV can be used to immunize mammals (including humans) to elicit high titers of virus neutralizing antibodies and protect the immunized mammal from disease caused by ZIKV. For example, a single immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against challenge with ZIKV. Another example is wherein two doses are administered (e.g., a first dose, followed by a second dose 4 weeks later). A booster dose (second dose or more) may be useful for persons with recurrent infection risk.”</p> <p>EX 1004 7:11: “Booster doses may be used, if needed.”</p> <p>EX 1004 7:30-8:2: “Ideally, only one dose is needed to effect protection against Zika infection for mammals, including humans.</p> <p>An exemplary dosage schedule entails an initial dose, then a second (booster) dose about 4 weeks later. However, this schedule is exemplary only, and someone skilled in the art would be able to determine without undue experimentation if and when any second dose is needed.”</p> <p>EX 1004 4:24-28: “With the information known about the dosing and schedule for other PIV flavivirus vaccines – such as Japanese encephalitis and tick-borne encephalitis – 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.”</p>	
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	<p>EX 1004 18:17-20: “Based on these models, and 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, or a booster dose at 4 weeks as described below.)”</p> <p>EX 1004 28:19-22: “An “adjuvant” is a substance that serves to enhance, accelerate, or prolong the antigen-specific immune response of an antigen when used in combination with specific vaccine antigens but do not stimulate an immune response when used alone.”</p> <p>EX 1004 42:9-10: Thomas teaches in Example 5. ZIKV PIV Performance in Human Trials for a 5µg dose that “[a]ntibody kinetics based on MN50 titers indicat[ed] a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff”.</p> <p>EX 1004 Table at page 42 Day 1 after prime administration, GMT of 5.0 for N=55 volunteers.</p>	
<p>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,</p>	<p>EX 1004 3:2-5: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.”</p> <p>EX 1004 42:4: “Seroconversion [is] measured by the MN50 assay”.</p> <p>EX 1004 42:19-20: Thomas teaches at the Table at page 42 that Geometric Mean Antibody Titers 14 or 28 days after the second (boost) administration (Day 43 or day</p>	<p>EX 1005 22:25-35: “seroconversion of a subject is assessed by performing a plaque reduction neutralization test (PRNT). Briefly, PRNT is used to determine the serum titer required to reduce the number of Zika virus plaques by 50% (PRNT50) as compared to a control serum antibody. . . . A threshold of neutralizing antibodies of 1:10 dilution of serum in a PRNT50 is generally accepted as evidence of protection (Hombach et al. Vaccine (2005) 23:5205-5211).”</p>

<p>as determined by the plaque reduction neutralization test (PRNT).</p>	<p>57) is greater than 10 times higher to that 28 days (day 29) after the first (prime) administration.</p> <p>EX 1004 42:19-20: The table shows data for group 16-0033 (N=25), group 16-0062 (N=20); group All (N=55). For each group, the GMT (Geometric Mean Titer) at day 43 or day 57 is more than 10 times the GMT at day 29. See 16-0033 (N=25), Day 29 (5.5), Day 43 (316.9), Day 57 (142.9). See 16-0062 (N=20), Day 29 (8.5), Day 57 (100.8). See All (N=55), Day 29 (7.0), Day 43 (437.9), Day 57 (173.1).</p>	<p>See also EX 1005 114:9-30 describing use of the PRNT assay in mice.</p> <p>EX 1005 114:32-35: Barbero teaches use of the same microneutralization assay described in Larocca et al., Nature 536: 474-478 (Jun. 28, 2016) to determine neutralizing antibody titers in mice.</p> <p>As background art, Liu (EX 1012) reports that good correlation was observed between the microneutralization assay and the PRNT assay.</p> <p>EX 1012 p. 73: “A good correlation . . . was observed between the two assays.”</p> <p>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”</p> <p>EX 1012 p. 77: “The results of our comparison of PRNT and ELISPOT-MNT show that there was significant agreement . . . between the two methods.”</p>
<p>13. The method of claim 1, wherein the antigen is purified.</p>	<p>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 (e.g., generating an immune response in a subject at risk of infection and/or in need of preventative treatment, or raising antibodies in a subject, or alleviating symptoms of ZIKV in an infected subject, and the like).”</p> <p>EX 1004: Abstract: “The invention generally relates to a purified inactivated Zika virus (ZIKV), methods for producing the purified</p>	

	<p>inactivated ZIKV, immunogenic compositions and vaccines comprising the purified inactivated ZIKV and methods for the prevention and/or treatment of infection by ZIKV.”</p> <p>EX 1004 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p>	
<p>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.</p>	<p>EX 1004 3:2-5: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.”</p> <p>EX 1004 3:23-27: Thomas teaches that ZIKV can be purified and the “level of purity is according to the guidelines of the U.S. Food and Drug Administration (FDA).”</p> <p>EX 1004 20:19-24: “Purification 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.”</p>	<p>EX 1005 14:29-31: “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).”</p>
<p>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.</p>	<p>EX 1004 3:2-5: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p>	<p>EX 1011 p. 6: Version 8 of NCT0292833 evaluates three dose levels of “5.0 mcg, 2.5 mcg and 10mcg of ZPIV.”</p> <p>EX 1011 p. 6: The doses are to be administered “by intramuscular (IM) injection on Days 1 and 29. The study will consist of a screening period of up to 28 days, a vaccination period in which subjects will receive a prime dose of vaccine on Day 1 followed by a boost on Day 29, and a</p>

	<p>EX 1004: 4:24-28: “With the information known about the dosing and schedule for other PIV flavivirus vaccines - such as Japanese encephalitis and tick-borne encephalitis - 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.”</p> <p>EX 1004: 40:18-26: “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</p> <p>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”</p> <p>EX 1004 18:17-20: “Based on these models, and 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, or a booster dose at 4 weeks as described below.)”</p> <p>EX 1004 42:9-11: “Antibody kinetics based on MN50 titers indicating a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff and then a robust and brisk rise in antibody titer for the Trial Group 2 and Trial Group 3 volunteers following dose 2.”</p>	<p>follow-up period of 12 months post boost vaccination.”</p> <p>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”</p> <p>EX 1011 p. 6: “The secondary objectives of this study are to 1. Assess . . . seroconversion rates, and peak Geometric Mean Titer (GMT)”</p> <p>EX 1011 p. 8, 11: 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.</p> <p>EX 1011 p. 8: 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.</p> <p>EX 1011 p. 10: The Peak GMT overall and by dosage group is measured by ZIKV ELISA and neutralization assay.</p> <p>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.</p> <p>EX 1011 p. 10: The proportion of subjects overall and by dosage group that seroconvert to ZIKV at each post-vaccination visit is assessed</p>
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	<p>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 (e.g., generating an immune response in a subject at risk of infection and/or in need of preventative treatment, or raising antibodies in a subject, or alleviating symptoms of ZIKV in an infected subject, and the like).”</p> <p>EX 1004: Abstract: “The invention generally relates to a purified inactivated Zika virus (ZIKV), methods for producing the purified inactivated ZIKV, immunogenic compositions and vaccines comprising the purified inactivated ZIKV and methods for the prevention and/or treatment of infection by ZIKV.”</p> <p>EX 1004 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p>	by neutralization titers in comparison with baseline.
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.	<p>EX 1004 3:2-5: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p> <p>EX 1004: 4:24-28: “With the information known about the dosing and schedule for other PIV flavivirus vaccines - such as Japanese encephalitis and tick-borne</p>	<p>EX 1011 p. 6: Version 8 of NCT0292833 evaluates three dose levels of “5.0 mcg, 2.5 mcg and 10mcg of ZPIV.”</p> <p>EX 1011 p. 6: The doses are to be administered “by intramuscular (IM) injection on Days 1 and 29. The study will consist of a screening period of up to 28 days, a vaccination period in which subjects will receive a prime dose of vaccine on Day 1 followed by a boost on Day 29, and a follow-up period of 12 months post boost vaccination.”</p>

	<p>encephalitis - 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.”</p> <p>EX 1004: 40:18-26: “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</p> <p>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”</p> <p>EX 1004 18:17-20: “Based on these models, and 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, or a booster dose at 4 weeks as described below.)”</p> <p>EX 1004 42:9-11: “Antibody kinetics based on MN50 titers indicating a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff and then a robust and brisk rise in antibody titer for the Trial Group 2 and Trial Group 3 volunteers following dose 2.”</p> <p>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 (e.g., generating</p>	<p>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”</p> <p>EX 1011 p. 6: “The secondary objectives of this study are to 1. Assess . . . seroconversion rates, and peak Geometric Mean Titer (GMT)”</p> <p>EX 1011 p. 8, 11: 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.</p> <p>EX 1011 p. 8: 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.</p> <p>EX 1011 p. 10: The Peak GMT overall and by dosage group is measured by ZIKV ELISA and neutralization assay.</p> <p>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.</p> <p>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 neutralization titers in comparison with baseline.</p>
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	<p>an immune response in a subject at risk of infection and/or in need of preventative treatment, or raising antibodies in a subject, or alleviating symptoms of ZIKV in an infected subject, and the like).”</p> <p>EX 1004: Abstract: “The invention generally relates to a purified inactivated Zika virus (ZIKV), methods for producing the purified inactivated ZIKV, immunogenic compositions and vaccines comprising the purified inactivated ZIKV and methods for the prevention and/or treatment of infection by ZIKV.”</p> <p>EX 1004 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p>	
<p>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.</p>	<p>EX 1004 3:2-5: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p> <p>EX 1004: 4:24-28: “With the information known about the dosing and schedule for other PIV flavivirus vaccines - such as Japanese encephalitis and tick-borne encephalitis - 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.”</p>	<p>EX 1011 p. 6: Version 8 of NCT0292833 evaluates three dose levels of “5.0 mcg, 2.5 mcg and 10mcg of ZPIV.”</p> <p>EX 1011 p. 6: The doses are to be administered “by intramuscular (IM) injection on Days 1 and 29. The study will consist of a screening period of up to 28 days, a vaccination period in which subjects will receive a prime dose of vaccine on Day 1 followed by a boost on Day 29, and a follow-up period of 12 months post boost vaccination.”</p> <p>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”</p>

	<p>EX 1004: 40:18-26: “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</p> <p>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”</p> <p>EX 1004 18:17-20: “Based on these models, and 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, or a booster dose at 4 weeks as described below.)”</p> <p>EX 1004 42:9-11: “Antibody kinetics based on MN50 titers indicating a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff and then a robust and brisk rise in antibody titer for the Trial Group 2 and Trial Group 3 volunteers following dose 2.”</p> <p>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 (e.g., generating an immune response in a subject at risk of infection and/or in need of preventative treatment, or raising antibodies in a subject,</p>	<p>EX 1011 p. 6: “The secondary objectives of this study are to 1. Assess . . . seroconversion rates, and peak Geometric Mean Titer (GMT)”</p> <p>EX 1011 p. 8, 11: 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.</p> <p>EX 1011 p. 8: 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.</p> <p>EX 1011 p. 10: The Peak GMT overall and by dosage group is measured by ZIKV ELISA and neutralization assay.</p> <p>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.</p> <p>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 neutralization titers in comparison with baseline.</p>
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	<p>or alleviating symptoms of ZIKV in an infected subject, and the like).”</p> <p>EX 1004: Abstract: “The invention generally relates to a purified inactivated Zika virus (ZIKV), methods for producing the purified inactivated ZIKV, immunogenic compositions and vaccines comprising the purified inactivated ZIKV and methods for the prevention and/or treatment of infection by ZIKV.”</p> <p>EX 1004 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p>	
<p>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.</p>	<p>EX 1004 3:2-5: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p> <p>EX 1004: 4:24-28: “With the information known about the dosing and schedule for other PIV flavivirus vaccines - such as Japanese encephalitis and tick-borne encephalitis - 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.”</p> <p>EX 1004: 40:18-26: “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</p>	<p>EX 1011 p. 6: Version 8 of NCT0292833 evaluates three dose levels of “5.0 mcg, 2.5 mcg and 10mcg of ZPIV.”</p> <p>EX 1011 p. 6: The doses are to be administered “by intramuscular (IM) injection on Days 1 and 29. The study will consist of a screening period of up to 28 days, a vaccination period in which subjects will receive a prime dose of vaccine on Day 1 followed by a boost on Day 29, and a follow-up period of 12 months post boost vaccination.”</p> <p>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”</p> <p>EX 1011 p. 6: “The secondary objectives of this study are to 1. Assess . . . seroconversion rates, and peak Geometric Mean Titer (GMT)”</p>

	<p>concentration required to effectively immunize a recipient</p> <p>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”</p> <p>EX 1004 18:17-20: “Based on these models, and 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, or a booster dose at 4 weeks as described below.)”</p> <p>EX 1004 42:9-11: “Antibody kinetics based on MN50 titers indicating a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff and then a robust and brisk rise in antibody titer for the Trial Group 2 and Trial Group 3 volunteers following dose 2.”</p> <p>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 (e.g., generating an immune response in a subject at risk of infection and/or in need of preventative treatment, or raising antibodies in a subject, or alleviating symptoms of ZIKV in an infected subject, and the like).”</p> <p>EX 1004: Abstract: “The invention generally relates to a purified inactivated Zika virus (ZIKV), methods for producing the purified</p>	<p>EX 1011 p. 8, 11: 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.</p> <p>EX 1011 p. 8: 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.</p> <p>EX 1011 p. 10: The Peak GMT overall and by dosage group is measured by ZIKV ELISA and neutralization assay.</p> <p>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.</p> <p>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 neutralization titers in comparison with baseline.</p>
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	<p>inactivated ZIKV, immunogenic compositions and vaccines comprising the purified inactivated ZIKV and methods for the prevention and/or treatment of infection by ZIKV.”</p> <p>EX 1004 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p>	
<p>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.</p>	<p>EX 1004: 7:32-33: “The method comprises administering to a subject a composition comprising, including or consisting essentially of, one or more of the purified inactivated ZIKV as described herein, in a pharmaceutically acceptable adjuvant, in an amount effective to cause an immune response (including raising antibodies that recognize ZIKV) in the subject.”</p> <p>EX 1004: 7:8-11: “Specifically, methods are provided for immunizing a mammal (especially a human) against ZIKV infection, which comprises administering to the mammal an amount of one or more of the vaccines disclosed herein to achieve effective immunization against ZIKV.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p> <p>EX 1004: 4:20-28: “Another example is wherein two doses are administered (e.g., a first dose, followed by a second dose 4 weeks later). A booster dose (second dose or more) may be useful for persons with recurrent infection risk. This is similar to the</p>	

	<p>booster dose regimen associated with the PIV for the flavivirus, Japanese encephalitis (JEV). With the information known about the dosing and schedule for other PIV flavivirus vaccines - such as Japanese encephalitis and tick-borne encephalitis - 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.”</p> <p>EX 1004: 40:18-26:</p> <p>“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</p> <p>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”</p> <p>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 (e.g., generating an immune response in a subject at risk of infection and/or in need of preventative treatment, or raising antibodies in a subject, or alleviating symptoms of ZIKV in an infected subject, and the like).”</p> <p>EX 1004: Abstract: “The invention generally relates to a purified inactivated Zika virus (ZIKV), methods for producing the purified</p>	
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	<p>inactivated ZIKV, immunogenic compositions and vaccines comprising the purified inactivated ZIKV and methods for the prevention and/or treatment of infection by ZIKV.”</p> <p>EX 1004 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p>	
<p>20. The method of claim 1, wherein the vaccine or immunogenic composition comprises a dose of about 10 µg of purified inactivated whole virus.</p>	<p>EX 1004 3:2-5: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p> <p>EX 1004: 4:24-28: “With the information known about the dosing and schedule for other PIV flavivirus vaccines - such as Japanese encephalitis and tick-borne encephalitis - 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.”</p> <p>EX 1004: 40:18-26: “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</p> <p>Trial 3 ZPIV is explored across a range of schedules in an attempt to define the optimal dosing schedule to effectively immunize a</p>	<p>EX 1011 p. 6: Version 8 of NCT0292833 evaluates three dose levels of “5.0 mcg, 2.5 mcg and 10mcg of ZPIV.”</p> <p>EX 1011 p. 6: The doses are to be administered “by intramuscular (IM) injection on Days 1 and 29. The study will consist of a screening period of up to 28 days, a vaccination period in which subjects will receive a prime dose of vaccine on Day 1 followed by a boost on Day 29, and a follow-up period of 12 months post boost vaccination.”</p> <p>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”</p> <p>EX 1011 p. 6: “The secondary objectives of this study are to 1. Assess . . . seroconversion rates, and peak Geometric Mean Titer (GMT)”</p> <p>EX 1011 p. 8, 11: 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.</p>

