

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BIONTECH SE and PFIZER INC.,
Petitioner

v.

MODERNATX, INC.,
Patent Owner

Case No.: IPR2023-01358

U.S. Patent No. 10,702,600

RESPONSIVE DECLARATION OF JAMES J. MOON, PH.D.

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I. INTRODUCTION

1. I have been retained by Petitioner as an independent expert consultant in this proceeding before the United States Patent and Trademark Office. I previously submitted a declaration in this proceeding, signed on August 25, 2023, which I understand has been labeled as Exhibit 1004 (my “August 25, 2023 Declaration”).¹

2. I have been asked to provide my responsive analysis to the opinions presented by Dr. Warren Chan in his May 29, 2024 declaration² (the “Chan Declaration”), which I understand has been marked as Exhibit 2198.³ In forming my opinions in this declaration, I have drawn upon my education and experience, as well as any other materials referred to herein.

¹ I also submitted a declaration in the related proceeding, IPR No. 2023-01359, which was likewise marked as Exhibit 1004.

² I understand that Dr. Chan has submitted the same declaration in this proceeding, and the parallel proceeding involving U.S. Patent No. 10,933,127 (IPR2023-01359), which was also marked as Exhibit 2198.

³ While I respond to various statements by Dr. Chan in this responsive declaration, the fact that I do not address any particular statement that Dr. Chan makes should not be taken as my agreement with any such statement(s).

**II. BY OCTOBER 2015, I HAD THE
EDUCATION AND EXPERIENCE OF A
POSA UNDER ANY APPLICABLE DEFINITION**

3. I previously summarized aspects of my educational background and other qualifications in my August 25, 2023 Declaration. (Ex. 1004 at ¶¶ 3-10.) I understand that my curriculum vitae, which provides further details regarding my experience and qualifications, was marked as Exhibit 1005 in this proceeding.

4. I understand that there are two relevant definitions of a person of ordinary skill in the art (“POSA”) with respect to the ’600 patent in this proceeding: one advanced by Petitioner and adopted (as modified) by the Board, and one advanced by Patent Owner. By October 2015, I had the qualifications and experience of a POSA, regardless of the definition applied. Further, my opinions expressed in this declaration, as well as those expressed in my August 25, 2023 Declaration, would remain the same regardless of which POSA definition is applied.

5. As I explained in my previous declaration, I understand that Petitioner has stated that a POSA with respect to the ’600 patent would include a research team with (1) one or more researchers with an advanced degree and experience in the fields of nucleic acids, including RNA-mediated mechanisms and/or nucleic acid therapeutics, gene therapy, and modified mRNA, working with (2) one or more individuals with an advanced degree and experience in drug delivery of

nucleic acid drugs, including lipid-based drug delivery systems, and (3) one or more individuals with an advanced degree and experience in vaccines and/or virology, molecular medicine, and/or infectious diseases. (Ex. 1004 at ¶ 16.)

I further understand that the Board applied this definition in its Institution Decision, clarifying that “[w]here Petitioner’s definition specifies work experience, we consider the duration of such experience to be three or more years.” (Paper 19 (“Institution Decision”) at 32.)

6. By October 2015, I possessed the education and experience of a POSA, as defined above. In particular, I would have been a member of the hypothetical research team having (2) an advanced degree and experience in drug delivery of nucleic acid drugs, including lipid-based drug delivery systems, working with (1) one or more researchers with an advanced degree and experience in the fields of nucleic acids, including RNA-mediated mechanisms and/or nucleic acid therapeutics, gene therapy, and modified mRNA, and (3) one or more individuals with an advanced degree and experience in vaccines and/or virology, molecular medicine, and/or infectious diseases.

7. By 2015, I had already been part of such teams, providing my expertise in delivery as part of research teams that also included subject matter experts in the payload to be delivered, as well as experts in the desired therapeutic outcome to be achieved—much like the hypothetical research team discussed

above. In fact, well before October 2015, I had specific experience delivering nucleic acids as part of a team of scientists, as envisioned by the Board's definition of a POSA. (*E.g.*, Ex. 1151.)

8. I understand that Patent Owner has argued that a POSA would have had an M.D. and/or Ph.D. in immunology, virology, biochemistry, chemistry, or a related discipline, and three or more years of work experience in such fields, and would have been part of a team including biochemists, chemists, drug delivery scientists, and/or clinicians. For the same reasons discussed above with respect to Petitioner's definition adopted as modified by the Board, I met Patent Owner's definition of a POSA by October 2015.

9. I further understand that Patent Owner stated, "Dr. Moon, Petitioner's expert on delivery, is not an expert in the field of nucleic acids or mRNA. Dr. Moon does not have an advanced degree in nucleic acid technology and does not have experience in that field beyond delivery." I am surprised by this criticism, and I disagree with Patent Owner's insinuation that I am not qualified to offer an opinion on the subject matter of this proceeding.

10. I am an expert in the delivery of nucleic acids, including mRNA, making me a POSA under any relevant definition. Much of my professional career has focused on the design and use of delivery mechanisms, which have been used (and continue to be used) to deliver nucleic acids, including in research that I have

conducted and supervised. For example, during my postdoctoral work, I focused primarily on the design and development of nanoparticles for vaccine applications. During this time, I published over 10 scientific articles on the use of nanoparticles, including lipid-based nanoparticles, to deliver vaccines. I designed and developed various nanoparticles, including lipid-based nanoparticles, to deliver immunogens and immunostimulatory agents for vaccination against various pathogens (including malaria sporozoites and HIV) and cancer. I have synthesized various nanoparticle formulations, including lipid-based nanoparticles, and performed in vitro and in vivo studies using such formulations.

11. In 2012, I joined the University of Michigan, Ann Arbor as an Assistant Professor in the Departments of Biomedical Engineering and Pharmaceutical Sciences, where I have since been made a Professor. My research group focuses on nanoparticle drug delivery systems that target organs for the treatment of cancer, infectious diseases, and autoimmune disorders, including vaccines against infectious pathogens. These therapies include the use of proteins, peptides, and nucleic acids (such as mRNA) that require safe delivery to the cells using, for example, lipid nanoparticles.

12. Further, one of my primary research focuses throughout my career has been the use of lipid-based nanoparticles in vaccine applications. In particular, I have developed various novel lipid-based nanoparticles for targeting and delivering

vaccine components to immune cells in lymphoid tissues. My laboratory has demonstrated that lipid nanoparticle-formulated vaccines elicit potent immune responses in various preclinical animal models, including mice and non-human primates. For instance, my laboratory has shown that lipid nanoparticles administered in nonhuman primates can elicit robust immune responses against Simian Immunodeficiency Virus (SIV).

13. It is not clear what additional experience “beyond delivery” Patent Owner is referencing and alleging that a POSA must have, and neither applicable definition appears to require that. I have, and in fact already had as of October 2015, the qualifications of a POSA, and I am qualified to offer the opinions presented in this and my previous declaration.