	<p>recipient and the potential requirement for booster doses to create durable immune responses”</p> <p>EX 1004 18:17-20: “Based on these models, and 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, or a booster dose at 4 weeks as described below.)”</p> <p>EX 1004 42:9-11: “Antibody kinetics based on MN50 titers indicating a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff and then a robust and brisk rise in antibody titer for the Trial Group 2 and Trial Group 3 volunteers following dose 2.”</p> <p>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 (e.g., generating an immune response in a subject at risk of infection and/or in need of preventative treatment, or raising antibodies in a subject, or alleviating symptoms of ZIKV in an infected subject, and the like).”</p> <p>EX 1004: Abstract: “The invention generally relates to a purified inactivated Zika virus (ZIKV), methods for producing the purified inactivated ZIKV, immunogenic compositions and vaccines comprising the purified inactivated ZIKV and methods for the prevention and/or treatment of infection by ZIKV.”</p>	<p>EX 1011 p. 8: 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.</p> <p>EX 1011 p. 10: The Peak GMT overall and by dosage group is measured by ZIKV ELISA and neutralization assay.</p> <p>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.</p> <p>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 neutralization titers in comparison with baseline.</p>
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	EX 1004 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”	
21. The method of claim 1, wherein the vaccine or immunogenic composition further comprises an aluminum salt adjuvant.	EX 1004 28:23-25: “Suitable inorganic adjuvants include, but are not limited to, for example, an aluminum salt, such as aluminum hydroxide gel (alum) or aluminum phosphate.”	
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 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.	EX 1004 28:19-22: “An ‘adjuvant’ is a substance that serves to enhance, accelerate, or prolong the antigen-specific immune response of an antigen when used in combination with specific vaccine antigens but do not stimulate an immune response when used alone.” EX 1004 17:1: Thomas teaches to use “a suitable amount of adjuvant.”	EX 1005 112:1-4: Aluminum hydroxide adjuvant “was added to a final concentration of 0.5 mg/ml Aluminium (1/20 v/v Alum 2% stock solution added) to prepare ZikaV Drug Product (DP).”
23. The method of claim 21, wherein the adjuvant is aluminum hydroxide.	EX 1004 28:23-24: “Suitable inorganic adjuvants include, but are not limited to, for example, an aluminum salt, such as aluminum hydroxide gel (alum)”	
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.	EX 1004 3:2-5: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.” EX 1004 4:31-5:1: Thomas teaches that the ZIKV vaccine “can be mixed with suitable adjuvants.” EX 1004 28:18-29:31: Thomas teaches many adjuvants.	EX 1005 112:1-4: Barbero teaches that aluminum hydroxide adjuvant “was added to a final concentration of 0.5 mg/ml Aluminium (1/20 v/v Alum 2% stock solution added) to prepare ZikaV Drug Product (DP).” EX 1005 112:4-7: Barbero further teaches that “[t]he DP was gently mixed for 5 min. An aliquot of the DP was removed, Alum sedimented by centrifugation and the clear supernatant analysed by SEC-HPLC. No ZikaV peak was detected in the supernatant indicating

	<p>EX 1004 41:7-8: Thomas teaches that the ZIKV used in Example 5. ZIKV PIV Performance in Human Trials is adjuvanted with alum.</p> <p>EX 1004 28:18-22: Thomas teaches to use adjuvants as a component of the ZIKV vaccine “to enhance, accelerate, or prolong the antigen-specific immune response of an antigen when used in combination with specific vaccine antigens but do not stimulate an immune response when used alone.”</p> <p>EX 1004 17:1. Thomas teaches to use “a suitable amount of adjuvant.”</p> <p>EX 1004 28:23-25: “Suitable inorganic adjuvants include, but are not limited to, for example, an aluminum salt, such as aluminum hydroxide gel (alum) or aluminum phosphate.”</p>	<p>complete adsorption (estimated as >95%) of viral particles on the mineral adjuvant.”</p>
<p>25. The method of claim 1, wherein the Zika virus is a clonal isolate, in particular from a plaque purified clonal Zika virus isolate.</p>	<p>EX 1004 3:23: “ZIKV can be purified to be free of pathogens and adventitious agents.”</p> <p>EX 1004 3:24-26: “The ZIKV infectious virus particle can be purified away from the host cell proteins (demonstrated by known procedures such as gradient centrifugation and column chromatography).”</p> <p>EX 1004 19:15-16: “A live ZIKV is purified so as to remove all pathogens and adventitious agents.”</p> <p>EX 1004 20:19-20. “Purification of the ZIKV may be performed by physical or chemical techniques or any combinations thereof that are routinely used in the art.”</p>	<p>EX 1006 p. 3156: “Plaque purification has been used for decades to ensure the homogeneity of virus stocks and to segregate discrete species from mixed virus populations [18-20].”</p> <p>EX 1006 p. 3156: “Our data suggest that plaque purification may be a rapid and efficient means by which vaccine seed virus purity can be enhanced.”</p> <p>EX 1006 p. 3157, 3.2-3.3: Murata used plaque purification to purify influenza virus from the adventitious agents of replicating and non-replicating viruses.</p> <p>EX 1006 p. 3158: “Our data suggest that plaque purification is a simple and rapid method for removing adventitious viruses.”</p>

		EX 1006 p. 3159: “our study corroborates the commonly invoked rule of thumb in virology calling for three rounds of serial plaque purification to ensure homogeneity starting from a mixed population. Plaque purification is an approach unencumbered by intellectual property constraints”
26. A method of vaccinating against Zika virus infection in a human subject in need thereof, the method comprising	<p>EX 1004: Abstract: “The invention generally relates to a purified inactivated Zika virus (ZIKV), methods for producing the purified inactivated ZIKV, immunogenic compositions and vaccines comprising the purified inactivated ZIKV and methods for the prevention and/or treatment of infection by ZIKV.”</p> <p>EX 1004: 4:15-20: “The purified, inactivated ZIKV can be used to immunize mammals (including humans) to elicit high titers of virus neutralizing antibodies and protect the immunized mammal from disease caused by ZIKV. For example, a single immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against challenge with ZIKV.”</p> <p>EX 1004: 6:33-7:2: “Also contemplated are methods and kits to induce immune responses to ZIKV, or raise antibodies that recognize ZIKV, in a mammal (especially humans).”</p> <p>EX 1004: 7:8-9: “Specifically, methods are provided for immunizing a mammal (especially a human) against ZIKV infection”.</p>	

	<p>EX 1004: 42:20-43: 1: “Based on the disclosure and the above data the compositions including inactivated ZIKV demonstrate that the compositions are immunogenic and that vaccines comprising inactivated ZIKV are protective against infection with ZIKV.”</p> <p>See also EX 1004 4:15-18; 5:2-6; 6:33-7:2; 5:8-9.</p> <p>EX 1004 18:16-20: Thomas teaches that “anti-Zika antibodies protect against infection in mice and non-human primates. ZIKV PIV generates robust anti-Zika antibodies in both models. Based on these models, and 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, or a booster dose at 4 weeks as described below).”</p>	
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,	<p>EX 1004: 7:2-6: “The method comprises administering to a subject a composition comprising, including or consisting essentially of, one or more of the purified inactivated ZIKV as described herein, in a pharmaceutically acceptable adjuvant, in an amount effective to cause an immune response (including raising antibodies that recognize ZIKV) in the subject.”</p> <p>EX 1004: 7:8-11: “Specifically, methods are provided for immunizing a mammal (especially a human) against ZIKV infection, which comprises administering to the mammal an amount of one or more of the</p>	

	<p>vaccines disclosed herein to achieve effective immunization against ZIKV.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p> <p>EX 1004: 4:20-28: “Another example is wherein two doses are administered (e.g., a first dose, followed by a second dose 4 weeks later). A booster dose (second dose or more) may be useful for persons with recurrent infection risk. This is similar to the booster dose regimen associated with the PIV for the flavivirus, Japanese encephalitis (JEV). With the information known about the dosing and schedule for other PIV flavivirus vaccines - such as Japanese encephalitis and tick-borne encephalitis - 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.”</p> <p>EX 1004: 40:18-26:</p> <p>“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</p> <p>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”</p>	
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<p>wherein the antigen is an inactivated whole virus,</p>	<p>EX 1004: 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p> <p>EX 1004: Abstract: “The invention generally relates to a purified inactivated Zika virus (ZIKV), methods for producing the purified inactivated ZIKV, immunogenic compositions and vaccines comprising the purified inactivated ZIKV and methods for the prevention and/or treatment of infection by ZIKV.”</p> <p>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 (e.g., generating an immune response in a subject at risk of infection and/or in need of preventative treatment, or raising antibodies in a subject, or alleviating symptoms of ZIKV in an infected subject, and the like).”</p>	
<p>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.</p>	<p>EX 1004 28:23-25: “Suitable inorganic adjuvants include, but are not limited to, for example, an aluminum salt, such as aluminum hydroxide gel (alum) or aluminum phosphate”)</p> <p>EX 1004 28:27: Thomas teaches the use of “acylated sugars”.</p> <p>EX 1004 30:20: Thomas teaches the use of a “sucrose solution”.</p>	<p>EX 1011 p. 6: Version 8 of NCT0292833 evaluates three dose levels of “5.0 mcg, 2.5 mcg and 10mcg of ZPIV.”</p> <p>EX 1011 p. 6: The doses are to be administered “by intramuscular (IM) injection on Days 1 and 29. The study will consist of a screening period of up to 28 days, a vaccination period in which subjects will receive a prime dose of vaccine on Day 1 followed by a boost on Day 29, and a follow-up period of 12 months post boost vaccination.”</p>

	<p>EX 1004 30:20-21: Thomas teaches use of “pharmaceutically acceptable buffer solutions.”</p> <p>EX 1004 3:2-5: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p> <p>EX 1004: 4:24-28: “With the information known about the dosing and schedule for other PIV flavivirus vaccines - such as Japanese encephalitis and tick-borne encephalitis - 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.”</p> <p>EX 1004: 40:18-26: “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</p> <p>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”</p> <p>EX 1004 18:17-20: “Based on these models, and what is already known in the field of flavivirus PIVs, extrapolation to human use</p>	<p>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”</p> <p>EX 1011 p. 6: “The secondary objectives of this study are to 1. Assess . . . seroconversion rates, and peak Geometric Mean Titer (GMT)”</p> <p>EX 1011 p. 8, 11: 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.</p> <p>EX 1011 p. 8: 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.</p> <p>EX 1011 p. 10: The Peak GMT overall and by dosage group is measured by ZIKV ELISA and neutralization assay.</p> <p>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.</p> <p>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 neutralization titers in comparison with baseline.</p>
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	<p>is reasonable for safe and effective dosages (e.g., a single dose, or a booster dose at 4 weeks as described below.)”</p> <p>EX 1004 42:9-11: “Antibody kinetics based on MN50 titers indicating a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff and then a robust and brisk rise in antibody titer for the Trial Group 2 and Trial Group 3 volunteers following dose 2.”</p>	
<p>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.</p>	<p>EX 1004: 37:31-32: “No specific clinical safety adverse effects related to the vaccine were observed.”</p> <p>EX 1004: 41:16-17: “There were no deaths, serious adverse events related to vaccination, or disenrollments related to an adverse event.”</p> <p>EX 1004 43:14-15: “ZPIV was well tolerated and safe in a small number of volunteers and moderate to highly immunogenic”.</p>	
<p>28. The method of claim 27, wherein the severe adverse event is a fever of a temperature of 39° C. or higher.</p>	<p>EX 1004: 37:31-32: “No specific clinical safety adverse effects related to the vaccine were observed.”</p> <p>EX 1004: 41:16-17: “There were no deaths, serious adverse events related to vaccination, or disenrollments related to an adverse event.”</p> <p>EX 1004 43:14-15: “ZPIV was well tolerated and safe in a small number of volunteers and moderate to highly immunogenic”.</p>	
<p>29. The method of claim 1, wherein the subject is from a Zika endemic region or from a Zika</p>	<p>EX 1004 40:27-32: “Trial 4: ZPIV will be administered in an area of Puerto Rico with a high rate of dengue virus priming as well as</p>	

non-endemic region travelling to an endemic region.	an areas having recently experienced a large Zika outbreak to understand safety and immunogenicity performance in scenarios where dengue and Zika are potentially endemic.”	
30. The method of claim 1, wherein the subject is 18 to 29 years of age or 30 to 49 years of age.	EX 1004: 41:13-15: “The mean age was 31.5 years with a decline in the mean age from Trial Group 2 (33.3) to Trial Group 1 (30.9) to Trial Group 3 (27.9).”	
31. The method of claim 1, wherein the subject is a female subject.	EX 1004: 4:5-7: “This is important when considering vaccination in known or potentially special populations such as those with immunodeficiencies (e.g., HIV) or those who are pregnant.” EX 1004: 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.” EX 1004: 41:12-13: “A relatively equal number of male and female volunteers were enrolled; 52 and 48%, respectively.”	
32. The method of claim 9, wherein the vaccine or immunogenic composition is administered by intramuscular or subcutaneous administration.	EX 1004: 9:10-12: “18. The method of any of claims 16 or 17, wherein the administering is via intramuscular injection, intradermal injection, subcutaneous injection, intravenous injection, oral administering, or intranasal administering.” EX 1004: 7:12-14: “Administration may be by any known route, such as transcutaneous injection, intramuscular injection, intradermal injection, subcutaneous injection, intravenous injection, oral, or intranasal inoculation.”	

<p>33. The method of claim 9, wherein the vaccine or immunogenic composition is administered one or more times.</p>	<p>EX 1004: 7:32-33: “An exemplary dosage schedule entails an initial dose, then a second (booster) dose about 4 weeks later.”</p> <p>EX 1004 4:18-20: “For example, a single immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against challenge with ZIKV.”</p> <p>EX 1004 7:30-8:2. “Ideally, only one dose is needed to effect protection against Zika infection for mammals, including humans. An exemplary dosage schedule entails an initial dose, then a second (booster) dose about 4 weeks later. However, this schedule is exemplary only, and someone skilled in this art would be able to determine without undue experimentation if and when any second dose is needed.”</p> <p>EX 1004 41:7-8: Example 5: ZIKV PIV Performance in Human Trials, Thomas teaches two doses, i.e. one or more times, were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.</p>	
<p>34. The method of claim 9, wherein the vaccine or immunogenic composition comprising a dose of 10 µg is administered one time.</p>	<p>EX 1004 3:2-5: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p> <p>EX 1004: 4:24-28: “With the information known about the dosing and schedule for other PIV flavivirus vaccines - such as</p>	<p>EX 1011 p. 6: Version 8 of NCT0292833 evaluates three dose levels of “5.0 mcg, 2.5 mcg and 10mcg of ZPIV.”</p> <p>EX 1011 p. 6: The doses are to be administered “by intramuscular (IM) injection on Days 1 and 29. The study will consist of a screening period of up to 28 days, a vaccination period in which subjects will receive a prime dose of vaccine on Day 1 followed by a boost on Day 29, and a follow-up period of 12 months post boost vaccination.”</p>

	<p>Japanese encephalitis and tick-borne encephalitis - 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.”</p> <p>EX 1004: 40:18-26: “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</p> <p>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”</p> <p>EX 1004 18:17-20: “Based on these models, and 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, or a booster dose at 4 weeks as described below.)”</p> <p>EX 1004 42:9-11: “Antibody kinetics based on MN50 titers indicating a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff and then a robust and brisk rise in antibody titer for the Trial Group 2 and Trial Group 3 volunteers following dose 2.”</p>	<p>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”</p> <p>EX 1011 p. 6: “The secondary objectives of this study are to 1. Assess . . . seroconversion rates, and peak Geometric Mean Titer (GMT)”</p> <p>EX 1011 p. 8, 11: 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.</p> <p>EX 1011 p. 8: 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.</p> <p>EX 1011 p. 10: The Peak GMT overall and by dosage group is measured by ZIKV ELISA and neutralization assay.</p> <p>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.</p> <p>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 neutralization titers in comparison with baseline.</p>
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<p>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.</p>	<p>EX 1004: 7:32-8:2: “An exemplary dosage schedule entails an initial dose, then a second (booster) dose about 4 weeks later. However, this schedule is exemplary only, and someone skilled in this art would be able to determine without undue experimentation if and when any second dose is needed.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p>	
<p>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.</p>	<p>EX 1004: 7:32-8:2: “An exemplary dosage schedule entails an initial dose, then a second (booster) dose about 4 weeks later. However, this schedule is exemplary only, and someone skilled in this art would be able to determine without undue experimentation if and when any second dose is needed.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p>	
<p>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).</p>	<p>EX 1004 34:26-28: Thomas teaches to determine generation of neutralizing antibodies titers to Zika virus using a “high-throughput ZIKV microneutralization (MN) assay” as described in Larocca et al., Vaccine protection against Zika virus from Brazil. Nature 536: 474-478 (Jun. 28, 2016).</p> <p>EX 1004 42:12-13: “Peak titers for Trial Group 1 and trial Group 3 volunteers occur on or about study day 43 (2 weeks post dose two) and are between 500 and 1000.”</p> <p>EX 1004 15:22-27: Thomas further teaches with reference to Figure 21 that at day 57</p>	<p>EX 1005 22: 25-35: “seroconversion of a subject is assessed by performing a plaque reduction neutralization test (PRNT). Briefly, PRNT is used to determine the serum titer required to reduce the number of Zika virus plaques by 50% (PRNT50) as compared to a control serum antibody. . . . A threshold of neutralizing antibodies of 1:10 dilution of serum in a PRNT50 is generally accepted as evidence of protection (Hombach et al. Vaccine (2005) 23:5205-5211).”</p> <p>See also EX 1005 114:9-30 describing use of the PRNT assay in mice.</p>

	<p>“[a]pproximately 10% of the cohort has titers of 1000 at this same time point.”</p> <p>EX 1004 15:20-21: Thomas provides Figure 20 which demonstrates geometric mean antibody titers determined by the MN50 assay based on the trial study groups of human volunteers.</p> <p>Ex 1004, Fig. 20: Figure 20 shows that members of group Z0001 5 mcg ZPIV generated neutralizing antibodies greater than 1000, as demonstrated by the error bars at around day 43 and day 57.</p> <p>EX 1004, Fig. 21: Figure 21 shows that members of 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).</p>	<p>EX 1005 114:32-35: Barbero teaches use of the same microneutralization assay described in Larocca et al., Nature 536: 474-478 (Jun. 28, 2016) to determine neutralizing antibody titers in mice.</p> <p>As background art, Liu (EX 1012) reports that good correlation was observed between the microneutralization assay and the PRNT assay.</p> <p>EX 1012 p. 73: “A good correlation . . . was observed between the two assays.”</p> <p>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”</p> <p>EX 1012 p. 77: “The results of our comparison of PRNT and ELISPOT-MNT show that there was significant agreement . . . between the two methods.”</p>
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.	<p>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%.”</p> <p>EX 1004 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.</p> <p>EX 1004: 41:9-10: “A total of 67 individuals were in this group, with 55 receiving ZPIV and 12 receiving placebo.”</p>	
39. The method of claim 9, wherein administration of the vaccine or immunogenic	EX 1004: In Example 5: ZIKV PIV Performance in Human Trials, Thomas	

<p>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.</p>	<p>teaches a seroconversion rate of 92% for 55 humans at day 57 after a boost administration. A seroconversion rate of 92% is within the claimed range of at least 60%. The Table indicates prime administration at day 1 and boost administration at day 29. Day 57 is 28 days after the boost administration.</p> <p>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%”.</p> <p>See also EX 1004 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.</p> <p>EX 1004 4:15-22: “The purified, inactivated ZIKV can be used to immunize mammals (including humans) to elicit high titers of virus neutralizing antibodies and protect the immunized mammal from disease caused by ZIKV. For example, a single immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against challenge with ZIKV. Another example is wherein two doses are administered (e.g., a first dose, followed by a second dose 4 weeks later). A booster dose (second dose or more) may be useful for persons with recurrent infection risk.”</p> <p>EX 1004 7:11: “Booster doses may be used, if needed.”</p>	
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	<p>EX 1004 7:30-32: “Ideally, only one dose is needed to effect protection against Zika infection for mammals, including humans.”</p> <p>EX 1004 7:32-8:2. “An exemplary dosage schedule entails an initial dose, then a second (booster) dose about 4 weeks later. However, this schedule is exemplary only, and someone skilled in the art would be able to determine without undue experimentation if and when any second dose is needed.”</p> <p>EX 1004 4:24-28: “With the information known about the dosing and schedule for other PIV flavivirus vaccines – such as Japanese encephalitis and tick-borne encephalitis – 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.”</p> <p>EX 1004 18:17-20: “Based on these models, and 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, or a booster dose at 4 weeks as described below.)”</p> <p>EX 1004 28:19-22: “An “adjuvant” is a substance that serves to enhance, accelerate, or prolong the antigen-specific immune response of an antigen when used in combination with specific vaccine antigens but do not stimulate an immune response when used alone.”</p> <p>EX 1004 42:9-10: Thomas teaches in Example 5. ZIKV PIV Performance in Human Trials for a 5μg dose that “[a]ntibody</p>	
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	<p>kinetics based on MN50 titers indicat[ed] a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff”.</p> <p>EX 1004 Table at page 42 Day 1 after prime administration, GMT of 5.0 for N=55 volunteers.</p>	
<p>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).</p>	<p>EX 1004 3:2-5: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.”</p> <p>EX 1004 42:4: “Seroconversion measured by the MN50 assay.”</p> <p>EX 1004 42:19-20: Thomas teaches at the Table at page 42 that Geometric Mean Antibody Titers 14 or 28 days after the second (boost) administration (Day 43 or day 57) is greater than 10 times higher to that 28 days (day 29) after the first (prime) administration.</p> <p>EX 1004 42:19-20: The table shows data for group 16-0033 (N=25), group 16-0062 (N=20); group All (N=55). For each group, the GMT (Geometric Mean Titer) at day 43 or day 57 is more than 10 times the GMT at day 29. See 16-0033 (N=25), Day 29 (5.5), Day 43 (316.9), Day 57 (142.9). See 16-0062 (N=20), Day 29 (8.5), Day 57 (100.8). See All (N=55), Day 29 (7.0), Day 43 (437.9), Day 57 (173.1).</p>	<p>EX 1005 22: 25-35: “seroconversion of a subject is assessed by performing a plaque reduction neutralization test (PRNT). Briefly, PRNT is used to determine the serum titer required to reduce the number of Zika virus plaques by 50% (PRNT50) as compared to a control serum antibody. . . . A threshold of neutralizing antibodies of 1:10 dilution of serum in a PRNT50 is generally accepted as evidence of protection (Hombach et al. Vaccine (2005) 23:5205-5211).”</p> <p>See also EX 1005 114:9-30 describing use of the PRNT assay in mice.</p> <p>EX 1005 114:32-35: Barbero teaches use of the same microneutralization assay described in Larocca et al., Nature 536: 474-478 (Jun. 28, 2016) to determine neutralizing antibody titers in mice.</p> <p>As background art, Liu (EX 1012) reports that good correlation was observed between the microneutralization assay and the PRNT assay.</p> <p>EX 1012 p. 73: “A good correlation . . . was observed between the two assays.”</p> <p>EX 1012 p. 76: “a good relationship between the two assay methods”. . . “there was no significant</p>

		<p>... disagreement between them ... the two assay methods agree reasonably well”</p> <p>EX 1012 p. 77: “The results of our comparison of PRNT and ELISPOT-MNT show that there was significant agreement ... between the two methods.”</p>
41. A method of vaccinating against Zika virus disease in a fetus or newborn in need thereof, the method comprising	<p>EX 1004 2:13-24: “Researchers estimate between 1-13% of ZIKV infections during the first trimester of pregnancy will result in microcephaly. In addition ZIKV has been causally associated with intrauterine growth retardation, and other congenital malformations in both humans (15-18) and mice (19-21). Several reports have shown that ZIKV can infect placental and fetal tissues, leading to prolonged viremia in pregnant women (23) and nonhuman primates (24). ZIKV also appears to target cortical neural progenitor cells (19-21, 25 and 26), which likely contributes to neuropathology. The increased incidence of microcephaly temporally related to the introduction of ZIKV in the Americas resulted in the World Health Organization establishing a Public Health Emergency of International Concern (PHEIC). It is also because of these severe outcomes that a protective vaccine is required.”</p> <p>EX 1004 3:2-12: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post-infection. Mechanisms of action of a prophylactic vaccine could include ... protecting the fetus during maternal infection</p>	

	<p>(infection during pregnancy occurs but vaccine induced immunity prevents fetal infection from taking hold).”</p> <p>EX 1004: 4:2-7: “The purified, inactivated ZIKV, when used in immunogenic compositions and vaccines, has a major advantage over attenuated virus vaccines and immunogenic compositions in that inactivated viruses are not infectious and therefore, cannot revert to virulence or cause disease. This is important when considering vaccination in known or potentially special populations such as those with immunodeficiencies (e.g., HIV) or those who are pregnant.”</p> <p>EX 1004 18:26-30: “Zika is unique in that there are congenital and neurologic outcomes believed to result from autoimmune versus direct viral effects, and additionally, a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p> <p>EX 1004: 38:30-39:2: “The 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.”</p>	
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<p>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,</p>	<p>EX 1004: 4:2-7: “The purified, inactivated ZIKV, when used in immunogenic compositions and vaccines, has a major advantage over attenuated virus vaccines and immunogenic compositions in that inactivated viruses are not infectious and therefore, cannot revert to virulence or cause disease. This is important when considering vaccination in known or potentially special populations such as those with immunodeficiencies (e.g., HIV) or those who are pregnant.”</p> <p>EX 1004: 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p>	
<p>wherein the antigen is an inactivated whole virus,</p>	<p>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 (e.g., generating an immune response in a subject at risk of infection and/or in need of preventative treatment, or raising antibodies in a subject, or alleviating symptoms of ZIKV in an infected subject, and the like).”</p> <p>EX 1004: Abstract: “The invention generally relates to a purified inactivated Zika virus (ZIKV), methods for producing the purified inactivated ZIKV, immunogenic compositions and vaccines comprising the purified inactivated ZIKV and methods for</p>	

	<p>the prevention and/or treatment of infection by ZIKV.”</p> <p>EX 1004 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p>	
<p>and wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn,</p>	<p>EX 1004: 3:2-12: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV,... and/or protecting the fetus during maternal infection (infection during pregnancy occurs but vaccine induced immunity prevents fetal infection from taking hold).”</p> <p>EX 1004 26:26-30: “Therefore, if vaccination does not cause any adverse events in the animal and induces an effective immune response (neutralizing antibodies) which protects against a live virus challenge in comparison to a placebo or another control this is typically supportive data to advance to human trials.”</p> <p>EX 1004 33:8-10: “Adoptive transfer studies are conducted demonstrating that the ZIKV PIV created antibodies and these antibodies protect against infection.”</p> <p>EX 1004 33:21-25. “For adoptive transfer studies, Balb/c mice are infused i.v. with IgG purified from PIV vaccinated monkeys at week 8 and were challenged by the i.v. route with 105 VP (102 PFU) ZIKV-BR. Rhesus monkeys are infused i.v. with IgG purified from PIV vaccinated monkeys at week 8 and</p>	<p>EX 1007 p. 2549: Faucette teaches that ‘[i]mmunization during pregnancy can generate maternal immune protection as well as elicit the production and transfer of antibodies cross the placenta . . . to provide early infant protection. Several successful vaccines are now recommended to all pregnant women worldwide.”</p> <p>EX 1007 p. 2549: “[I]mmunization of pregnant women has emerged as an alternative strategy to combat neonatal infection. It relies on the transfer of maternal vaccine-induced humoral immunity to the fetus during gestation . . . to confer early immune protection until routine vaccination of the child is initiated.”</p> <p>EX 1007 p. 2549: “Several successful maternal vaccines, such as Tetanus-Diphtheria-Pertussis (Tdap) vaccine and inactivated influenza vaccine (IIV), are now universally recommended by the Center for Disease Control and prevention (CDC) to all pregnant women.”</p> <p>EX 1007 p. 2550: “Maternal vaccination aims protect the both the mother and neonate.”</p> <p>EX 1007 p. 2552: “Underpinning the idea of maternal immunization is that the transport of vaccine-induced maternal immunoglobulin G (IgG) antibody across the placenta by neonatal Fc receptor (FcRn) expressed on trophoblasts</p>

	<p>were challenged by the s.c. (SQ) route with 106 VP (103 PFU) ZIKV-BR.”</p> <p>EX 1004 38:5-15: Thomas explored “the observed protection by adoptive transfer studies.” In mice infused with vaccine-elicited, ZIKV-specific IgG and then challenged with ZIKV-BR, “[t]he higher two doses of purified IgG provides complete protection following ZIKV challenge”</p> <p>EX 1004 38:17-22. In rhesus monkeys infused with vaccine-elicited, ZIKV-specific IgG and then challenged with ZIKV-BR, “one animal is completely protected and the other showed a blip of viremia on days 3-5 (Fig. 12B).”</p> <p>EX 1004 38:24-26: “Taken together, these data demonstrate that purified IgG from ZIKV PIV vaccinated rhesus monkeys provided passive protection following adoptive transfer in both rodents and primates.”</p> <p>EX 1004 38:30-39:2: “The 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.”</p> <p>EX 1004 38:5-16; 38:17-22; 8:24-26; 38:30 to 39:2: Thomas teaches that neutralizing</p>	<p>across [citations omitted], confers fetal and early infant immune protection (Fig. 1A). The amount of IgG transferred across the placenta to the fetus correlates with IgG concentration in the maternal circulation”</p> <p>EX 1007 p. 2552: “IgG transfer from the mother to the fetus can occur as early as gestational week 13, with the largest amount transferred during the third trimester of pregnancy (Fig. 1B). [Citations omitted.] Additional passive immunity in the form of vaccine-induced IgA, IgG and IgM secreted into colostrum and breast milk is transferred during breastfeeding.”</p> <p>EX 1007 p. 2552: “Maternal immunization presents unique benefits to the mother, fetus and the newborn by inducing active immunity in the mother and the transfer of passive humoral immunity across the placenta to the fetus.”</p> <p>EX 1007 p. 2552: “the vaccines effectiveness is due to both passive antibody transport and reduction of maternal exposure. Therefore, immunizing pregnant women can circumvent the multiple disadvantages of attempting to directly immunize neonates immediately after birth.”</p> <p>EX 1007 p. 2552: “Another important, albeit less obvious, benefit of maternal vaccination may involve the function of maternal antibodies in promoting the immune maturation and modulation in infants. Animal studies found 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</p>
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	<p>antibodies generated in one animal can be adoptively transferred to another animal, and that such neutralizing antibodies provide a vaccine effective amount to the recipient animal.</p> <p>EX 1004 39:15-16: Thomas teaches with respect to the adoptive transfer data in mice and rhesus monkeys that “[t]aken together, these data are reasonably predictive for how ZIKV vaccines will perform in humans.”</p>	selection against potentially autoreactive B cell populations.”
wherein the antigen is purified.	<p>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 (e.g., generating an immune response in a subject at risk of infection and/or in need of preventative treatment, or raising antibodies in a subject, or alleviating symptoms of ZIKV in an infected subject, and the like).”</p> <p>EX 1004: Abstract: “The invention generally relates to a purified inactivated Zika virus (ZIKV), methods for producing the purified inactivated ZIKV, immunogenic compositions and vaccines comprising the purified inactivated ZIKV and methods for the prevention and/or treatment of infection by ZIKV.”</p> <p>EX 1004 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p>	
42. The method of claim 41, wherein the main peak of the antigen when analyzed by size	EX 1004 3:2-5: “There is an urgent need for a vaccine capable of inducing a protective	EX 1005 14:29-31: “the residual impurity of the final virus preparation with respect to all