III. DR. CHAN’S OPINIONS ARE NOT WITHIN HIS EXPERIENCE AND/OR EXPERTISE

14. Unlike my own experience with vaccine compositions, Dr. Chan, by his own admission, does not have such experience. (Ex. 1152 at 101:12-21, 158:14-159:2, 160:2-7.) For instance, Dr. Chan testified that his research in infectious diseases has focused on diagnostics as opposed to vaccines. (Ex. 1152 at 20:10-21:21.) Dr. Chan also testified that he has never developed a vaccine, and that his expertise did not include “the specifics of the mechanism” or “the details” of vaccines:

Q. Dr. Chan, do you know what a vaccine is?

A. I know what a vaccine does, but *the specifics of the mechanism, the details, that is not my area of expertise, right.* My area of expertise is focused on the delivery system. And that's one part. The second part of my expertise is to be able to -- it's how the engineers do these things, which is you measure the outcome of it, right.

(Ex. 1152 at 101:12-21 (emphasis added).)

Q. So you don't know if a vaccine elicits or provokes an immune response; is that right?

A. *Again, I'm focused on the delivery part. That is my expertise, right.*

(Ex. 1152 at 116:11-14 (emphasis added).)

Q. So are you qualified to opine on how vaccines work?

....

A. *Again, I'm a delivery expert, right.* Designing particles, designing formulations, looking at the transport and delivery system, and measuring outcome and being able to evaluate that outcome. *Then I essentially work with collaborators who can provide another part of the equation, right.* This is actually how a lot of academia works nowadays, right.

(Ex. 1152 at 158:14-159:2 (emphasis added).)

15. Despite his limited experience with the development of vaccines, Dr. Chan offers opinions regarding vaccine development and how vaccines elicit an

immune response throughout his Declaration. (Ex. 2198 at ¶¶ 67-73, 180-212.)

For example, Dr. Chan provides opinions on various studies of the immunogenicity of nucleic acid vaccines (Ex. 2198 at ¶¶ 190-96), as well as opinions regarding the purported differences between self-amplifying mRNA vaccines and non-amplifying mRNA vaccines. (Ex. 2198 at ¶¶ 197-207.)

16. Dr. Chan's deposition testimony demonstrated the gap between his experience and the opinions he presents in his Declaration. Specifically, Dr. Chan testified at deposition that he lacked the expertise to discuss opinions expressly provided in his Declaration. For example, Dr. Chan states in his declaration that "*[i]mmunological memory is the basis mechanism of vaccines.*" (Ex. 2198 at ¶ 68.) But during his deposition, Dr. Chan testified that he was not able to provide this same opinion:

Q. Do you agree that *immunological memory is the basis of vaccines*?

A. *No. But, again, you're asking me things that are not in my area of purview – or my expertise.*

(Ex. 1152 at 160:2-7 (emphasis added).)

17. This was not an isolated occurrence. Likewise, Dr. Chan's declaration states that "*beyond the antigenic protein translated from the mRNA, the immunogenicity of every component of the mRNA vaccine may contribute to*

the immunogenicity of the vaccine as a whole.” (Ex. 2198 at ¶ 182.) But when asked whether he agreed with this statement at deposition, Dr. Chan testified that he could not offer the same opinion:

Q. Do you agree that *beyond the antigen[ic] protein translated from the mRNA, the immunogenicity of every component of the mRNA vaccine may contribute to the immunogenicity of the vaccine as a whole?*

...

A. Yes. It's -- so what I mean by that is that the question you're asking is very general, right. The term “immunogenicity,” it's very -- every component is general, right. I can work on specificity. *So if you provide more specific questions, then I can address that, right.*

Q. So you're unable to answer that question, as phrased?

A. As you present it.

(Ex. 1152 at 150:19-151:12 (emphasis added).) Thus, although Dr. Chan offers opinions in his declaration regarding the function of mRNA vaccines and the immune response to vaccines, he was unable to confirm them to be accurate in deposition.

**IV. DR. CHAN DOES NOT DISPUTE THE FACTS
OF MY TECHNOLOGY OVERVIEW AND DOES
NOT ACCOUNT FOR RELEVANT DELIVERY SYSTEMS**

18. As I explained in my August 25, 2023 Declaration, the claims of the '600 patent recite generic compositions comprising mRNA formulated in lipid nanoparticles. (*E.g.*, Ex. 1004 at ¶ 45.) The claims further recite generic compositions of mRNA formulated in lipid nanoparticles, composed of the four well-established lipids known to be used in lipid nanoparticles, at broad ranges of ratios that encompassed lipid nanoparticle formulations known in the prior art.⁴ (*E.g.*, Ex. 1004 at ¶ 45.) To “provide a foundation for better understanding the disclosures related to lipid delivery systems in the '600 patent and prior art,” I included in my previous declaration an overview of the historical evolution of lipid nanoparticle delivery systems and the components thereof, as well as the use of such lipid-based delivery systems to deliver nucleic acids. (Ex. 1004 at ¶¶ 19-44.) That section of my previous declaration was titled, “Technology Overview.”

⁴ In fact, as I discuss below in Section V.B, the lipid nanoparticle formulations actually used in the examples of the '600 patent are a copy of those described in Schrum, which were in turn a copy of those previously disclosed in earlier scientific literature by well-known lipid nanoparticle formulation scientists.

19. Dr. Chan does not dispute the analysis provided in my Technology Overview, and does not identify any aspect of my Technology Overview that he believes to be inaccurate. Instead, Dr. Chan only states in a conclusory manner that “the technology overview section in Dr. Moon’s declaration is indeed far from comprehensive.” (Ex. 2198 at ¶ 37.) Dr. Chan, however, does not identify anything that he believes that I omitted from my discussion of lipid nanoparticle delivery systems.

20. Dr. Chan’s Declaration also includes a technological background section. But Dr. Chan’s “Technology Background” section curiously avoids discussing lipid nanoparticles in any meaningful way, and he does not discuss their development, prominence, or established use for the delivery of nucleic acids. Instead, Dr. Chan’s Technology Background discusses only delivery technologies *other than* lipid nanoparticle delivery systems. (Ex. 2198 at ¶¶ 37-73.) Of the fourteen distinct headings or sub-headings falling within Dr. Chan’s Technology Background section, not one focuses on lipid nanoparticle delivery systems, which were a well-established delivery approach by October 2015, including for the delivery of mRNA and other nucleic acids. (Ex. 1004 at ¶¶ 27-34, 49-122.) Accordingly, while Dr. Chan may identify other known technologies, he does not appear to dispute the information that I previously presented about lipid nanoparticle systems.

21. Further, although Dr. Chan focuses on a number of other delivery technologies in his technological background section, the availability of other delivery technologies is not relevant to whether Schrum discloses a lipid nanoparticle mRNA vaccine. As discussed in my original declaration and below, Schrum expressly instructs the POSA to use lipid nanoparticles as a delivery vehicle for mRNA vaccines. Although this teaching is not questioned, I address the other delivery systems discussed in Dr. Chan's declaration in greater detail in Sections V.C.4 and VI.A.4, and explain why Dr. Chan's analysis was incomplete and inaccurate.