<p>exclusion chromatography is more than 85% of the total area under the curve in the size exclusion chromatography.</p>	<p>immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.”</p> <p>EX 1004 3:23-27: Thomas teaches that ZIKV can be purified and the “level of purity is according to the guidelines of the U.S. Food and Drug Administration (FDA).”</p> <p>EX 1004 20:19-24: “Purification 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.”</p>	<p>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).”</p>
<p>43. A method of vaccinating against Zika virus disease in a fetus or newborn in need thereof, the method comprising</p>	<p>EX 1004 2:13-24: “Researchers estimate between 1-13% of ZIKV infections during the first trimester of pregnancy will result in microcephaly. In addition ZIKV has been causally associated with intrauterine growth retardation, and other congenital malformations in both humans (15-18) and mice (19-21). Several reports have shown that ZIKV can infect placental and fetal tissues, leading to prolonged viremia in pregnant women (23) and nonhuman primates (24). ZIKV also appears to target cortical neural progenitor cells (19-21, 25 and 26), which likely contributes to neuropathology. The increased incidence of microcephaly temporally related to the introduction of ZIKV in the Americas resulted in the World Health Organization establishing a Public Health Emergency of International Concern (PHEIC). It is also</p>	

	<p>because of these severe outcomes that a protective vaccine is required.”</p> <p>EX 1004 3:2-12: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post-infection. Mechanisms of action of a prophylactic vaccine could include . . . protecting the fetus during maternal infection (infection during pregnancy occurs but vaccine induced immunity prevents fetal infection from taking hold).”</p> <p>EX 1004: 4:2-7: “The purified, inactivated ZIKV, when used in immunogenic compositions and vaccines, has a major advantage over attenuated virus vaccines and immunogenic compositions in that inactivated viruses are not infectious and therefore, cannot revert to virulence or cause disease. This is important when considering vaccination in known or potentially special populations such as those with immunodeficiencies (e.g., HIV) or those who are pregnant.”</p> <p>EX 1004 18:26-30: “Zika is unique in that there are congenital and neurologic outcomes believed to result from autoimmune versus direct viral effects, and additionally, a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p> <p>EX 1004: 38:30-39:2: “The adoptive transfer studies demonstrate that vaccine-elicited antibodies are sufficient for protection</p>	
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	<p>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.”</p>	
<p>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,</p>	<p>EX 1004: 4:2-7: “The purified, inactivated ZIKV, when used in immunogenic compositions and vaccines, has a major advantage over attenuated virus vaccines and immunogenic compositions in that inactivated viruses are not infectious and therefore, cannot revert to virulence or cause disease. This is important when considering vaccination in known or potentially special populations such as those with immunodeficiencies (e.g., HIV) or those who are pregnant.”</p> <p>EX 1004: 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p>	
<p>wherein the antigen is an inactivated whole virus, and</p>	<p>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 (e.g., generating an immune response in a subject at risk of infection and/or in need of preventative treatment, or raising antibodies in a subject,</p>	

	<p>or alleviating symptoms of ZIKV in an infected subject, and the like).”</p> <p>EX 1004: Abstract: “The invention generally relates to a purified inactivated Zika virus (ZIKV), methods for producing the purified inactivated ZIKV, immunogenic compositions and vaccines comprising the purified inactivated ZIKV and methods for the prevention and/or treatment of infection by ZIKV.”</p> <p>EX 1004 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p>	
<p>wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn,</p>	<p>EX 1004: 3:2-12: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV,... and/or protecting the fetus during maternal infection (infection during pregnancy occurs but vaccine induced immunity prevents fetal infection from taking hold).”</p> <p>EX 1004 26:26-30: “Therefore, if vaccination does not cause any adverse events in the animal and induces an effective immune response (neutralizing antibodies) which protects against a live virus challenge in comparison to a placebo or another control this is typically supportive data to advance to human trials.”</p> <p>EX 1004 33:8-10: “Adoptive transfer studies are conducted demonstrating that the ZIKV PIV created antibodies and these antibodies protect against infection.”</p>	<p>EX 1007 p. 2549: Faucette teaches that “[i]mmunization during pregnancy can generate maternal immune protection as well as elicit the production and transfer of antibodies cross the placenta . . . to provide early infant protection. Several successful vaccines are now recommended to all pregnant women worldwide.”</p> <p>EX 1007, p. 254:9 “[I]mmunization of pregnant women has emerged as an alternative strategy to combat neonatal infection. It relies on the transfer of maternal vaccine-induced humoral immunity to the fetus during gestation . . . to confer early immune protection until routine vaccination of the child is initiated.”</p> <p>EX 1007 p. 2549: “Several successful maternal vaccines, such as Tetanus-Diphtheria-Pertussis (Tdap) vaccine and inactivated influenza vaccine (IIV), are now universally recommended by the</p>

	<p>EX 1004 33:21-25. “For adoptive transfer studies, Balb/c mice are infused i.v. with IgG purified from PIV vaccinated monkeys at week 8 and were challenged by the i.v. route with 105 VP (102 PFU) ZIKV-BR. Rhesus monkeys are infused i.v. with IgG purified from PIV vaccinated monkeys at week 8 and were challenged by the s.c. (SQ) route with 106 VP (103 PFU) ZIKV-BR.”</p> <p>EX 1004 38:5-16: Thomas explored “the observed protection by adoptive transfer studies.” In mice infused with vaccine-elicited, ZIKV-specific IgG and then challenged with ZIKV-BR, “[t]he higher two doses of purified IgG provides complete protection following ZIKV challenge”</p> <p>EX 1004 38:17-22. In rhesus monkeys infused with vaccine-elicited, ZIKV-specific IgG and then challenged with ZIKV-BR, “one animal is completely protected and the other showed a blip of viremia on days 3-5 (Fig. 12B).”</p> <p>EX 1004 38:24-26: “Taken together, these data demonstrate that purified IgG from ZIKV PIV vaccinated rhesus monkeys provided passive protection following adoptive transfer in both rodents and primates.”</p> <p>EX 1004 38:30-39:2: “The 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</p>	<p>Center for Disease Control and prevention (CDC) to all pregnant women.”</p> <p>EX 1007 p. 2550: “Maternal vaccination aims protect the both the mother and neonate.”</p> <p>EX 1007 p. 2552: “Underpinning the idea of maternal immunization is that the transport of vaccine-induced maternal immunoglobulin G (IgG) antibody across the placenta by neonatal Fc receptor (FcRn) expressed on trophoblasts across [citations omitted], confers fetal and early infant immune protection (Fig. 1A). The amount of IgG transferred across the placenta to the fetus correlates with IgG concentration in the maternal circulation”</p> <p>EX 1007 p. 2552: “IgG transfer from the mother to the fetus can occur as early as gestational week 13, with the largest amount transferred during the third trimester of pregnancy (Fig. 1B). [Citations omitted.] Additional passive immunity in the form of vaccine-induced IgA, IgG and IgM secreted into colostrum and breast milk is transferred during breastfeeding.”</p> <p>EX 1007 p. 2552: “Maternal immunization presents unique benefits to the mother, fetus and the newborn by inducing active immunity in the mother and the transfer of passive humoral immunity across the placenta to the fetus.”</p> <p>EX 1007 p. 2552: “the vaccines effectiveness is due to both passive antibody transport and reduction of maternal exposure. Therefore, immunizing pregnant women can circumvent the multiple disadvantages of attempting to directly immunize neonates immediately after birth.”</p>
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	<p>achievable by these vaccine platforms in humans, thus raising optimism for the development of a ZIKV vaccine for humans.”</p> <p>EX 1004 38:5-16; 38:17-22; 8:24-26; 38:30 to 39:2: Thomas teaches that neutralizing antibodies generated in one animal can be adoptively transferred to another animal, and that such neutralizing antibodies provide a vaccine effective amount to the recipient animal.</p> <p>EX 1004 39:15-16: 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.”</p>	<p>EX 1007 p. 2552: “Another important, albeit less obvious, benefit of maternal vaccination may involve the function of maternal antibodies in promoting the immune maturation and modulation in infants. Animal studies found 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.”</p>
<p>wherein the vaccine or immunogenic composition comprises a dose of from about 10 µg to about 40 µg of purified inactivated whole virus.</p>	<p>EX 1004 3:2-5: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p> <p>EX 1004: 4:24-28: “With the information known about the dosing and schedule for other PIV flavivirus vaccines - such as Japanese encephalitis and tick-borne encephalitis - 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.”</p> <p>EX 1004: 40:18-26: “Trial 2 ZPIV is explored across a range of antigen doses in</p>	<p>EX 1011 p. 6: Version 8 of NCT0292833 evaluates three dose levels of “5.0 mcg, 2.5 mcg and 10mcg of ZPIV.”</p> <p>EX 1011 p. 6: The doses are to be administered “by intramuscular (IM) injection on Days 1 and 29. The study will consist of a screening period of up to 28 days, a vaccination period in which subjects will receive a prime dose of vaccine on Day 1 followed by a boost on Day 29, and a follow-up period of 12 months post boost vaccination.”</p> <p>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”</p>

	<p>an attempt to define the optimal dose of antigen as well as lower limits of antigen concentration required to effectively immunize a recipient</p> <p>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”</p> <p>EX 1004 18:17-20: “Based on these models, and 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, or a booster dose at 4 weeks as described below.)”</p> <p>EX 1004 42:9-11: “Antibody kinetics based on MN50 titers indicating a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff and then a robust and brisk rise in antibody titer for the Trial Group 2 and Trial Group 3 volunteers following dose 2.”</p> <p>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 (e.g., generating an immune response in a subject at risk of infection and/or in need of preventative treatment, or raising antibodies in a subject, or alleviating symptoms of ZIKV in an infected subject, and the like).”</p>	<p>EX 1011 p. 6: “The secondary objectives of this study are to 1. Assess . . . seroconversion rates, and peak Geometric Mean Titer (GMT)”</p> <p>EX 1011 p. 8, 11: 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.</p> <p>EX 1011 p. 8: 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.</p> <p>EX 1011 p. 10: The Peak GMT overall and by dosage group is measured by ZIKV ELISA and neutralization assay.</p> <p>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.</p> <p>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 neutralization titers in comparison with baseline.</p>
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	<p>EX 1004: Abstract: “The invention generally relates to a purified inactivated Zika virus (ZIKV), methods for producing the purified inactivated ZIKV, immunogenic compositions and vaccines comprising the purified inactivated ZIKV and methods for the prevention and/or treatment of infection by ZIKV.”</p> <p>EX 1004 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p>	
<p>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.</p>	<p>EX 1004 3:2-5: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p> <p>EX 1004: 4:24-28: “With the information known about the dosing and schedule for other PIV flavivirus vaccines - such as Japanese encephalitis and tick-borne encephalitis - 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.”</p> <p>EX 1004: 40:18-26: “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</p>	<p>EX 1011 p. 6: Version 8 of NCT0292833 evaluates three dose levels of “5.0 mcg, 2.5 mcg and 10mcg of ZPIV.”</p> <p>EX 1011 p. 6: The doses are to be administered “by intramuscular (IM) injection on Days 1 and 29. The study will consist of a screening period of up to 28 days, a vaccination period in which subjects will receive a prime dose of vaccine on Day 1 followed by a boost on Day 29, and a follow-up period of 12 months post boost vaccination.”</p> <p>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”</p> <p>EX 1011 p. 6: “The secondary objectives of this study are to 1. Assess . . . seroconversion rates, and peak Geometric Mean Titer (GMT)”</p> <p>EX 1011 p. 8, 11: Eligible study participants in Group 1 (5.0 mcg ZPIV), Group 2 (2.5 mcg ZPIV) and Group 3 (10.0 mcg ZPIV) included</p>

	<p>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”</p> <p>EX 1004 18:17-20: “Based on these models, and 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, or a booster dose at 4 weeks as described below.)”</p> <p>EX 1004 42:9-11: “Antibody kinetics based on MN50 titers indicating a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff and then a robust and brisk rise in antibody titer for the Trial Group 2 and Trial Group 3 volunteers following dose 2.”</p> <p>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 (e.g., generating an immune response in a subject at risk of infection and/or in need of preventative treatment, or raising antibodies in a subject, or alleviating symptoms of ZIKV in an infected subject, and the like).”</p> <p>EX 1004: Abstract: “The invention generally relates to a purified inactivated Zika virus (ZIKV), methods for producing the purified inactivated ZIKV, immunogenic compositions and vaccines comprising the purified inactivated ZIKV and methods for</p>	<p>both men and women (nonpregnant) between the ages of 18 and 49.</p> <p>EX 1011 p. 8: 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.</p> <p>EX 1011 p. 10: The Peak GMT overall and by dosage group is measured by ZIKV ELISA and neutralization assay.</p> <p>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.</p> <p>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 neutralization titers in comparison with baseline.</p>
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	<p>the prevention and/or treatment of infection by ZIKV.”</p> <p>EX 1004 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p>	
<p>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.</p>	<p>EX 1004 3:2-5: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p> <p>EX 1004: 4:24-28: “With the information known about the dosing and schedule for other PIV flavivirus vaccines - such as Japanese encephalitis and tick-borne encephalitis - 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.”</p> <p>EX 1004: 40:18-26: “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</p> <p>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</p>	<p>EX 1011 p. 6: Version 8 of NCT0292833 evaluates three dose levels of “5.0 mcg, 2.5 mcg and 10mcg of ZPIV.”</p> <p>EX 1011 p. 6: The doses are to be administered “by intramuscular (IM) injection on Days 1 and 29. The study will consist of a screening period of up to 28 days, a vaccination period in which subjects will receive a prime dose of vaccine on Day 1 followed by a boost on Day 29, and a follow-up period of 12 months post boost vaccination.”</p> <p>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”</p> <p>EX 1011 p. 6: “The secondary objectives of this study are to 1. Assess . . . seroconversion rates, and peak Geometric Mean Titer (GMT)”</p> <p>EX 1011 p. 8, 11: 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.</p> <p>EX 1011 p. 8: Experimental Group 3 will be administered 10 mcg ZPIV (aluminum hydroxide adjuvant) in a homologous prime-boost regimen</p>

	<p>booster doses to create durable immune responses”</p> <p>EX 1004 18:17-20: “Based on these models, and 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, or a booster dose at 4 weeks as described below.)”</p> <p>EX 1004 42:9-11: “Antibody kinetics based on MN50 titers indicating a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff and then a robust and brisk rise in antibody titer for the Trial Group 2 and Trial Group 3 volunteers following dose 2.”</p> <p>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 (e.g., generating an immune response in a subject at risk of infection and/or in need of preventative treatment, or raising antibodies in a subject, or alleviating symptoms of ZIKV in an infected subject, and the like).”</p> <p>EX 1004: Abstract: “The invention generally relates to a purified inactivated Zika virus (ZIKV), methods for producing the purified inactivated ZIKV, immunogenic compositions and vaccines comprising the purified inactivated ZIKV and methods for the prevention and/or treatment of infection by ZIKV.”</p>	<p>on Day 1 and Day 29. Experimental Group 3 includes 25 subjects of which 5 are given a placebo.</p> <p>EX 1011 p. 10: The Peak GMT overall and by dosage group is measured by ZIKV ELISA and neutralization assay.</p> <p>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.</p> <p>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 neutralization titers in comparison with baseline.</p>
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	EX 1004 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”	
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.	<p>EX 1004 3:2-5: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p> <p>EX 1004: 4:24-28: “With the information known about the dosing and schedule for other PIV flavivirus vaccines - such as Japanese encephalitis and tick-borne encephalitis - 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.”</p> <p>EX 1004: 40:18-26: “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</p> <p>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”</p> <p>EX 1004 18:17-20: “Based on these models, and what is already known in the field of</p>	<p>EX 1011 p. 6: Version 8 of NCT0292833 evaluates three dose levels of “5.0 mcg, 2.5 mcg and 10mcg of ZPIV.”</p> <p>EX 1011 p. 6: The doses are to be administered “by intramuscular (IM) injection on Days 1 and 29. The study will consist of a screening period of up to 28 days, a vaccination period in which subjects will receive a prime dose of vaccine on Day 1 followed by a boost on Day 29, and a follow-up period of 12 months post boost vaccination.”</p> <p>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”</p> <p>EX 1011 p. 6: “The secondary objectives of this study are to 1. Assess . . . seroconversion rates, and peak Geometric Mean Titer (GMT)”</p> <p>EX 1011 p. 8, 11: 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.</p> <p>EX 1011 p. 8: 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</p>

	<p>flavivirus PIVs, 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.)”</p> <p>EX 1004 42:9-11: “Antibody kinetics based on MN50 titers indicating a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff and then a robust and brisk rise in antibody titer for the Trial Group 2 and Trial Group 3 volunteers following dose 2.”</p> <p>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 (e.g., generating an immune response in a subject at risk of infection and/or in need of preventative treatment, or raising antibodies in a subject, or alleviating symptoms of ZIKV in an infected subject, and the like).”</p> <p>EX 1004: Abstract: “The invention generally relates to a purified inactivated Zika virus (ZIKV), methods for producing the purified inactivated ZIKV, immunogenic compositions and vaccines comprising the purified inactivated ZIKV and methods for the prevention and/or treatment of infection by ZIKV.”</p> <p>EX 1004 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p>	<p>includes 25 subjects of which 5 are given a placebo.</p> <p>EX 1011 p. 10: The Peak GMT overall and by dosage group is measured by ZIKV ELISA and neutralization assay.</p> <p>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.</p> <p>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 neutralization titers in comparison with baseline.</p>
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<p>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.</p>	<p>EX 1004: 7:2-6: “The method comprises administering to a subject a composition comprising, including or consisting essentially of, one or more of the purified inactivated ZIKV as described herein, in a pharmaceutically acceptable adjuvant, in an amount effective to cause an immune response (including raising antibodies that recognize ZIKV) in the subject.”</p> <p>EX 1004: 7:8-11: “Specifically, methods are provided for immunizing a mammal (especially a human) against ZIKV infection, which comprises administering to the mammal an amount of one or more of the vaccines disclosed herein to achieve effective immunization against ZIKV.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p> <p>EX 1004: 4:20-28: “Another example is wherein two doses are administered (e.g., a first dose, followed by a second dose 4 weeks later). A booster dose (second dose or more) may be useful for persons with recurrent infection risk. This is similar to the booster dose regimen associated with the PIV for the flavivirus, Japanese encephalitis (JEV). With the information known about the dosing and schedule for other PIV flavivirus vaccines - such as Japanese encephalitis and tick-borne encephalitis - 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.”</p>	
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	<p>EX 1004: 40:18-26:</p> <p>“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</p> <p>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”</p>	
<p>48. The method of claim 9, wherein the vaccine or immunogenic composition comprises a dose of about 10 µg of purified inactivated whole virus.</p>	<p>EX 1004 3:2-5: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p> <p>EX 1004: 4:24-28: “With the information known about the dosing and schedule for other PIV flavivirus vaccines - such as Japanese encephalitis and tick-borne encephalitis - 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.”</p> <p>EX 1004: 40:18-26: “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</p>	<p>EX 1011 p. 6: Version 8 of NCT0292833 evaluates three dose levels of “5.0 mcg, 2.5 mcg and 10mcg of ZPIV.”</p> <p>EX 1011 p. 6: The doses are to be administered “by intramuscular (IM) injection on Days 1 and 29. The study will consist of a screening period of up to 28 days, a vaccination period in which subjects will receive a prime dose of vaccine on Day 1 followed by a boost on Day 29, and a follow-up period of 12 months post boost vaccination.”</p> <p>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”</p> <p>EX 1011 p. 6: “The secondary objectives of this study are to 1. Assess . . . seroconversion rates, and peak Geometric Mean Titer (GMT)”</p> <p>EX 1011 p. 8, 11: Eligible study participants in Group 1 (5.0 mcg ZPIV), Group 2 (2.5 mcg</p>

	<p>concentration required to effectively immunize a recipient</p> <p>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”</p> <p>EX 1004 18:17-20: “Based on these models, and 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, or a booster dose at 4 weeks as described below.)”</p> <p>EX 1004 42:9-11: “Antibody kinetics based on MN50 titers indicating a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff and then a robust and brisk rise in antibody titer for the Trial Group 2 and Trial Group 3 volunteers following dose 2.”</p> <p>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 (e.g., generating an immune response in a subject at risk of infection and/or in need of preventative treatment, or raising antibodies in a subject, or alleviating symptoms of ZIKV in an infected subject, and the like).”</p> <p>EX 1004: Abstract: “The invention generally relates to a purified inactivated Zika virus (ZIKV), methods for producing the purified</p>	<p>ZPIV) and Group 3 (10.0 mcg ZPIV) included both men and women (nonpregnant) between the ages of 18 and 49.</p> <p>EX 1011 p. 8: 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.</p> <p>EX 1011 p. 10: The Peak GMT overall and by dosage group is measured by ZIKV ELISA and neutralization assay.</p> <p>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.</p> <p>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 neutralization titers in comparison with baseline.</p>
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	<p>inactivated ZIKV, immunogenic compositions and vaccines comprising the purified inactivated ZIKV and methods for the prevention and/or treatment of infection by ZIKV.”</p> <p>EX 1004 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p>	
<p>49. A method of vaccinating against Zika virus disease in a fetus or newborn in need thereof, the method comprising</p>	<p>EX 1004 2:13-24: “Researchers estimate between 1-13% of ZIKV infections during the first trimester of pregnancy will result in microcephaly. In addition ZIKV has been causally associated with intrauterine growth retardation, and other congenital malformations in both humans (15-18) and mice (19-21). Several reports have shown that ZIKV can infect placental and fetal tissues, leading to prolonged viremia in pregnant women (23) and nonhuman primates (24). ZIKV also appears to target cortical neural progenitor cells (19-21, 25 and 26), which likely contributes to neuropathology. The increased incidence of microcephaly temporally related to the introduction of ZIKV in the Americas resulted in the World Health Organization establishing a Public Health Emergency of International Concern (PHEIC). It is also because of these severe outcomes that a protective vaccine is required.”</p> <p>EX 1004 3:2-12: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV</p>	

	<p>post-infection. Mechanisms of action of a prophylactic vaccine could include . . . protecting the fetus during maternal infection (infection during pregnancy occurs but vaccine induced immunity prevents fetal infection from taking hold).”</p> <p>EX 1004: 4:2-7: “The purified, inactivated ZIKV, when used in immunogenic compositions and vaccines, has a major advantage over attenuated virus vaccines and immunogenic compositions in that inactivated viruses are not infectious and therefore, cannot revert to virulence or cause disease. This is important when considering vaccination in known or potentially special populations such as those with immunodeficiencies (e.g., HIV) or those who are pregnant.”</p> <p>EX 1004 18:26-30: “Zika is unique in that there are congenital and neurologic outcomes believed to result from autoimmune versus direct viral effects, and additionally, a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p> <p>EX 1004: 38:30-39:2: “The 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</p>	
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	development of a ZIKV vaccine for humans.”	
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,	<p>EX 1004: 4:2-7: “The purified, inactivated ZIKV, when used in immunogenic compositions and vaccines, has a major advantage over attenuated virus vaccines and immunogenic compositions in that inactivated viruses are not infectious and therefore, cannot revert to virulence or cause disease. This is important when considering vaccination in known or potentially special populations such as those with immunodeficiencies (e.g., HIV) or those who are pregnant.”</p> <p>EX 1004: 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p>	
wherein the antigen is an inactivated whole virus,	<p>EX 1004: 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p> <p>EX 1004: Abstract: “The invention generally relates to a purified inactivated Zika virus (ZIKV), methods for producing the purified inactivated ZIKV, immunogenic compositions and vaccines comprising the purified inactivated ZIKV and methods for the prevention and/or treatment of infection by ZIKV.”</p>	

	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 (e.g., generating an immune response in a subject at risk of infection and/or in need of preventative treatment, or raising antibodies in a subject, or alleviating symptoms of ZIKV in an infected subject, and the like).”	
and wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn,	<p>EX 1004: 3:2-12: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV,... and/or protecting the fetus during maternal infection (infection during pregnancy occurs but vaccine induced immunity prevents fetal infection from taking hold).”</p> <p>EX 1004 26:26-30: “Therefore, if vaccination does not cause any adverse events in the animal and induces an effective immune response (neutralizing antibodies) which protects against a live virus challenge in comparison to a placebo or another control this is typically supportive data to advance to human trials.”</p> <p>EX 1004 33:8-10: “Adoptive transfer studies are conducted demonstrating that the ZIKV PIV created antibodies and these antibodies protect against infection.”</p> <p>EX 1004 33:21-25. “For adoptive transfer studies, Balb/c mice are infused i.v. with IgG purified from PIV vaccinated monkeys at week 8 and were challenged by the i.v. route with 105 VP (102 PFU) ZIKV-BR. Rhesus</p>	<p>EX 1007 p. 2549: Faucette teaches that “[i]mmunization during pregnancy can generate maternal immune protection as well as elicit the production and transfer of antibodies cross the placenta . . . to provide early infant protection. Several successful vaccines are now recommended to all pregnant women worldwide.”</p> <p>EX 1007 p. 2549 “[I]mmunization of pregnant women has emerged as an alternative strategy to combat neonatal infection. It relies on the transfer of maternal vaccine-induced humoral immunity to the fetus during gestation . . . to confer early immune protection until routine vaccination of the child is initiated.”</p> <p>EX 1007 p. 2549: “Several successful maternal vaccines, such as Tetanus-Diphtheria-Pertussis (Tdap) vaccine and inactivated influenza vaccine (IIV), are now universally recommended by the Center for Disease Control and prevention (CDC) to all pregnant women.”</p> <p>EX 1007 p. 2550: “Maternal vaccination aims protect the both the mother and neonate.”</p>

	<p>monkeys are infused i.v. with IgG purified from PIV vaccinated monkeys at week 8 and were challenged by the s.c. (SQ) route with 106 VP (103 PFU) ZIKV-BR.”</p> <p>EX 1004 38:5-16: Thomas explored “the observed protection by adoptive transfer studies.” In mice infused with vaccine-elicited, ZIKV-specific IgG and then challenged with ZIKV-BR, “[t]he higher two doses of purified IgG provides complete protection following ZIKV challenge”</p> <p>EX 1004 38:17-22. In rhesus monkeys infused with vaccine-elicited, ZIKV-specific IgG and then challenged with ZIKV-BR, “one animal is completely protected and the other showed a blip of viremia on days 3-5 (Fig. 12B).”</p> <p>EX 1004 38:24-26: “Taken together, these data demonstrate that purified IgG from ZIKV PIV vaccinated rhesus monkeys provided passive protection following adoptive transfer in both rodents and primates.”</p> <p>EX 1004 38:30-39:2: “The 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.”</p>	<p>EX 1007 p. 2552: “Underpinning the idea of maternal immunization is that the transport of vaccine-induced maternal immunoglobulin G (IgG) antibody across the placenta by neonatal Fc receptor (FcRn) expressed on trophoblasts across [citations omitted], confers fetal and early infant immune protection (Fig. 1A). The amount of IgG transferred across the placenta to the fetus correlates with IgG concentration in the maternal circulation”</p> <p>EX 1007 p. 2552: “IgG transfer from the mother to the fetus can occur as early as gestational week 13, with the largest amount transferred during the third trimester of pregnancy (Fig. 1B). [Citations omitted.] Additional passive immunity in the form of vaccine-induced IgA, IgG and IgM secreted into colostrum and breast milk is transferred during breastfeeding.”</p> <p>EX 1007 p. 2552: “Maternal immunization presents unique benefits to the mother, fetus and the newborn by inducing active immunity in the mother and the transfer of passive humoral immunity across the placenta to the fetus.”</p> <p>EX 1007 p. 2552: “the vaccines effectiveness is due to both passive antibody transport and reduction of maternal exposure. Therefore, immunizing pregnant women can circumvent the multiple disadvantages of attempting to directly immunize neonates immediately after birth.”</p> <p>EX 1007 p. 2552: “Another important, albeit less obvious, benefit of maternal vaccination may involve the function of maternal antibodies in promoting the immune maturation and modulation in infants. Animal studies found that maternally derived antibodies have a profound</p>
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	<p>EX 1004 38:5-16; 38:17-22; 8:24-26; 38:30 to 39:2: Thomas teaches that neutralizing antibodies generated in one animal can be adoptively transferred to another animal, and that such neutralizing antibodies provide a vaccine effective amount to the recipient animal.</p> <p>EX 1004 39:15-16: Thomas teaches with respect to the adoptive transfer data in mice and rhesus monkeys that “[t]aken together, these data are reasonably predictive for how ZIKV vaccines will perform in humans.”</p>	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.”
wherein the vaccine or immunogenic composition further comprises an aluminum salt adjuvant.	EX 1004 28:23-25: “Suitable inorganic adjuvants include, but are not limited to, for example, an aluminum salt, such as aluminum hydroxide gel (alum) or aluminum phosphate.”	
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.	<p>EX 1004 28:19-22: “An ‘adjuvant’ is a substance that serves to enhance, accelerate, or prolong the antigen-specific immune response of an antigen when used in combination with specific vaccine antigens but do not stimulate an immune response when used alone.”</p> <p>EX 1004 17:1: Thomas teaches to use “a suitable amount of adjuvant.”</p>	EX 1005 112:1-4: Aluminum hydroxide adjuvant “was added to a final concentration of 0.5 mg/ml Aluminium (1/20 v/v Alum 2% stock solution added) to prepare ZikaV Drug Product (DP).”
51. The method of claim 49, wherein the adjuvant is aluminum hydroxide.	EX 1004 28:23-24: “Suitable inorganic adjuvants include, but are not limited to, for example, an aluminum salt, such as aluminum hydroxide gel (alum)”	
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	EX 1004 3:2-5: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from	EX 1005 112:1-4: Barbero teaches that aluminum hydroxide adjuvant “was added to a final concentration of 0.5 mg/ml Aluminium

<p>98%, or at least 99%, or 100% of the antigen are adsorbed to the adjuvant.</p>	<p>ZIKV, as well as compositions to treat ZIKV post infection.”</p> <p>EX 1004 4:31-5:1: Thomas teaches that the ZIKV vaccine “can be mixed with suitable adjuvants.”</p> <p>EX 1004 28:18-29:31: Thomas teaches many adjuvants.</p> <p>EX 1004 41:7-8: Thomas teaches that the ZIKV used in Example 5. ZIKV PIV Performance in Human Trials is adjuvanted with alum.</p> <p>EX 1004 28:18-22: Thomas teaches to use adjuvants as a component of the ZIKV vaccine “to enhance, accelerate, or prolong the antigen-specific immune response of an antigen when used in combination with specific vaccine antigens but do not stimulate an immune response when used alone.”</p> <p>EX 1004 17:1. Thomas teaches to use “a suitable amount of adjuvant.”</p> <p>EX 1004 28:23-25: “Suitable inorganic adjuvants include, but are not limited to, for example, an aluminum salt, such as aluminum hydroxide gel (alum) or aluminum phosphate.”</p>	<p>(1/20 v/v Alum 2% stock solution added) to prepare ZikaV Drug Product (DP).”</p> <p>EX 1005 112:4-7: Barbero further teaches that “[t]he DP was gently mixed for 5 min. An aliquot of the DP was removed, Alum sedimented by centrifugation and the clear supernatant analysed by SEC-HPLC. No ZikaV peak was detected in the supernatant indicating complete adsorption (estimated as >95%) of viral particles on the mineral adjuvant.”</p>
<p>53. A method of vaccinating against Zika virus disease in a fetus or newborn in need thereof, the method comprising</p>	<p>EX 1004 2:13-24: “Researchers estimate between 1-13% of ZIKV infections during the first trimester of pregnancy will result in microcephaly. In addition ZIKV has been causally associated with intrauterine growth retardation, and other congenital malformations in both humans (15-18) and mice (19-21). Several reports have shown</p>	