V. SCHRUM DISCLOSES THE USE OF LIPID NANOPARTICLES TO DELIVER MRNA, INCLUDING IMMUNOGEN-ENCODING MRNA (GROUND 1)

A. Schrum Discloses Every Lipid Nanoparticle-Related Limitation of the Challenged Claims

22. In my August 25, 2023 Declaration, I explained that Schrum discloses lipid nanoparticle systems for the delivery of mRNA, including lipid nanoparticle systems containing an ionizable cationic lipid, a neutral lipid, cholesterol, and a PEG-modified lipid within the broad ranges of lipids recited in the asserted claims. (Ex. 1004 at ¶¶ 62-93.) For example, Schrum discloses (and contains specific examples showing) the *in vivo* delivery of mRNA using lipid nanoparticle delivery systems wherein "[t]he LNPs were formulated at a 20:1 weight ratio of total lipid to modified mRNA with a final lipid molar ratio of 50:10:38.5:1.5 (***DLin-KC2-***

DMA:DSPC:Cholesterol:PEG-c-DOMG.” (Ex. 1009 at ¶ 995 (emphasis added).

See also Ex. 1004 at ¶ 68.) These formulations are identical to the lipid nanoparticle formulation utilized in the only examples of the ’600 patent that disclose testing a betacoronavirus vaccine (*see* Section V.B, below).

23. Given these teachings, Dr. Chan has not disputed that Schrum discloses the administration of mRNA formulated in a lipid nanoparticle, and specifically a lipid nanoparticle wherein the lipids are within the ranges of “20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid,” as recited in claims 1, 11, 12, 16, and 26. Schrum plainly teaches these limitations.

B. Schrum Discloses the Very Lipid Nanoparticles Used in the ’600 Patent

24. Dr. Chan also ignores that the only delivery systems used in the ’600 patent for a betacoronavirus vaccine were lipid nanoparticle formulations of the prior art, which further underscores that the lipid nanoparticles used and claimed in the ’600 patent are not novel. In asserting that “[t]he ’600 patent reports data on compositions containing mRNA encoding a betacoronavirus spike protein or spike protein subunit formulated in lipid nanoparticles,” Dr. Chan cites Examples 23 and 24 of the ’600 patent. (Ex. 2198 at ¶ 76.) Those are the only two examples in the ’600 patent that describe making and using a betacoronavirus vaccine (specifically, a MERS vaccine, injected into mice and rabbits). But, those examples purport to

use the very *same lipid nanoparticle formulations* described in Schrum, which Schrum in turn pulled from the prior art.

25. The lipid nanoparticle formulation of Examples 23 and 24 of the '600 patent is described in Example 20, which states that “in experiments where a lipid nanoparticle (LNP) formulation is used”:

[T]he formulation may include a cationic lipid, non-cationic lipid, PEG lipid and structural lipid in the ratios 50:10:1.5:38.5. The cationic lipid is DLin-KC2-DMA (50 mol %) or DLin-MC3-DMA (50 mol %), the non-cationic lipid is DSPC (10 mol %), the PEG lipid is PEG-DOMG (1.5 mol %) and the structural lipid is cholesterol (38.5 mol %), for example.

(Ex. 1001 at 212:47-54.)

26. Accordingly, Examples 23 and 24—to which Dr. Chan points—purport to have used (a) four well-known, generic lipid components (cationic lipid, non-cationic lipid, PEG lipid, and structural lipid); (b) a ratio of the components (50:10:1.5:38.5), and (c) a combination of four specific lipids (DLin-KC2-DMA or DLin-MC3-DMA), DSPC, PEG, and cholesterol.

27. These are the same lipid nanoparticle formulations described in Schrum. For instance, Example 27 of Schrum describes formulating modified mRNA in lipid nanoparticle formulations containing 50 mol % DLin-MC3-DMA, 10 mol % DSPC, 38.5 mol % cholesterol, and 1.5 mol % PEG-c-DOMG.

(Ex. 1009 at ¶¶ 1032-33.) Likewise, Example 16 of Schrum teaches that mRNA

encapsulated in lipid nanoparticle formulations having a “modified mRNA with a final lipid molar ratio of 50:10:38.5:1.5 (DLin-KC2-DMA:DSPC:Cholesterol:Peg-c-DOMG)” achieved efficient expression of the encoded protein *in vivo*. (Ex. 1009 at ¶¶ 995-98.) So, Schrum teaches the same lipid nanoparticle formulations, using the same lipids at the same ratios, as the examples of the ’600 patent.

28. Earlier prior art references had, in fact, already described how the lipid nanoparticle formulations described in Schrum (and later used in the ’600 patent) can be used to deliver nucleic acids. By 2010, the DLin-KC2-DMA-based lipid nanoparticle delivery system had been disclosed in scientific publications. (Ex. 1153 at 1363 (teaching that lipid nanoparticles “were prepared with the ionizable lipid DLin-KC2-DMA, distearylphosphatidyl choline [DSPC], cholesterol, and PEG-DMG . . . [with] a component molar ratio of ~50/10/38.5/1.5 (DLin-KC2-DMA/distearylphosphatidyl choline [DSPC]/cholesterol/PEG-DMG.”).) And by 2012, the DLin-MC3-DMA-based lipid nanoparticle delivery system was also described in scientific publications. (Ex. 1082 at 8533 (teaching the use of lipid nanoparticles “containing the highly potent amino lipid [DLin-MC3-DMA], DSPC, cholesterol and PEG-lipid (50/10/38.5/1.5).”).)

C. Schrum Discloses the Use of Lipid Nanoparticles to Deliver mRNA Vaccines and Directs a POSA to Lipid Nanoparticle Systems

29. Because Dr. Chan cannot dispute that the lipid nanoparticles claimed in the '600 patent were already disclosed in the prior art, Dr. Chan instead argues that “Schrum does not disclose the use of mRNA encoding an immunogen encapsulated in a lipid nanoparticle as a vaccine against a pathogen.” (Ex. 2198 at ¶ 99.)⁵

30. Dr. Chan is mistaken. Schrum teaches formulating immunogen-encoding mRNA in a lipid nanoparticle delivery system for use in a vaccine. (Ex. 1009 at ¶ 397.) Further, Schrum directs a POSA to the delivery of mRNA (including mRNA encoding an immunogen) using lipid nanoparticles throughout the reference, including in its working examples and claims.

⁵ In his Technology Background, Dr. Chan, appears to recognize that a POSA would have been familiar with the use of lipid nanoparticle systems to deliver nucleic acid vaccines. (Ex. 2198 at ¶ 38 (“Researchers were experimenting with many delivery systems that were available to a POSA. Some of them were lipid-based, like lipid nanoparticles.”).)

1. Schrum Teaches the Use of Lipid Nanoparticles to Deliver an mRNA Vaccine

31. Under its “SUMMARY OF INVENTION” heading, as the very first “delivery agent” or “formulation” for the delivery of the “modified nucleic acid” payload, Schrum calls out lipid nanoparticle systems. Schrum teaches that “[i]n one embodiment, the formulation comprising the modified mRNA is a nanoparticle which may comprise at least one lipid.” (Ex. 1009 at ¶ 6.) The disclosed lipid nanoparticle system is made up of the four standard lipid components combined at known molar ratios. (Ex. 1009 at ¶ 8.) As Schrum states, “The formulations of modified mRNA may comprise a fusogenic lipid,⁶ cholesterol and a PEG lipid. The formulation may have a molar ratio 50:10:38.5:1.5-3.0 (cationic lipid: fusogenic lipid: cholesterol: PEG lipid).” (Ex. 1009 at ¶ 8.)

32. Likewise, the first sections of Schrum under the heading, “Formulations,” teach the use of lipid-based systems, including lipid nanoparticle systems, for the delivery of mRNA. (Ex. 1009 at ¶¶ 363, 378.) Within those sections discussing formulations, Schrum teaches that lipid nanoparticles “may be used to improve the efficacy of modified nucleic acid molecules or mmRNA

⁶ As I explained in my earlier declaration, a POSA would understand that the “fusogenic” lipid described in Schrum is a “neutral” lipid. (See Ex. 1004 at ¶ 70 n.11.) Dr. Chan does not disagree.

directed protein production as these formulations may be able to increase cell transfection by the modified nucleic acid molecule or mmRNA; and/or increase the translation of encoded protein.” (Ex. 1009 at ¶ 406.) And of the lipid-based systems described, Schrum teaches that lipid nanoparticle formulations “have about a 10,000-100,000-fold increase in protein production compared to an administration of an intravenous (IV)-lipoplex formulation for the same dosage of modified mRNA.” (Ex. 1009 at ¶ 998.)

33. Schrum further teaches the use of mRNA vaccines to induce an immune response in embodiments where the “encoded protein” of the disclosed mRNA compositions encodes an immunogen. In fact, Schrum provides an entire section devoted to mRNA vaccines, which is the first section of the patent describing uses of the mRNA. (Ex. 1009 at ¶¶ 340-50.)

34. Beyond devoting an entire section to mRNA vaccines, paragraph 397 of Schrum teaches the delivery of immunogen-encoding mRNA vaccines using lipid nanoparticles. Paragraph 397 states that “*an immune response may be elicited* by delivering a lipid nanoparticle which may include a nanospecies, a polymer and an immunogen . . . The immunogen may be a recombinant protein, a modified RNA described herein. In one embodiment, *the lipid nanoparticle may be formulated for use in a vaccine such as, but not limited to, against a pathogen.*” (Ex. 1009 at ¶ 397 (emphasis added).)

35. A POSA would have readily understood that Schrum's disclosure that "*an immune response may be elicited* by delivering a lipid nanoparticle" refers to a lipid nanoparticle-based vaccine composition. In fact, Schrum uses nearly identical language in its discussion of mRNA vaccines. Under the heading, "Activation of the Immune Response: *Vaccines*," Schrum teaches that "[i]n one embodiment of the present invention, *mRNA molecules may be used to elicit or provoke an immune response* in an organism." (Ex. 1009 at ¶ 340 (emphasis added).) Moreover, under the same "Vaccines" heading, Schrum also explains that the mRNA vaccines can "encode an immunogen," consistent with paragraph 397's reference to a modified mRNA *immunogen*. (Ex. 1009 at ¶¶ 342 (emphasis added), 397.) Accordingly, paragraph 397 of Schrum pairs (1) Schrum's disclosure of mRNA vaccines encoding for an immunogen with (2) Schrum's disclosure of formulating mRNA in a lipid nanoparticle system in a straightforward manner.

36. The text of paragraph 397 further makes clear that it contemplates administering mRNA encoding an immunogen, formulated in a lipid nanoparticle, for vaccination. As noted, the first sentence of the paragraph reads, "[i]n one embodiment, *an immune response may be elicited* by delivering *a lipid nanoparticle* which may include a nanospecies, a polymer and an immunogen . . . The immunogen may be a recombinant protein, *a modified RNA described*

herein.” (Ex. 1009 at ¶ 397 (emphasis added).) The paragraph further states that “[i]n one embodiment, *the lipid nanoparticle* may be formulated for use in a *vaccine* such as, but not limited to, against a pathogen.” (Ex. 1009 at ¶ 397 (emphasis added).) That is, the first sentence of paragraph 397 refers to “*a* lipid nanoparticle” while the last sentence refers to “*the* lipid nanoparticle.” A POSA would have understood that Schrum’s use of the term “*the* lipid nanoparticle” as referencing the same lipid nanoparticle previously described—*i.e.*, the lipid nanoparticle encapsulating immunogen-encoding mRNA of the first sentence used to elicit an immune response.

37. Consistent with this interpretation, Dr. Chan also reads Schrum’s reference to “*the lipid nanoparticle*” in paragraph 397 as pointing to a specific lipid nanoparticle formulation:

Q. Now, when it says “the lipid nanoparticle,” which lipid nanoparticle is that referring to in your reading of paragraph 397?

A. So the lipid nanoparticles, the way I interpret this, they use the article “the” in front, right. *It’s “the formulation,” the magic formulation that is involved in that process, right.*

...

I’m just saying if you combine with the article part, right, “the” and “a,” I teach it all the time to my students, that

article is very important in how it describes something.

When I see something is “a” versus “the,” it means very different things, right.

(Ex. 1152 at 186:1-188:8 (emphasis added).)

Q. And would it be a fair reading that “the lipid nanoparticle” in the last sentence is referring to the same lipid nanoparticle that is in the first sentence of paragraph 397?

A. Again, from a semantics perspective, right, in the first one, it says “a lipid nanoparticle,” which means it's not specific, it's a broad range. ***In the last sentence, it says “the.” “The” means it's one. It's the main one. It's the magic one.***

(Ex. 1152 at 186:20-187:7 (emphasis added).)

38. I agree that Schrum’s reference to “the” lipid nanoparticle in the last sentence of paragraph 397 refers to a specific lipid nanoparticle. In the context of paragraph 397, a POSA would understand that “***the*** lipid nanoparticle” used for vaccination “against a pathogen” of the final sentence of paragraph 397 refers back to the lipid nanoparticle formulation in the first sentence of paragraph 397—“a lipid nanoparticle which may include,” among other things, an immunogen-encoding modified mRNA “described herein.”

39. As to the specific lipid nanoparticle formulation to be used for such a vaccine application, Schrum repeatedly points to the lipid nanoparticle made up of 50 mol % ionizable cationic lipid, 38.5 mol % cholesterol, 10 mol % neutral lipid, and 1.5 mol % PEG-modified lipid. (Ex. 1009 at ¶¶ 8, 38, 950, 995, 999, 1027, 1032, 1046, 1050, 1178, 1289, 1294, claim 12.) This four-component lipid nanoparticle formulation described in Schrum is (in Dr. Chan's words) "the main one . . . the magic one" implicated by Paragraph 397's use of the article, "the." (Ex. 1152 at 187:6-7.) A POSA would have therefore understood that Schrum discloses and directs a POSA to the use of such a four-component lipid nanoparticle system for the delivery of immunogen-encoding mRNA to induce an immune response as a vaccine.