	<p>that ZIKV can infect placental and fetal tissues, leading to prolonged viremia in pregnant women (23) and nonhuman primates (24). ZIKV also appears to target cortical neural progenitor cells (19-21, 25 and 26), which likely contributes to neuropathology. The increased incidence of microcephaly temporally related to the introduction of ZIKV in the Americas resulted in the World Health Organization establishing a Public Health Emergency of International Concern (PHEIC). It is also because of these severe outcomes that a protective vaccine is required.”</p> <p>EX 1004 3:2-12: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post-infection. Mechanisms of action of a prophylactic vaccine could include . . . protecting the fetus during maternal infection (infection during pregnancy occurs but vaccine induced immunity prevents fetal infection from taking hold).”</p> <p>EX 1004: 4:2-7: “The purified, inactivated ZIKV, when used in immunogenic compositions and vaccines, has a major advantage over attenuated virus vaccines and immunogenic compositions in that inactivated viruses are not infectious and therefore, cannot revert to virulence or cause disease. This is important when considering vaccination in known or potentially special populations such as those with</p>	
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	<p>immunodeficiencies (e.g., HIV) or those who are pregnant.”</p> <p>EX 1004 18:26-30: “Zika is unique in that there are congenital and neurologic outcomes believed to result from autoimmune versus direct viral effects, and additionally, a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p> <p>EX 1004: 38:30-39:2: “The 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.”</p>	
<p>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,</p>	<p>EX 1004: 4:2-7: “The purified, inactivated ZIKV, when used in immunogenic compositions and vaccines, has a major advantage over attenuated virus vaccines and immunogenic compositions in that inactivated viruses are not infectious and therefore, cannot revert to virulence or cause disease. This is important when considering vaccination in known or potentially special populations such as those with immunodeficiencies (e.g., HIV) or those who are pregnant.”</p> <p>EX 1004: 18:28-30: “a purified inactivated whole virus is advantageous because of its</p>	

	<p>potential for a superior safety profile in special populations like pregnant women.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p>	
<p>wherein the antigen is an inactivated whole virus, and</p>	<p>EX 1004: 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p> <p>EX 1004: Abstract: “The invention generally relates to a purified inactivated Zika virus (ZIKV), methods for producing the purified inactivated ZIKV, immunogenic compositions and vaccines comprising the purified inactivated ZIKV and methods for the prevention and/or treatment of infection by ZIKV.”</p> <p>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 (e.g., generating an immune response in a subject at risk of infection and/or in need of preventative treatment, or raising antibodies in a subject, or alleviating symptoms of ZIKV in an infected subject, and the like).”</p>	
<p>wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn,</p>	<p>EX 1004: 3:2-12: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV,... and/or protecting the fetus during maternal infection (infection during pregnancy occurs but vaccine induced</p>	<p>EX 1007 p. 2549: Faucette teaches that “[i]mmunization during pregnancy can generate maternal immune protection as well as elicit the production and transfer of antibodies cross the placenta . . . to provide early infant protection. Several successful vaccines are now</p>

	<p>immunity prevents fetal infection from taking hold).”</p> <p>EX 1004 26:26-30: “Therefore, if vaccination does not cause any adverse events in the animal and induces an effective immune response (neutralizing antibodies) which protects against a live virus challenge in comparison to a placebo or another control this is typically supportive data to advance to human trials.”</p> <p>EX 1004 33:8-10: “Adoptive transfer studies are conducted demonstrating that the ZIKV PIV created antibodies and these antibodies protect against infection.”</p> <p>EX 1004 33:21-25. “For adoptive transfer studies, Balb/c mice are infused i.v. with IgG purified from PIV vaccinated monkeys at week 8 and were challenged by the i.v. route with 105 VP (102 PFU) ZIKV-BR. Rhesus monkeys are infused i.v. with IgG purified from PIV vaccinated monkeys at week 8 and were challenged by the s.c. (SQ) route with 106 VP (103 PFU) ZIKV-BR.”</p> <p>EX 1004 38:5-16: Thomas explored “the observed protection by adoptive transfer studies.” In mice infused with vaccine-elicited, ZIKV-specific IgG and then challenged with ZIKV-BR, “[t]he higher two doses of purified IgG provides complete protection following ZIKV challenge”</p> <p>EX 1004 38:17-22. In rhesus monkeys infused with vaccine-elicited, ZIKV-specific IgG and then challenged with ZIKV-BR, “one animal is completely protected and the</p>	<p>recommended to all pregnant women worldwide.”</p> <p>EX 1007 p. 2549: “[I]mmunization of pregnant women has emerged as an alternative strategy to combat neonatal infection. It relies on the transfer of maternal vaccine-induced humoral immunity to the fetus during gestation . . . to confer early immune protection until routine vaccination of the child is initiated.”</p> <p>EX 1007 p. 2549: “Several successful maternal vaccines, such as Tetanus-Diphtheria-Pertussis (Tdap) vaccine and inactivated influenza vaccine (IIV), are now universally recommended by the Center for Disease Control and prevention (CDC) to all pregnant women.”</p> <p>EX 1007 p. 2550: “Maternal vaccination aims protect the both the mother and neonate.”</p> <p>EX 1007 p. 2552: “Underpinning the idea of maternal immunization is that the transport of vaccine-induced maternal immunoglobulin G (IgG) antibody across the placenta by neonatal Fc receptor (FcRn) expressed on trophoblasts across [citations omitted], confers fetal and early infant immune protection (Fig. 1A). The amount of IgG transferred across the placenta to the fetus correlates with IgG concentration in the maternal circulation”</p> <p>EX 1007 p. 2552: “IgG transfer from the mother to the fetus can occur as early as gestational week 13, with the largest amount transferred during the third trimester of pregnancy (Fig. 1B). [Citations omitted.] Additional passive immunity in the form of vaccine-induced IgA, IgG and IgM</p>
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	<p>other showed a blip of viremia on days 3-5 (Fig. 12B).”</p> <p>EX 1004 38:24-26: “Taken together, these data demonstrate that purified IgG from ZIKV PIV vaccinated rhesus monkeys provided passive protection following adoptive transfer in both rodents and primates.”</p> <p>EX 1004 38:30-39:2: “The 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.”</p> <p>EX 1004 38:5-16; 38:17-22; 8:24-26; 38:30 to 39:2: Thomas teaches that neutralizing antibodies generated in one animal can be adoptively transferred to another animal, and that such neutralizing antibodies provide a vaccine effective amount to the recipient animal.</p> <p>EX 1004 39:15-16: 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.”</p>	<p>secreted into colostrum and breast milk is transferred during breastfeeding.”</p> <p>EX 1007 p. 2552: “Maternal immunization presents unique benefits to the mother, fetus and the newborn by inducing active immunity in the mother and the transfer of passive humoral immunity across the placenta to the fetus.”</p> <p>EX 1007 p. 2552: “the vaccines effectiveness is due to both passive antibody transport and reduction of maternal exposure. Therefore, immunizing pregnant women can circumvent the multiple disadvantages of attempting to directly immunize neonates immediately after birth.”</p> <p>EX 1007 p. 2552: “Another important, albeit less obvious, benefit of maternal vaccination may involve the function of maternal antibodies in promoting the immune maturation and modulation in infants. Animal studies found 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.”</p>
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<p>wherein the Zika virus is a clonal isolate, in particular from a plaque purified clonal Zika virus isolate.</p>	<p>EX 1004 3:23: “ZIKV can be purified to be free of pathogens and adventitious agents.”</p> <p>EX 1004 3:24-26: “The ZIKV infectious virus particle can be purified away from the host cell proteins (demonstrated by known procedures such as gradient centrifugation and column chromatography).”</p> <p>EX 1004 19:15-16: “A live ZIKV is purified so as to remove all pathogens and adventitious agents.”</p> <p>EX 1004 20:19-20. “Purification of the ZIKV may be performed by physical or chemical techniques or any combinations thereof that are routinely used in the art.”</p>	<p>EX 1006 p. 3156: “Plaque purification has been used for decades to ensure the homogeneity of virus stocks and to segregate discrete species from mixed virus populations [18-20].”</p> <p>EX 1006 p. 3156: “Our data suggest that plaque purification may be a rapid and efficient means by which vaccine seed virus purity can be enhanced.”</p> <p>EX 1006 p. 3157, 3.2-3.3: Murata used plaque purification to purify influenza virus from the adventitious agents of replicating and non-replicating viruses.</p> <p>EX 1006 p. 3158: “Our data suggest that plaque purification is a simple and rapid method for removing adventitious viruses.”</p> <p>EX 1006 p. 3159: “our study corroborates the commonly invoked rule of thumb in virology calling for three rounds of serial plaque purification to ensure homogeneity starting from a mixed population. Plaque purification is an approach unencumbered by intellectual property constraints”</p>
<p>54. A method of vaccinating against Zika virus disease in a fetus or newborn in need thereof, the method comprising</p>	<p>EX 1004 2:13-24: “Researchers estimate between 1-13% of ZIKV infections during the first trimester of pregnancy will result in microcephaly. In addition ZIKV has been causally associated with intrauterine growth retardation, and other congenital malformations in both humans (15-18) and mice (19-21). Several reports have shown that ZIKV can infect placental and fetal tissues, leading to prolonged viremia in pregnant women (23) and nonhuman primates (24). ZIKV also appears to target</p>	

	<p>cortical neural progenitor cells (19-21, 25 and 26), which likely contributes to neuropathology. The increased incidence of microcephaly temporally related to the introduction of ZIKV in the Americas resulted in the World Health Organization establishing a Public Health Emergency of International Concern (PHEIC). It is also because of these severe outcomes that a protective vaccine is required.”</p> <p>EX 1004 3:2-12: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post-infection. Mechanisms of action of a prophylactic vaccine could include . . . protecting the fetus during maternal infection (infection during pregnancy occurs but vaccine induced immunity prevents fetal infection from taking hold).”</p> <p>EX 1004: 4:2-7: “The purified, inactivated ZIKV, when used in immunogenic compositions and vaccines, has a major advantage over attenuated virus vaccines and immunogenic compositions in that inactivated viruses are not infectious and therefore, cannot revert to virulence or cause disease. This is important when considering vaccination in known or potentially special populations such as those with immunodeficiencies (e.g., HIV) or those who are pregnant.”</p> <p>EX 1004 18:26-30: “Zika is unique in that there are congenital and neurologic outcomes believed to result from autoimmune versus</p>	
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<p>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,</p>	<p>EX 1004: 4:2-7: “The purified, inactivated ZIKV, when used in immunogenic compositions and vaccines, has a major advantage over attenuated virus vaccines and immunogenic compositions in that inactivated viruses are not infectious and therefore, cannot revert to virulence or cause disease. This is important when considering vaccination in known or potentially special populations such as those with immunodeficiencies (e.g., HIV) or those who are pregnant.”</p> <p>EX 1004: 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p>	

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wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn,	EX 1004: 3:2-12: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV,... and/or protecting the fetus during maternal infection (infection during pregnancy occurs but vaccine induced immunity prevents fetal infection from taking hold).”	EX 1007 p. 2549: Faucette teaches that “[i]mmunization during pregnancy can generate maternal immune protection as well as elicit the production and transfer of antibodies cross the placenta . . . to provide early infant protection. Several successful vaccines are now recommended to all pregnant women worldwide.”

	<p>EX 1004 26:26-30: “Therefore, if vaccination does not cause any adverse events in the animal and induces an effective immune response (neutralizing antibodies) which protects against a live virus challenge in comparison to a placebo or another control this is typically supportive data to advance to human trials.”</p> <p>EX 1004 33:8-10: “Adoptive transfer studies are conducted demonstrating that the ZIKV PIV created antibodies and these antibodies protect against infection.”</p> <p>EX 1004 33:21-25. “For adoptive transfer studies, Balb/c mice are infused i.v. with IgG purified from PIV vaccinated monkeys at week 8 and were challenged by the i.v. route with 105 VP (102 PFU) ZIKV-BR. Rhesus monkeys are infused i.v. with IgG purified from PIV vaccinated monkeys at week 8 and were challenged by the s.c. (SQ) route with 106 VP (103 PFU) ZIKV-BR.”</p> <p>EX 1004 38:5-16: Thomas explored “the observed protection by adoptive transfer studies.” In mice infused with vaccine-elicited, ZIKV-specific IgG and then challenged with ZIKV-BR, “[t]he higher two doses of purified IgG provides complete protection following ZIKV challenge”</p> <p>EX 1004 38:17-22. In rhesus monkeys infused with vaccine-elicited, ZIKV-specific IgG and then challenged with ZIKV-BR, “one animal is completely protected and the other showed a blip of viremia on days 3-5 (Fig. 12B).”</p>	<p>EX 1007 p. 2549: “[I]mmunization of pregnant women has emerged as an alternative strategy to combat neonatal infection. It relies on the transfer of maternal vaccine-induced humoral immunity to the fetus during gestation . . . to confer early immune protection until routine vaccination of the child is initiated.”</p> <p>EX 1007 p. 2549: “Several successful maternal vaccines, such as Tetanus-Diphtheria-Pertussis (Tdap) vaccine and inactivated influenza vaccine (IIV), are now universally recommended by the Center for Disease Control and prevention (CDC) to all pregnant women.”</p> <p>EX 1007 p. 2550: “Maternal vaccination aims protect the both the mother and neonate.”</p> <p>EX 1007 p. 2552: “Underpinning the idea of maternal immunization is that the transport of vaccine-induced maternal immunoglobulin G (IgG) antibody across the placenta by neonatal Fc receptor (FcRn) expressed on trophoblasts across [citations omitted], confers fetal and early infant immune protection (Fig. 1A). The amount of IgG transferred across the placenta to the fetus correlates with IgG concentration in the maternal circulation”</p> <p>EX 1007 p. 2552: “IgG transfer from the mother to the fetus can occur as early as gestational week 13, with the largest amount transferred during the third trimester of pregnancy (Fig. 1B). [Citations omitted.] Additional passive immunity in the form of vaccine-induced IgA, IgG and IgM secreted into colostrum and breast milk is transferred during breastfeeding.”</p>
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	<p>EX 1004 38:24-26: “Taken together, these data demonstrate that purified IgG from ZIKV PIV vaccinated rhesus monkeys provided passive protection following adoptive transfer in both rodents and primates.”</p> <p>EX 1004 38:30-39:2: “The 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.”</p> <p>EX 1004 38:5-16; 38:17-22; 8:24-26; 38:30 to 39:2: Thomas teaches that neutralizing antibodies generated in one animal can be adoptively transferred to another animal, and that such neutralizing antibodies provide a vaccine effective amount to the recipient animal.</p> <p>EX 1004 39:15-16: Thomas teaches with respect to the adoptive transfer data in mice and rhesus monkeys that “[t]aken together, these data are reasonably predictive for how ZIKV vaccines will perform in humans.”</p>	<p>EX 1007 p. 2552: “Maternal immunization presents unique benefits to the mother, fetus and the newborn by inducing active immunity in the mother and the transfer of passive humoral immunity across the placenta to the fetus.”</p> <p>EX 1007 p. 2552: “the vaccines effectiveness is due to both passive antibody transport and reduction of maternal exposure. Therefore, immunizing pregnant women can circumvent the multiple disadvantages of attempting to directly immunize neonates immediately after birth.”</p> <p>EX 1007 p. 2552: “Another important, albeit less obvious, benefit of maternal vaccination may involve the function of maternal antibodies in promoting the immune maturation and modulation in infants. Animal studies found 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.”</p>
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.	EX 1004 28:23-25: “Suitable inorganic adjuvants include, but are not limited to, for example, an aluminum salt, such as aluminum hydroxide gel (alum) or aluminum phosphate”)	<p>EX 1011 p. 6: Version 8 of NCT0292833 evaluates three dose levels of “5.0 mcg, 2.5 mcg and 10mcg of ZPIV.”</p> <p>EX 1011 p. 6: The doses are to be administered “by intramuscular (IM) injection on Days 1 and</p>