40. In his declaration Dr. Chan states that "[a] POSA would have understood that Schrum's ¶ 397 explicitly describes two separate embodiments. The first embodiment is described in all sentences of ¶ 397 except the last sentence. . . . The second embodiment is described in the last sentence only." (Ex. 2198, ¶ 100-01 (emphasis added)). During his deposition, however, Dr. Chan explained that he was unable to testify that paragraph 397 describes alternative embodiments:

Q. Do you understand [paragraph 397] to be alternative embodiments?

A. *That, I don't know.* I'm just saying if you combine with the article part, right, “the” and “a,” I teach it all the time to my students, that article is very important in how it describes something. When I see something is “a” versus “the,” it means very different things, right.

Q. I just want to be clear. It's your opinion that you don't know whether paragraph 397 discloses alternative embodiments, correct?

...

A. Again, you can use all the legal terms. I'm just saying that “a” lipid nanoparticle and “the” may not be linked because “the” just refers to a specific thing, right. It is like the magic formulation. We use that all the time, the term “magic formulation” when we design particle system. When you have “a,” it's “a” something, right, doesn't mean it's “the” something.

(Ex. 1152 at 187:22-188:30 (emphasis added).)

41. With respect to the last sentence in paragraph 397, Dr. Chan also states in his declaration that “[the sentence] does not mention mRNA at all” and contends that “Schrum discloses many different nucleic acids that can be formulated in a lipid nanoparticle.” (Ex. 2198 at ¶ 101.) Dr. Chan’s opinion, however, ignores the fact that the *only* nucleic acid referenced in paragraph 397 is the “modified RNA described herein.” Moreover, Schrum’s vaccine disclosure

itself refers to mRNA. (Ex. 1009 at ¶ 340 (“In one embodiment of the present invention, **mRNA molecules** may be used to elicit or provoke an immune response in an organism. The **mRNA molecules** may encode an immunogenic peptide or polypeptide.”) (emphasis added).)

42. To conclude that “Schrum discloses many different nucleic acids that can be formulated in a lipid nanoparticle,” Dr. Chan points in part to paragraph 22 of Schrum. (Ex. 2198 at ¶ 101.) But at deposition, Dr. Chan could not identify any vaccines that used the nucleic acids in paragraph 22:

Q. So in paragraph 22, there's a number of different types of nucleic acid listed, correct?

A. Yeah.

....

Q. Of those types of nucleic acids listed, are you aware of any of them being used in vaccines against infectious diseases as of 2015?

A. *Again, as I said, I did not pay attention to that part of the equation, right.*

(Ex. 1152 at 127:16-18, 134:14-18 (emphasis added).)

43. Because Schrum teaches mRNA vaccines, a POSA would have understood that Schrum’s statement in paragraph 397 that “the lipid nanoparticle may be formulated for use in a vaccine such as, but not limited to, against a

pathogen” refers to a lipid nanoparticle that encapsulates mRNA. This is further confirmed by the immediate sentence prior, which states that “the immunogen may be a recombinant protein, *a modified RNA described herein*,” (Ex. 1009 at ¶ 397 (emphasis added)), as well as by the examples in Schrum, which use mRNA-loaded lipid nanoparticles as opposed to empty lipid nanoparticles.

**2. Schrum’s Working Examples
Further Direct a POSA to Deliver
mRNA Using a Lipid Nanoparticle System**

44. Schrum’s working examples reinforce its express disclosures of the use of lipid nanoparticle systems to deliver mRNA, including immunogen-encoding mRNA for purposes of vaccination. In these examples, Schrum demonstrates the use of lipid nanoparticle systems to deliver mRNA. In fact, Dr. Chan agreed that “Schrum includes more working examples using lipid nanoparticles than with examples of other carriers.” (Ex. 2198 at ¶ 160.)

45. Despite that, Dr. Chan conspicuously avoids Schrum’s disclosure of lipid nanoparticle technology, and instead concludes that the working examples of Schrum direct a POSA only to “using PLGA for delivery” and “to fibrin as a carrier for mRNA.” (Ex. 2198 at ¶¶ 132, 139.) He includes no such section for lipid nanoparticles, however, despite the wealth of Schrum’s disclosure relating to lipid nanoparticle delivery systems.

46. Dr. Chan never explains why he ignores the examples describing the use of lipid nanoparticle delivery systems, but instead focuses on the delivery approaches described in fewer examples in Schrum (Ex. 2198 at ¶ 119 (“five working examples” of PLGA), ¶ 141 (describing two examples with delivery vehicle, fibrin, one of which (Example 80, Ex. 1009 at ¶¶ 1275-86) also encapsulated mRNA into lipid nanoparticles before mixing with fibrin). By comparison, there are at least twenty-nine examples in Schrum that describe formulating mRNA in lipid nanoparticle delivery systems. (Ex. 1009 at ¶¶ 944-72 (Examples 9-14), 995-1020 (Examples 16-22), 1022-1036 (Examples 24-27), 1046-51 (Examples 29-30), 1089-1100 (Example 37), 1178-81 (Example 55), 1218 (Example 66), 1275-95 (Examples 80-84), 1303-05 (Example 89), 1323-24 (Example 94).) That is, Schrum includes nearly five times as many examples describing the use of lipid nanoparticle systems for mRNA as it does for PLGA and nearly twenty-five times as many examples as compared to fibrin (alone).

47. These examples of Schrum further demonstrate the efficient production of protein using mRNA-loaded lipid nanoparticles as well as the benefits of such lipid nanoparticle systems as compared to other delivery approaches. For instance, Example 16 of Schrum discloses that “the LNP

formulations described above⁷ have about a 10,000-100,000-fold increase in protein production compared to an administration of an intravenous (IV)-lipoplex formulation for the same dosage of modified mRNA.” (Ex. 1009 at ¶ 998.) And, other examples of Schrum demonstrate efficient expression of the encoded protein when mRNA was delivered via lipid nanoparticle systems in vivo, including in rats (e.g., Example 17, ¶¶ 1000-01), non-human primates (e.g., Examples 21-22, ¶¶ 1010-20), and mice (e.g., Example 27, ¶¶ 1031-36). Again, each of these

⁷ The lipid nanoparticles of Example 16 were “formulated at a 20:1 weight ratio of total lipid to modified mRNA with final lipid molar ratio of 50:10:38.5:1.5 (DLin-KC2-DMA:DSPC:Cholesterol:Peg-c-DOMG).” (Ex. 1009 at ¶ 995.) This is the same lipid nanoparticle formulation as one of the two formulations used in the examples of the ’600 patent for a betacoronavirus vaccine. (See Ex. 1001 at 212:47-54 (“In experiments where a lipid nanoparticle (LNP) formulation is used, the formulation may include a cationic lipid, non-cationic lipid, PEG lipid and structural lipid in the ratios 50:10:1.5:38.5. The cationic lipid is DLin-KC2-DMA (50 mol %) or DLin-MC3-DMA (50 mol %), the non-cationic lipid is DSPC (10 mol %), the PEG lipid is PEG-DOMG (1.5 mol %) and the structural lipid is cholesterol (38.5 mol %).”).)

examples used a four-component lipid nanoparticle at the same 50:10:38.5:1.5 molar ratios (i.e., 50 mol % ionizable cationic lipid, 10% DSPC, 38.5 mol % cholesterol, and 1.5 mol % PEG-lipid) that I have previously discussed. (e.g. Ex. 1009 at ¶¶ 999-1000 (Example 17), 1010-12 (Examples 21-22), 1032 (Example 27).)

48. Providing at least twenty-nine examples using lipid nanoparticles and additional disclosures in the specification, Schrum directs a POSA to the use of such a delivery system for the administration of mRNA, including immunogen-encoding mRNA. (Ex. 1009 at ¶ 397.)⁸

⁸ I disagree with Dr. Chan's conclusion that the examples of Schrum involving lipid nanoparticles should be discounted because they do not "involve[] an mRNA vaccine." (Ex. 2198 at ¶ 160.) As the Board noted, correctly, "Schrum's disclosure of provoking an immune response by administering mRNA encoding an antigen (i.e., a vaccine) is consistent with and supported by its disclosure of administering mRNA encoding a therapeutic protein. In both cases, administration of mRNA causes cells to produce a desired protein." (Decision at 47 (citations omitted).) Tellingly, Dr. Chan also relies on examples in Schrum that do not involve an mRNA vaccine in his own opinions about other delivery systems. (e.g.,

3. Schrum's Claims Reinforce Its Disclosure of Delivering mRNA Using a Lipid Nanoparticle System

49. Dr. Chan cites the claims included in the Schrum publication as a reason a POSA would look to a PLGA microsphere formulation. In particular, Dr. Chan writes, “Based on the detailed and extensive disclosure of using PLGA to formulate mRNA, claims 15-27 of Schrum are directed to PLGA formulations.” (Ex. 2198 at ¶ 127.) Again, he includes no such discussion for lipid nanoparticle systems.

50. The fact that Schrum has claims that recite PLGA formulations has no bearing on whether it also teaches the claimed lipid nanoparticle formulations, and a POSA would recognize that it does so; Schrum as a whole discloses and points to lipid nanoparticle formulations, independently of its inclusion of PLGA formulations. But in any event, Dr. Chan ignores the fact that far more claims—twenty-three claims in total—of Schrum are directed to lipid nanoparticle delivery systems than to PLGA formulations.⁹ These claims are:

Ex. 2198 at ¶¶ 119-26 (citing examples using PLGA microspheres loaded with mRNA encoding reporter or therapeutic proteins).)

⁹ Dr. Chan's reading of the claims is also incorrect. (Ex. 2198 at ¶ 127.) Dr. Chan states that “claims 15-27 of Schrum are directed to PLGA formulations.”

3. The method of claim 1, wherein the formulation comprising the modified mRNA is a nanoparticle and wherein said nanoparticle comprises at least one lipid.
4. The method of claim 3, wherein the lipid is selected from the group consisting of DLin-DMA, DLin-K-DMA, 98N12-5, C12-200, DLin-MC3-DMA, DLin-KC2-DMA, DODMA, PLGA, PEG, PEG-DMG and PEGylated lipids.
5. The method of claim 3, wherein the lipid is cationic lipid.
6. The method of claim 5, wherein the cationic lipid is selected from the group consisting of DLin-DMA, DLin-K-DMA, DLin-MC3-DMA, DLin-KC2-DMA, and DODMA.
7. The method of claim 3, wherein the lipid to modified mRNA weight ratio is between 10:1, and 30:1.

(Ex. 2198 at ¶ 127.) But claim 25 is a further dependent claim from claim 11, which recites a lipid nanoparticle formulation, and therefore is likewise directed to lipid nanoparticles. Further, claims 26 and 27, which depend upon claim 25, equally are directed to lipid nanoparticle formulations. Claims 25-27 are not, therefore, directed to PLGA formulations as Dr. Chan states.

8. The method of claim 7, wherein the mean size of the nanoparticle formulation comprising the modified mRNA is between 60-225 nm.

9. The method of claim 8, wherein the PDI of the nanoparticle formulation comprising the modified mRNA is between 0.03 and 0.15.

10. The method of claim 3, wherein the zeta potential of the lipid is from -10 to +10 at a pH of 7.4

11. The method of claim 7, wherein the nanoparticle formulation comprising the modified mRNA further comprises a fusogenic lipid, cholesterol, and a PEG lipid.

12. The method of claim 11, wherein the nanoparticle formulation comprising the modified mRNA has a molar ratio of 50:10:38.5:1.5-3.0 (Cationic Lipid: fusogenic lipid:Cholesterol:PEG-lipid).

13. The method of claim 12, wherein the PEG lipid is selected from PEG-c-DOMG and PEG-DMG and the fusogenic lipid is DSPC.

25. The method of claim 11, wherein said mammalian cells or tissues occurs via a route of administration selected from the group consisting of intravenous, intramuscular, intravitreal, intrathecal, intratumoral, pulmonary, and subcutaneous.

26. The method of claim 25, wherein the polypeptide of interest is detectable in the serum for up to 72 hours after contacting at levels higher than the levels prior to contacting.

27. The method of claim 26, wherein the polypeptide of interest is detectable in the serum of female subjects at levels greater than in the serum of male subjects.

30. The method of claim 1, wherein the formulation comprising the modified mRNA comprises a rapidly eliminated lipid nanoparticle.

31. The method of claim 30, wherein the rapidly eliminated lipid nanoparticle comprises an reLNP lipid, fusogenic lipid, cholesterol and a PEG lipid at a molar ratio of 50:10:38.5:1.5 (reLNP Lipid:Fusogenic lipid:Cholesterol:PEG lipid).

32. The method of claim 31, wherein the fusogenic lipid is DSPC and the PEG lipid is PEG-c-DOMG.

33. The method of claim 31 wherein the reLNP lipid is selected from the group consisting of DLin-DMA with an internal ester, DLin-DMA with a terminal ester, DLin-MC3-DMA with an internal ester, and DLin-MC3-DMA with a terminal ester.

34. The method of claim 30, wherein the total lipid to modified mRNA weight ratio is between 10:1 and 30:1.

51. The method of claim 25 or 50, wherein said polypeptide of interest is produced in said cell or tissue in a location systemic from the location of contacting.

52. The method of claim 51, wherein the route of administration is either via intramuscular or subcutaneous.

53. The method of claim 3, wherein the lipid nanoparticle formulation is further formulated in a sealant.

54. The method of claim 53, wherein said sealant is a fibrin sealant.

(Ex. 1009 at p. 197-98.)

51. The twenty-three claims of Schrum excerpted above are directed to the use of lipid nanoparticles to deliver modified mRNA. By comparison, correcting for Dr. Chan's mistake with respect to claims 25-27 (addressed in footnote 13), only ten claims of Schrum (claims 15-24) refer to the use of PLGA microsphere formulations. Thus, applying Dr. Chan's own reasoning that the claims of Schrum direct a POSA to the claimed delivery approach (Ex. 2198 at ¶ 127), the claims of Schrum, in fact, direct a POSA to lipid nanoparticles.