	<p>EX 1004 28:27: Thomas teaches the use of “acylated sugars”.</p> <p>EX 1004 30:20: Thomas teaches the use of a “sucrose solution”.</p> <p>EX 1004 30:20-21: Thomas teaches use of “pharmaceutically acceptable buffer solutions.”</p> <p>EX 1004 3:2-5: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post infection.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p> <p>EX 1004: 4:24-28: “With the information known about the dosing and schedule for other PIV flavivirus vaccines - such as Japanese encephalitis and tick-borne encephalitis - 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.”</p> <p>EX 1004: 40:18-26: “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</p> <p>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</p>	<p>29. The study will consist of a screening period of up to 28 days, a vaccination period in which subjects will receive a prime dose of vaccine on Day 1 followed by a boost on Day 29, and a follow-up period of 12 months post boost vaccination.”</p> <p>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”</p> <p>EX 1011 p. 6: “The secondary objectives of this study are to 1. Assess . . . seroconversion rates, and peak Geometric Mean Titer (GMT)”</p> <p>EX 1011 p. 8, 11: 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.</p> <p>EX 1011 p. 8: 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.</p> <p>EX 1011 p. 10: The Peak GMT overall and by dosage group is measured by ZIKV ELISA and neutralization assay.</p> <p>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.</p>
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	<p>booster doses to create durable immune responses”</p> <p>EX 1004 18:17-20: “Based on these models, and 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, or a booster dose at 4 weeks as described below.)”</p> <p>EX 1004 42:9-11: “Antibody kinetics based on MN50 titers indicating a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff and then a robust and brisk rise in antibody titer for the Trial Group 2 and Trial Group 3 volunteers following dose 2.”</p>	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 neutralization titers in comparison with baseline.
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.	<p>EX 1004: 37:31-32: “No specific clinical safety adverse effects related to the vaccine were observed.”</p> <p>EX 1004: 41:16-17: “There were no deaths, serious adverse events related to vaccination, or disenrollments related to an adverse event.”</p> <p>EX 1004 43:14-15: “ZPIV was well tolerated and safe in a small number of volunteers and moderate to highly immunogenic”.</p>	
56. The method of claim 55, wherein the severe adverse event is a fever of a temperature of 39° C. or higher.	<p>EX 1004: 37:31-32: “No specific clinical safety adverse effects related to the vaccine were observed.”</p> <p>EX 1004: 41:16-17: “There were no deaths, serious adverse events related to vaccination, or disenrollments related to an adverse event.”</p>	

	EX 1004 43:14-15: “ZPIV was well tolerated and safe in a small number of volunteers and moderate to highly immunogenic”.	
57. A method of vaccinating against Zika virus disease in a fetus or newborn in need thereof, the method comprising	<p>EX 1004 2:13-24: “Researchers estimate between 1-13% of ZIKV infections during the first trimester of pregnancy will result in microcephaly. In addition ZIKV has been causally associated with intrauterine growth retardation, and other congenital malformations in both humans (15-18) and mice (19-21). Several reports have shown that ZIKV can infect placental and fetal tissues, leading to prolonged viremia in pregnant women (23) and nonhuman primates (24). ZIKV also appears to target cortical neural progenitor cells (19-21, 25 and 26), which likely contributes to neuropathology. The increased incidence of microcephaly temporally related to the introduction of ZIKV in the Americas resulted in the World Health Organization establishing a Public Health Emergency of International Concern (PHEIC). It is also because of these severe outcomes that a protective vaccine is required.”</p> <p>EX 1004 3:2-12: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post-infection. Mechanisms of action of a prophylactic vaccine could include . . . protecting the fetus during maternal infection (infection during pregnancy occurs but vaccine induced immunity prevents fetal infection from taking hold).”</p>	

	<p>EX 1004: 4:2-7: “The purified, inactivated ZIKV, when used in immunogenic compositions and vaccines, has a major advantage over attenuated virus vaccines and immunogenic compositions in that inactivated viruses are not infectious and therefore, cannot revert to virulence or cause disease. This is important when considering vaccination in known or potentially special populations such as those with immunodeficiencies (e.g., HIV) or those who are pregnant.”</p> <p>EX 1004 18:26-30: “Zika is unique in that there are congenital and neurologic outcomes believed to result from autoimmune versus direct viral effects, and additionally, a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p> <p>EX 1004: 38:30-39:2: “The 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.”</p>	
administering to a pregnant human subject a vaccine or immunogenic composition	EX 1004: 4:2-7: “The purified, inactivated ZIKV, when used in immunogenic compositions and vaccines, has a major advantage over attenuated virus vaccines and	

<p>comprising a dose of from about 1 µg to about 40 µg of an antigen from a Zika virus,</p>	<p>immunogenic compositions in that inactivated viruses are not infectious and therefore, cannot revert to virulence or cause disease. This is important when considering vaccination in known or potentially special populations such as those with immunodeficiencies (e.g., HIV) or those who are pregnant.”</p> <p>EX 1004: 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p>	
<p>wherein the antigen is an inactivated whole virus, and</p>	<p>EX 1004: 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p> <p>EX 1004: Abstract: “The invention generally relates to a purified inactivated Zika virus (ZIKV), methods for producing the purified inactivated ZIKV, immunogenic compositions and vaccines comprising the purified inactivated ZIKV and methods for the prevention and/or treatment of infection by ZIKV.”</p> <p>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 (e.g., generating an immune response in a subject at risk of infection and/or in need of preventative</p>	

	treatment, or raising antibodies in a subject, or alleviating symptoms of ZIKV in an infected subject, and the like).”	
wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn,	<p>EX 1004: 3:2-12: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV,... and/or protecting the fetus during maternal infection (infection during pregnancy occurs but vaccine induced immunity prevents fetal infection from taking hold).”</p> <p>EX 1004 26:26-30: “Therefore, if vaccination does not cause any adverse events in the animal and induces an effective immune response (neutralizing antibodies) which protects against a live virus challenge in comparison to a placebo or another control this is typically supportive data to advance to human trials.”</p> <p>EX 1004 33:8-10: “Adoptive transfer studies are conducted demonstrating that the ZIKV PIV created antibodies and these antibodies protect against infection.”</p> <p>EX 1004 33:21-25. “For adoptive transfer studies, Balb/c mice are infused i.v. with IgG purified from PIV vaccinated monkeys at week 8 and were challenged by the i.v. route with 105 VP (102 PFU) ZIKV-BR. Rhesus monkeys are infused i.v. with IgG purified from PIV vaccinated monkeys at week 8 and were challenged by the s.c. (SQ) route with 106 VP (103 PFU) ZIKV-BR.”</p> <p>EX 1004 38:5-16: Thomas explored “the observed protection by adoptive transfer</p>	<p>EX 1007 p. 2549: Faucette teaches that “[i]mmunization during pregnancy can generate maternal immune protection as well as elicit the production and transfer of antibodies cross the placenta . . . to provide early infant protection. Several successful vaccines are now recommended to all pregnant women worldwide.”</p> <p>EX 1007 p. 2549: “[I]mmunization of pregnant women has emerged as an alternative strategy to combat neonatal infection. It relies on the transfer of maternal vaccine-induced humoral immunity to the fetus during gestation . . . to confer early immune protection until routine vaccination of the child is initiated.”</p> <p>EX 1007 p. 2549: “Several successful maternal vaccines, such as Tetanus-Diphtheria-Pertussis (Tdap) vaccine and inactivated influenza vaccine (IIV), are now universally recommended by the Center for Disease Control and prevention (CDC) to all pregnant women.”</p> <p>EX 1007 p. 2550: “Maternal vaccination aims protect the both the mother and neonate.”</p> <p>EX 1007 p. 2552: “Underpinning the idea of maternal immunization is that the transport of vaccine-induced maternal immunoglobulin G (IgG) antibody across the placenta by neonatal Fc receptor (FcRn) expressed on trophoblasts across [citations omitted], confers fetal and early infant immune protection (Fig. 1A). The amount of IgG transferred across the placenta to the fetus</p>

	<p>studies.” In mice infused with vaccine-elicited, ZIKV-specific IgG and then challenged with ZIKV-BR, “[t]he higher two doses of purified IgG provides complete protection following ZIKV challenge”</p> <p>EX 1004 38:17-22. In rhesus monkeys infused with vaccine-elicited, ZIKV-specific IgG and then challenged with ZIKV-BR, “one animal is completely protected and the other showed a blip of viremia on days 3-5 (Fig. 12B).”</p> <p>EX 1004 38:24-26: “Taken together, these data demonstrate that purified IgG from ZIKV PIV vaccinated rhesus monkeys provided passive protection following adoptive transfer in both rodents and primates.”</p> <p>EX 1004 38:30-39:2: “The 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.”</p> <p>EX 1004 38:5-16; 38:17-22; 8:24-26; 38:30 to 39:2: Thomas teaches that neutralizing antibodies generated in one animal can be adoptively transferred to another animal, and that such neutralizing antibodies provide a</p>	<p>correlates with IgG concentration in the maternal circulation”</p> <p>EX 1007 p. 2552: “IgG transfer from the mother to the fetus can occur as early as gestational week 13, with the largest amount transferred during the third trimester of pregnancy (Fig. 1B). [Citations omitted.] Additional passive immunity in the form of vaccine-induced IgA, IgG and IgM secreted into colostrum and breast milk is transferred during breastfeeding.”</p> <p>EX 1007 p. 2552: “Maternal immunization presents unique benefits to the mother, fetus and the newborn by inducing active immunity in the mother and the transfer of passive humoral immunity across the placenta to the fetus.”</p> <p>EX 1007 p. 2552: “the vaccines effectiveness is due to both passive antibody transport and reduction of maternal exposure. Therefore, immunizing pregnant women can circumvent the multiple disadvantages of attempting to directly immunize neonates immediately after birth.”</p> <p>EX 1007 p. 2552: “Another important, albeit less obvious, benefit of maternal vaccination may involve the function of maternal antibodies in promoting the immune maturation and modulation in infants. Animal studies found 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.”</p>
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	<p>vaccine effective amount to the recipient animal.</p> <p>EX 1004 39:15-16: Thomas teaches with respect to the adoptive transfer data in mice and rhesus monkeys that “[t]aken together, these data are reasonably predictive for how ZIKV vaccines will perform in humans.”</p>	
<p>wherein the pregnant human subject is from a Zika endemic region or from a Zika non-endemic region travelling to an endemic region.</p>	<p>EX 1004 40:27-32: “Trial 4: 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 to understand safety and immunogenicity performance in scenarios where dengue and Zika are potentially endemic.”</p>	
<p>58. A method of vaccinating against Zika virus disease in a fetus or newborn in need thereof, the method comprising</p>	<p>EX 1004 2:13-24: “Researchers estimate between 1-13% of ZIKV infections during the first trimester of pregnancy will result in microcephaly. In addition ZIKV has been causally associated with intrauterine growth retardation, and other congenital malformations in both humans (15-18) and mice (19-21). Several reports have shown that ZIKV can infect placental and fetal tissues, leading to prolonged viremia in pregnant women (23) and nonhuman primates (24). ZIKV also appears to target cortical neural progenitor cells (19-21, 25 and 26), which likely contributes to neuropathology. The increased incidence of microcephaly temporally related to the introduction of ZIKV in the Americas resulted in the World Health Organization establishing a Public Health Emergency of International Concern (PHEIC). It is also</p>	

	<p>because of these severe outcomes that a protective vaccine is required.”</p> <p>EX 1004 3:2-12: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV, as well as compositions to treat ZIKV post-infection. Mechanisms of action of a prophylactic vaccine could include . . . protecting the fetus during maternal infection (infection during pregnancy occurs but vaccine induced immunity prevents fetal infection from taking hold).”</p> <p>EX 1004: 4:2-7: “The purified, inactivated ZIKV, when used in immunogenic compositions and vaccines, has a major advantage over attenuated virus vaccines and immunogenic compositions in that inactivated viruses are not infectious and therefore, cannot revert to virulence or cause disease. This is important when considering vaccination in known or potentially special populations such as those with immunodeficiencies (e.g., HIV) or those who are pregnant.”</p> <p>EX 1004 18:26-30: “Zika is unique in that there are congenital and neurologic outcomes believed to result from autoimmune versus direct viral effects, and additionally, a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p> <p>EX 1004: 38:30-39:2: “The adoptive transfer studies demonstrate that vaccine-elicited antibodies are sufficient for protection</p>	
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	<p>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.”</p>	
<p>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,</p>	<p>EX 1004: 4:2-7: “The purified, inactivated ZIKV, when used in immunogenic compositions and vaccines, has a major advantage over attenuated virus vaccines and immunogenic compositions in that inactivated viruses are not infectious and therefore, cannot revert to virulence or cause disease. This is important when considering vaccination in known or potentially special populations such as those with immunodeficiencies (e.g., HIV) or those who are pregnant.”</p> <p>EX 1004: 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p> <p>EX 1004: 41:7-8: “Two doses were administered at 0 and 28 days, 5 µg per dose, and adjuvanted with alum.”</p>	
<p>wherein the antigen is an inactivated whole virus, and</p>	<p>EX 1004: 18:28-30: “a purified inactivated whole virus is advantageous because of its potential for a superior safety profile in special populations like pregnant women.”</p> <p>EX 1004: Abstract: “The invention generally relates to a purified inactivated Zika virus (ZIKV), methods for producing the purified</p>	

	<p>inactivated ZIKV, immunogenic compositions and vaccines comprising the purified inactivated ZIKV and methods for the prevention and/or treatment of infection by ZIKV.”</p> <p>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 (e.g., generating an immune response in a subject at risk of infection and/or in need of preventative treatment, or raising antibodies in a subject, or alleviating symptoms of ZIKV in an infected subject, and the like).”</p>	
<p>wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn,</p>	<p>EX 1004: 3:2-12: “There is an urgent need for a vaccine capable of inducing a protective immune response against infection from ZIKV,... and/or protecting the fetus during maternal infection (infection during pregnancy occurs but vaccine induced immunity prevents fetal infection from taking hold).”</p> <p>EX 1004 26:26-30: “Therefore, if vaccination does not cause any adverse events in the animal and induces an effective immune response (neutralizing antibodies) which protects against a live virus challenge in comparison to a placebo or another control this is typically supportive data to advance to human trials.”</p> <p>EX 1004 33:8-10: “Adoptive transfer studies are conducted demonstrating that the</p>	<p>EX 1007 p. 2549: Faucette teaches that “[i]mmunization during pregnancy can generate maternal immune protection as well as elicit the production and transfer of antibodies cross the placenta . . . to provide early infant protection. Several successful vaccines are now recommended to all pregnant women worldwide.”</p> <p>EX 1007 p. 2549: “[I]mmunization of pregnant women has emerged as an alternative strategy to combat neonatal infection. It relies on the transfer of maternal vaccine-induced humoral immunity to the fetus during gestation . . . to confer early immune protection until routine vaccination of the child is initiated.”</p> <p>EX 1007 p. 2549: “Several successful maternal vaccines, such as Tetanus-Diphtheria-Pertussis (Tdap) vaccine and inactivated influenza vaccine (IIV), are now universally recommended by the</p>

	<p>ZIKV PIV created antibodies and these antibodies protect against infection.”</p> <p>EX 1004 33:21-25. “For adoptive transfer studies, Balb/c mice are infused i.v. with IgG purified from PIV vaccinated monkeys at week 8 and were challenged by the i.v. route with 105 VP (102 PFU) ZIKV-BR. Rhesus monkeys are infused i.v. with IgG purified from PIV vaccinated monkeys at week 8 and were challenged by the s.c. (SQ) route with 106 VP (103 PFU) ZIKV-BR.”</p> <p>EX 1004 38:5-16: Thomas explored “the observed protection by adoptive transfer studies.” In mice infused with vaccine-elicited, ZIKV-specific IgG and then challenged with ZIKV-BR, “[t]he higher two doses of purified IgG provides complete protection following ZIKV challenge”</p> <p>EX 1004 38:17-22. In rhesus monkeys infused with vaccine-elicited, ZIKV-specific IgG and then challenged with ZIKV-BR, “one animal is completely protected and the other showed a blip of viremia on days 3-5 (Fig. 12B).”</p> <p>EX 1004 38:24-26: “Taken together, these data demonstrate that purified IgG from ZIKV PIV vaccinated rhesus monkeys provided passive protection following adoptive transfer in both rodents and primates.”</p> <p>EX 1004 38:30-39:2: “The adoptive transfer studies demonstrate that vaccine-elicited antibodies are sufficient for protection against ZIKV challenge. Moreover, passive</p>	<p>Center for Disease Control and prevention (CDC) to all pregnant women.”</p> <p>EX 1007 p. 2550: “Maternal vaccination aims protect the both the mother and neonate.”</p> <p>EX 1007 p. 2552: “Underpinning the idea of maternal immunization is that the transport of vaccine-induced maternal immunoglobulin G (IgG) antibody across the placenta by neonatal Fc receptor (FcRn) expressed on trophoblasts across [citations omitted], confers fetal and early infant immune protection (Fig. 1A). The amount of IgG transferred across the placenta to the fetus correlates with IgG concentration in the maternal circulation”</p> <p>EX 1007 p. 2552: “IgG transfer from the mother to the fetus can occur as early as gestational week 13, with the largest amount transferred during the third trimester of pregnancy (Fig. 1B). [Citations omitted.] Additional passive immunity in the form of vaccine-induced IgA, IgG and IgM secreted into colostrum and breast milk is transferred during breastfeeding.”</p> <p>EX 1007 p. 2552: “Maternal immunization presents unique benefits to the mother, fetus and the newborn by inducing active immunity in the mother and the transfer of passive humoral immunity across the placenta to the fetus.”</p> <p>EX 1007 p. 2552: “the vaccines effectiveness is due to both passive antibody transport and reduction of maternal exposure. Therefore, immunizing pregnant women can circumvent the multiple disadvantages of attempting to directly immunize neonates immediately after birth.”</p>
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	<p>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.”</p> <p>EX 1004 38:5-16; 38:17-22; 8:24-26; 38:30 to 39:2: Thomas teaches that neutralizing antibodies generated in one animal can be adoptively transferred to another animal, and that such neutralizing antibodies provide a vaccine effective amount to the recipient animal.</p> <p>EX 1004 39:15-16: Thomas teaches with respect to the adoptive transfer data in mice and rhesus monkeys that “[t]aken together, these data are reasonably predictive for how ZIKV vaccines will perform in humans.”</p>	<p>EX 1007 p. 2552: “Another important, albeit less obvious, benefit of maternal vaccination may involve the function of maternal antibodies in promoting the immune maturation and modulation in infants. Animal studies found 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.”</p>
wherein the pregnant human subject is 18 to 29 years of age or 30 to 49 years of age.	<p>EX 1004: 41:13-15: “The mean age was 31.5 years with a decline in the mean age from Trial Group 2 (33.3) to Trial Group 1 (30.9) to Trial Group 3 (27.9).”</p>	
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%.	<p>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%.”</p> <p>EX 1004 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.</p>	