4. The Other Delivery Approaches Identified by Dr. Chan Do Not Detract from Schrum's Disclosure of Lipid Nanoparticles as a Delivery Vehicle for mRNA Vaccines

52. As I explain above, Schrum expressly directs a POSA to deliver an mRNA vaccine using lipid nanoparticles. Rather than addressing the lipid

nanoparticles in Schrum, Dr. Chan's Declaration focuses on several other delivery mechanisms for nucleic acids. Schrum's other teachings (as well as those of Geall) do not detract from its lipid nanoparticle-related disclosures.

i) Delivery Mechanisms Disclosed in Schrum

53. In his Declaration, Dr. Chan states that "Schrum discloses a wide range of carriers for delivery of nucleic acids." (Ex. 2198 at ¶ 106.) But as I explain above, Schrum specifically teaches a POSA to deliver mRNA vaccines in lipid nanoparticles. The availability of other delivery mechanisms does not detract from Schrum's express lipid nanoparticle-related teachings, including that "an immune response may be elicited by delivering a lipid nanoparticle" and "the lipid nanoparticle may be formulated for use in a vaccine." (Ex. 1009 at ¶ 397.)

54. In his declaration, Dr. Chan points to scientific papers and patent documents cited in Schrum for the proposition that "Schrum again broadly directs the POSA to many potential available carriers." (Ex. 2198 at ¶ 108.) For instance, Dr. Chan points to Geall 2012 (Ex. 2021). (Ex. 2198 at ¶ 109.) That reference, however, teaches in its abstract that "nonviral delivery of a 9-kb self-amplifying RNA [vaccine encoding an infectious disease immunogen] *encapsulated within an LNP substantially increased immunogenicity compared with delivery of unformulated RNA.*" (Ex. 2021 at 14604 (emphasis added).) So, if a POSA were to consider the literature cited by Schrum, as Dr. Chan suggests, they would only

be further directed to lipid nanoparticle systems, particularly in view of Schrum's disclosures that I have discussed above.

55. As I have noted, Dr. Chan asserts that a POSA would have focused on PLGA/PLGA microspheres and fibrin as delivery mechanisms for a vaccine. (Ex. 2198 at ¶¶ 114-38 (discussing PLGA formulations), ¶¶ 139-45 (discussing fibrin formulations).) Schrum, however, does not expressly identify either material as a delivery mechanism for an mRNA vaccine by name, as it does for lipid nanoparticles. Aside from a general discussion of PLGA, Dr. Chan identifies only five examples in Schrum that use PLGA, none of which provide *in vivo* results. (Ex. 2198 at ¶¶ 120-26.) By comparison, Schrum tests lipid nanoparticles encapsulating mRNA in more than two-dozen examples and using at least three different *in vivo* animal models—each of which confirms that lipid nanoparticles are an effective delivery vehicle for mRNA. (*Supra* Section V.C.2.)

56. In his Declaration, Dr. Chan also cites to an expert review paper that I co-authored titled “Biomaterials for Nanoparticle Vaccine Delivery Systems.” (Ex. 2198 at ¶ 135.) In that paper, I provide an overview of nanoparticle vaccine carriers, including PLGA. As I explain in my review article, however, “PLGA particles have been utilized to deliver *a wide range of protein and peptide antigens*.” (Ex. 2077 at 2572 (emphasis added).) In other words, my article discusses using PLGA to deliver protein antigens, not mRNA.

57. With respect to fibrin, Dr. Chan is similarly unable to identify any disclosure in Schrum to suggest the use of fibrin to deliver an mRNA vaccine. Dr. Chan identifies only two examples of fibrin in Schrum, both of which relate to *in vitro* testing with reporter proteins (luciferase), and one of which ***also used a lipid nanoparticle system***. (Ex. 2198 at ¶¶ 139-45; Ex. 1009 at ¶¶ 1275-86 (Example 80 describing use of lipid nanoparticles).)

ii) Delivery Mechanisms Disclosed in Geall

58. Additionally, Dr. Chan points to Geall (Ex. 1010) as disclosing additional potential delivery approaches for an mRNA vaccine. (Ex. 2198 at ¶ 146.) With respect to Geall, Dr. Chan states that Geall points to “(i) liposomes, (ii) non-toxic and biodegradable polymer microparticles, and (iii) cationic submicron oil-in-water emulsions.” (Ex. 2198 at ¶ 146.) As a preliminary matter, Dr. Chan does not suggest that Geall’s disclosure of additional nucleic acid delivery systems would somehow negate Schrum’s instruction to formulate a vaccine using lipid nanoparticles. (*See* Ex. 1009 at ¶ 397.)

59. To the extent a POSA would have looked to the delivery systems disclosed in Geall, it would have only confirmed Schrum’s disclosure that lipid

nanoparticles are a suitable delivery vehicle for mRNA vaccines.¹⁰ Using three different animal models, Geall determined that liposomes, which are a type of lipid nanoparticle (i.e., particles made of lipids that are nanosized), were highly effective for delivering a self-amplifying mRNA vaccine. In the mouse model, Geall “confirmed that the 0.1µg of liposome-encapsulated RNA gave much higher anti-F IgG responses (15 days post-second dose) than 0.1µg of delivered DNA, and even was more immunogenic than 20µg plasmid DNA encoding the F antigen, delivered by electroporation.” (Ex. 1010 at 35:3-6.) In rats, “liposome encapsulation increased F-specific IgG titers by 8.3-fold compared to naked RNA and increased PRNT titers by 9.5-fold.” (Ex. 1010 at 35:7-9.) The results reported in Geall

¹⁰ Although Geall calls the lipid formulations “liposomes,” the formulations have the same components as the formulations referred to as lipid nanoparticles in the ’600 patent, as they consist of an ionizable cationic lipid (40% DlinDMA), cholesterol (48%), a phospholipid (10% DSPC), and a PEG-lipid (2% PEG-conjugated DMG). (E.g., Ex. 1004 at ¶¶ 56-57.) The formulation was also synthesized using a well-understood process for making liposomes, which are a type of lipid nanoparticle, in which the lipids were dissolved in ethanol and mixed with the RNA using a T-mixer. (Ex. 1010 at 31:4-32:16 (describing methods of “[l]iposomal encapsulation”).)

therefore would have reinforced Schrum's instruction to use lipid nanoparticles to deliver an mRNA vaccine.

D. Dr. Chan Ignored Schrum's Disclosures of mRNA Formulated in Lipid Nanoparticle Delivery Systems

60. In his declaration, Dr. Chan writes that "a POSA reading Schrum would have no reason to focus on the combination of mRNA and LNP." (Ex. 2198 at ¶ 160.) In reaching this conclusion, however, Dr. Chan simply discounted Schrum's teachings of lipid nanoparticles in favor of considering only what he considered to be the "focus" of Schrum. A POSA would not do so, and would instead consider all of the teachings of Schrum, including its significant teachings regarding lipid nanoparticle systems.

61. Dr. Chan's deposition testimony confirms that he did not consider Schrum for all that it teaches, as a POSA would have done:

Q. [S]o is your opinion as expressed in your declaration focused on what the patent is as a whole?

A. *It is focused on the contextual nature of the patent, right.*

Q. And so you didn't analyze the specific examples in the patent?

A. Again, when you read any kind of document, you understand what the document is about and then you focus on that and you also look in the details of things, but you

essentially have to look at the contextual nature of what is presented to you.