	EX 1004: 41:9-10: A total of 67 individuals were in this group, with 55 receiving ZPIV and 12 receiving placebo.	
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.	<p>EX 1004: In Example 5: ZIKV PIV Performance in Human Trials, Thomas teaches a seroconversion rate of 92% for 55 humans at day 57 after a boost administration. A seroconversion rate of 92% is above the claimed 80%. The Table indicates prime administration at day 1 and boost administration at day 29. Day 57 is 28 days after the boost administration.</p> <p>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%”.</p> <p>See also EX 1004 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.</p> <p>EX 1004 4:15-22: “The purified, inactivated ZIKV can be used to immunize mammals (including humans) to elicit high titers of virus neutralizing antibodies and protect the immunized mammal from disease caused by ZIKV. For example, a single immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against challenge with ZIKV. Another example is wherein two doses are administered (e.g., a first dose, followed by a second dose 4 weeks later). A booster dose</p>	

	<p>(second dose or more) may be useful for persons with recurrent infection risk.”</p> <p>EX 1004 7:11: “Booster doses may be used, if needed.”</p> <p>EX 1004 7:30-32: “Ideally, only one dose is needed to effect protection against Zika infection for mammals, including humans.”</p> <p>EX 1004 7:32-8:2. “An exemplary dosage schedule entails an initial dose, then a second (booster) dose about 4 weeks later. However, this schedule is exemplary only, and someone skilled in the art would be able to determine without undue experimentation if and when any second dose is needed.”</p> <p>EX 1004 4:24-28: “With the information known about the dosing and schedule for other PIV flavivirus vaccines – such as Japanese encephalitis and tick-borne encephalitis – 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.”</p> <p>EX 1004 18:17-20: “Based on these models, and 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, or a booster dose at 4 weeks as described below.)”</p> <p>EX 1004 28:19-22: “An “adjuvant” is a substance that serves to enhance, accelerate, or prolong the antigen-specific immune response of an antigen when used in combination with specific vaccine antigens</p>	
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	<p>but do not stimulate an immune response when used alone.”</p> <p>EX 1004 42:9-10: Thomas teaches in Example 5. ZIKV PIV Performance in Human Trials for a 5µg dose that “[a]ntibody kinetics based on MN50 titers indicat[ed] a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff”.</p> <p>EX 1004 Table at page 42 Day 1 after prime administration, GMT of 5.0 for N=55 volunteers.</p>	
<p>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.</p>	<p>EX 1004: In Example 5: ZIKV PIV Performance in Human Trials, Thomas teaches a seroconversion rate of 92% for 55 humans at day 57 after a boost administration. A seroconversion rate of 92% is above the claimed 90%. The Table indicates prime administration at day 1 and boost administration at day 29. Day 57 is 28 days after the boost administration.</p> <p>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%”.</p> <p>EX 1004 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.</p> <p>EX 1004 4:15-22: “The purified, inactivated ZIKV can be used to immunize mammals (including humans) to elicit high titers of</p>	

	<p>virus neutralizing antibodies and protect the immunized mammal from disease caused by ZIKV. For example, a single immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against challenge with ZIKV. Another example is wherein two doses are administered (e.g., a first dose, followed by a second dose 4 weeks later). A booster dose (second dose or more) may be useful for persons with recurrent infection risk.”</p> <p>EX 1004 7:11: “Booster doses may be used, if needed.”</p> <p>EX 1004 7:30-32: “Ideally, only one dose is needed to effect protection against Zika infection for mammals, including humans.”</p> <p>EX 1004 7:32-8:2. “An exemplary dosage schedule entails an initial dose, then a second (booster) dose about 4 weeks later. However, this schedule is exemplary only, and someone skilled in the art would be able to determine without undue experimentation if and when any second dose is needed.”</p> <p>EX 1004 4:24-28: “With the information known about the dosing and schedule for other PIV flavivirus vaccines – such as Japanese encephalitis and tick-borne encephalitis – 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.”</p> <p>EX 1004 18:17-20: “Based on these models, and what is already known in the field of flavivirus PIVs, extrapolation to human use</p>	
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	<p>is reasonable for safe and effective dosages (e.g., a single dose, or a booster dose at 4 weeks as described below.)”</p> <p>EX 1004 28:19-22: “An “adjuvant” is a substance that serves to enhance, accelerate, or prolong the antigen-specific immune response of an antigen when used in combination with specific vaccine antigens but do not stimulate an immune response when used alone.”</p> <p>EX 1004 42:9-10: Thomas teaches in Example 5. ZIKV PIV Performance in Human Trials for a 5µg dose that “[a]ntibody kinetics based on MN50 titers indicat[ed] a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff”.</p> <p>EX 1004 Table at page 42 Day 1 after prime administration, GMT of 5.0 for N=55 volunteers.</p>	
<p>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.</p>	<p>In Example 5: ZIKV PIV Performance in Human Trials, Thomas teaches a seroconversion rate of 92% for 55 humans at day 57 after a boost administration. A seroconversion rate of 92% is below the claimed 95%. The Table indicates prime administration at day 1 and boost administration at day 29. Day 57 is 28 days after the boost administration.</p> <p>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</p>	

	<p>rates of Trial 2 Group 92%, Trial 1 Group 88%, and Trial 3 Group 100%”.</p> <p>EX 1004 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.</p> <p>EX 1004 4:15-22: “The purified, inactivated ZIKV can be used to immunize mammals (including humans) to elicit high titers of virus neutralizing antibodies and protect the immunized mammal from disease caused by ZIKV. For example, a single immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against challenge with ZIKV. Another example is wherein two doses are administered (e.g., a first dose, followed by a second dose 4 weeks later). A booster dose (second dose or more) may be useful for persons with recurrent infection risk.”</p> <p>EX 1004 7:11: “Booster doses may be used, if needed.”</p> <p>EX 1004 7:30-32: “Ideally, only one dose is needed to effect protection against Zika infection for mammals, including humans.”</p> <p>EX 1004 7:32-8:2. “An exemplary dosage schedule entails an initial dose, then a second (booster) dose about 4 weeks later. However, this schedule is exemplary only, and someone skilled in the art would be able to determine without undue experimentation if and when any second dose is needed.”</p> <p>EX 1004 4:24-28: “With the information known about the dosing and schedule for other PIV flavivirus vaccines – such as</p>	
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	<p>Japanese encephalitis and tick-borne encephalitis – 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.”</p> <p>EX 1004 18:17-20: “Based on these models, and 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, or a booster dose at 4 weeks as described below.)”</p> <p>EX 1004 28:19-22: “An “adjuvant” is a substance that serves to enhance, accelerate, or prolong the antigen-specific immune response of an antigen when used in combination with specific vaccine antigens but do not stimulate an immune response when used alone.”</p> <p>EX 1004 42:9-10: Thomas teaches in Example 5. ZIKV PIV Performance in Human Trials for a 5µg dose that “[a]ntibody kinetics based on MN50 titers indicat[ed] a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff”.</p> <p>EX 1004 Table at page 42 Day 1 after prime administration, GMT of 5.0 for N=55 volunteers.</p>	
63. The method of claim 26, wherein the sugar is sucrose.	<p>EX 1004 28:27: Thomas teaches the use of “acylated sugars”.</p> <p>EX 1004 30:20: Thomas teaches the use of a “sucrose solution”.</p>	

<p>64. The method of claim 54, wherein the sugar is sucrose.</p>	<p>EX 1004 28:27: Thomas teaches the use of “acylated sugars”.</p> <p>EX 1004 30:20: Thomas teaches the use of a “sucrose solution”.</p>	
<p>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.</p>	<p>EX 1004: In Example 5: ZIKV PIV Performance in Human Trials, Thomas teaches a seroconversion rate of 92% for 55 humans at day 57 after a boost administration. A seroconversion rate of 92% is above the claimed 70%. The Table indicates prime administration at day 1 and boost administration at day 29. Day 57 is 28 days after the boost administration.</p> <p>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%”.</p> <p>EX 1004 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.</p> <p>EX 1004 4:15-22: “The purified, inactivated ZIKV can be used to immunize mammals (including humans) to elicit high titers of virus neutralizing antibodies and protect the immunized mammal from disease caused by ZIKV. For example, a single immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against challenge with ZIKV. Another example is wherein two doses are administered (e.g., a first dose, followed by a</p>	

	<p>second dose 4 weeks later). A booster dose (second dose or more) may be useful for persons with recurrent infection risk.”</p> <p>EX 1004 7:11: “Booster doses may be used, if needed.”</p> <p>EX 1004 7:30-32: “Ideally, only one dose is needed to effect protection against Zika infection for mammals, including humans.”</p> <p>EX 1004 7:32-8:2. “An exemplary dosage schedule entails an initial dose, then a second (booster) dose about 4 weeks later. However, this schedule is exemplary only, and someone skilled in the art would be able to determine without undue experimentation if and when any second dose is needed.”</p> <p>EX 1004 4:24-28: “With the information known about the dosing and schedule for other PIV flavivirus vaccines – such as Japanese encephalitis and tick-borne encephalitis – 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.”</p> <p>EX 1004 18:17-20: “Based on these models, and 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, or a booster dose at 4 weeks as described below.)”</p> <p>EX 1004 28:19-22: “An “adjuvant” is a substance that serves to enhance, accelerate, or prolong the antigen-specific immune response of an antigen when used in combination with specific vaccine antigens</p>	
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	<p>but do not stimulate an immune response when used alone.”</p> <p>EX 1004 42:9-10: Thomas teaches in Example 5. ZIKV PIV Performance in Human Trials for a 5µg dose that “[a]ntibody kinetics based on MN50 titers indicat[ed] a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff”.</p> <p>EX 1004 Table at page 42 Day 1 after prime administration, GMT of 5.0 for N=55 volunteers.</p>	
<p>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.</p>	<p>EX 1004: In Example 5: ZIKV PIV Performance in Human Trials, Thomas teaches a seroconversion rate of 92% for 55 humans at day 57 after a boost administration. A seroconversion rate of 92% is above the claimed 80%. The Table indicates prime administration at day 1 and boost administration at day 29. Day 57 is 28 days after the boost administration.</p> <p>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%”.</p> <p>EX 1004 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.</p> <p>EX 1004 4:15-22: “The purified, inactivated ZIKV can be used to immunize mammals (including humans) to elicit high titers of</p>	

	<p>virus neutralizing antibodies and protect the immunized mammal from disease caused by ZIKV. For example, a single immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against challenge with ZIKV. Another example is wherein two doses are administered (e.g., a first dose, followed by a second dose 4 weeks later). A booster dose (second dose or more) may be useful for persons with recurrent infection risk.”</p> <p>EX 1004 7:11: “Booster doses may be used, if needed.”</p> <p>EX 1004 7:30-32: “Ideally, only one dose is needed to effect protection against Zika infection for mammals, including humans.”</p> <p>EX 1004 7:32-8:2. “An exemplary dosage schedule entails an initial dose, then a second (booster) dose about 4 weeks later. However, this schedule is exemplary only, and someone skilled in the art would be able to determine without undue experimentation if and when any second dose is needed.”</p> <p>EX 1004 4:24-28: “With the information known about the dosing and schedule for other PIV flavivirus vaccines – such as Japanese encephalitis and tick-borne encephalitis – 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.”</p> <p>EX 1004 18:17-20: “Based on these models, and what is already known in the field of flavivirus PIVs, extrapolation to human use</p>	
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	<p>is reasonable for safe and effective dosages (e.g., a single dose, or a booster dose at 4 weeks as described below.)”</p> <p>EX 1004 28:19-22: “An “adjuvant” is a substance that serves to enhance, accelerate, or prolong the antigen-specific immune response of an antigen when used in combination with specific vaccine antigens but do not stimulate an immune response when used alone.”</p> <p>EX 1004 42:9-10: Thomas teaches in Example 5. ZIKV PIV Performance in Human Trials for a 5µg dose that “[a]ntibody kinetics based on MN50 titers indicat[ed] a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff”.</p> <p>EX 1004 Table at page 42 Day 1 after prime administration, GMT of 5.0 for N=55 volunteers.</p>	
<p>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.</p>	<p>EX 1004: In Example 5: ZIKV PIV Performance in Human Trials, Thomas teaches a seroconversion rate of 92% for 55 humans at day 57 after a boost administration. A seroconversion rate of 92% is above the claimed 90%. The Table indicates prime administration at day 1 and boost administration at day 29. Day 57 is 28 days after the boost administration.</p> <p>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</p>	

	<p>rates of Trial 2 Group 92%, Trial 1 Group 88%, and Trial 3 Group 100%”.</p> <p>EX 1004 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.</p> <p>EX 1004 4:15-22: “The purified, inactivated ZIKV can be used to immunize mammals (including humans) to elicit high titers of virus neutralizing antibodies and protect the immunized mammal from disease caused by ZIKV. For example, a single immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against challenge with ZIKV. Another example is wherein two doses are administered (e.g., a first dose, followed by a second dose 4 weeks later). A booster dose (second dose or more) may be useful for persons with recurrent infection risk.”</p> <p>EX 1004 7:11: “Booster doses may be used, if needed.”</p> <p>EX 1004 7:30-32: “Ideally, only one dose is needed to effect protection against Zika infection for mammals, including humans.”</p> <p>EX 1004 7:32-8:2. “An exemplary dosage schedule entails an initial dose, then a second (booster) dose about 4 weeks later. However, this schedule is exemplary only, and someone skilled in the art would be able to determine without undue experimentation if and when any second dose is needed.”</p> <p>EX 1004 4:24-28: “With the information known about the dosing and schedule for other PIV flavivirus vaccines – such as</p>	
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	<p>Japanese encephalitis and tick-borne encephalitis – 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.”</p> <p>EX 1004 18:17-20: “Based on these models, and 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, or a booster dose at 4 weeks as described below.)”</p> <p>EX 1004 28:19-22: “An “adjuvant” is a substance that serves to enhance, accelerate, or prolong the antigen-specific immune response of an antigen when used in combination with specific vaccine antigens but do not stimulate an immune response when used alone.”</p> <p>EX 1004 42:9-10: Thomas teaches in Example 5. ZIKV PIV Performance in Human Trials for a 5µg dose that “[a]ntibody kinetics based on MN50 titers indicat[ed] a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff”.</p> <p>EX 1004 Table at page 42 Day 1 after prime administration, GMT of 5.0 for N=55 volunteers.</p>	
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