Because if you don't do that, then you write – any kind of document, this is – I tell my students this all the time, *you write things that are not relevant to what is really the main point of what is presented to you.*

(Ex. 1152 at 65:2-20 (emphasis added).)

62. Dr. Chan used this procedure of limiting his review of Schrum to his (faulty) interpretation of Schrum's "focus" as the basis of his opinion that a POSA "*would not look at*" Schrum's disclosure of lipid nanoparticle delivery systems.

(Ex. 1152 at 56:17-18.) For example, he testified:

Q. In your view, does Schrum disclose an mRNA vaccine against betacoronavirus?

...

A. So when I actually read this – let me just go through.

So when I actually read through this particular patent [*i.e.*, Schrum] the first time, and even all the subsequent times afterwards, right – I just want to go to the first page – *I had a certain impression of this particular – this particular patent, right.*

And *my impression of this patent is actually a polymer PLGA nanoparticle, microparticle patent*, right, that was focused on protein replacement therapy.

Q. So you understand my question is not what the patent is focused on, right?

A. I understand, right, but I'm just telling you, like, as a POSA, right, in this area, when I look at this particular patent, I am – *to me, it is a polymer – PLGA polymer patent* with little sprinkles of different things inside. But *I would not look at these other things, right.*

(Ex. 1152 at 55:17-56:18 (emphasis added).)

63. By constantly referring back to his assertion of “focus,” Dr. Chan avoided answering whether or not Schrum disclosed mRNA formulated in a lipid nanoparticle delivery system and the use of such systems for vaccination:

Q. Are there examples of lipid nanoparticles in Schrum?

A. There are contextual – I'm providing an answer for you based on the contextual nature of what is the main focus of this particular patent [*i.e.*, Schrum], right.

The main focus of this particular patent is the polymer, fibrin, controlled-release system and for protein replacement therapy.

(Ex. 1152 at 63:13-63:21 (emphasis added).)

64. Dr. Chan does not address the extensive disclosure of lipid nanoparticles in Schrum because, he admits, he did “not look at these other things [*i.e.*, lipid nanoparticles].” Moreover, his attempt to dismiss Schrum's disclosure

of lipid nanoparticles as only a “*little sprinkle*[]” within a “PLGA polymer patent” (Ex. 1152 at 56:14-17 (emphasis added)) entirely fails to apply Schrum’s extensive disclosures regarding lipid nanoparticle systems. Even if a POSA was to consider only the “focus” of Schrum, it is my opinion that Schrum focuses primarily on lipid nanoparticle delivery systems for the reasons discussed above. And unlike Dr. Chan, I have reviewed the entirety of Schrum from the perspective of a POSA, and have explained its disclosures and teachings based on Schrum itself. (Ex. 1004 at ¶¶ 50-53, 58-93.)

VI. A POSA WOULD HAVE HAD GOOD REASON TO APPLY SCHRUM’S TEACHINGS AND WOULD REASONABLY EXPECT TO SUCCESSFULLY DO SO (GROUNDS 2-4)

65. As I explained in my August 25, 2023 Declaration, Schrum (as well as Geall) discloses the use of lipid nanoparticles, specifically lipid nanoparticles containing a cationic lipid, neutral lipid, cholesterol, and PEG-modified lipid (within the broad ratios recited in the claims of the ’600 patent) for the delivery of nucleic acids, including mRNA. (E.g., Ex. 1004 at Sections IX-X.) And as I previously noted, I understand that Dr. Griffin has concluded that the prior art—specifically Schrum in view of Geall, Yang, or Altmeyer—discloses the remaining limitations of the challenged claims, including the use of mRNA encoding a betacoronavirus spike protein for vaccination.

66. In his declaration, Dr. Chan opines that a POSA would not be motivated to combine these disclosures of the prior art to arrive at the claimed compositions with a reasonable expectation of success. (Ex. 2198 at ¶ 196.) More specifically, Dr. Chan opines that “a POSA, based on Schrum and Geall¹¹, would not have been motivated to deliver an mRNA vaccine, let alone BetaCoV S protein mRNA in particular, using lipid nanoparticles with [a] reasonable expectation of success.” (Ex. 2198 at ¶ 196.)

67. I disagree. Based on the teachings of the prior art, including those of Schrum itself, a POSA would have good reason to formulate immunogen-encoding mRNA—such as a betacoronavirus spike protein-encoding mRNA—in a lipid nanoparticle delivery system. Particularly, a POSA would have good reason to formulate immunogen-encoding mRNA using a known four-component lipid nanoparticle formulation falling within the broad lipid ranges claimed in the ’600 patent, using well-known methods of manufacture. While the claims refer only to

¹¹ Dr. Chan groups together his analysis for all of Grounds 2-4, predominantly “incorporat[ing] all of [his] opinions from Section VIII (for Ground 2) here with respect to Ground 3,” as well as “with respect to Ground 4.” (Ex. 2198 at ¶¶ 209, 212.) Therefore, my discussion in this section in response to Dr. Chan’s analysis of Ground 2 relates equally to Grounds 3 and 4.

a composition, I note that Dr. Chan argues that a POSA “would not have been motivated to deliver a mRNA vaccine . . . using lipid nanoparticles with reasonable expectation of success.” (Ex. 2198 at ¶ 196.) I disagree; a POSA would reasonably expect to successfully encapsulate the immunogen-encoding mRNA in a lipid nanoparticle system and to use such a formulation for vaccine applications to induce an immune response.

**A. A POSA Would Have Been Motivated
to Formulate Immunogen-Encoding mRNA in
a Lipid Nanoparticle Delivery System by October 2015**

**1. A POSA Would Have Been Motivated to Use
Lipid Nanoparticles Based on the Disclosure in Schrum**

68. Consistent with his approach discussed above with respect to Ground 1, Dr. Chan fails to consider Schrum’s teachings in concluding that “[a] POSA, based on Schrum and Geall, would not have been motivated to deliver a mRNA vaccine, let alone BetaCoV S protein mRNA in particular, using lipid nanoparticles.” (Ex. 2198 at ¶ 196.) Instead, Dr. Chan repeats that “Schrum and Geall both present various options of carrier systems in addition to multiple nucleic acids” without considering the full teachings of Schrum. (Ex. 2198 at ¶ 164.) Dr. Chan’s failure to analyze Schrum’s teachings is consistent with his deposition testimony that “he would not look at” the express disclosures of the reference with respect to lipid nanoparticles. (Ex. 1152 at 55:17-56:18.)

69. Contrary to Dr. Chan’s analysis, I understand that the motivation to combine prior art teachings can come from the prior art references (i.e., such as from Schrum), themselves. And, as I have discussed at length in this and my previous declaration, Schrum provides ample teachings regarding the use of lipid nanoparticle systems for the delivery of mRNA, including for vaccine applications. (*Supra*, Section V.)

70. Schrum’s disclosure would have motivated a POSA to formulate mRNA (including immunogen-encoding mRNA) in the disclosed four-component lipid nanoparticle systems. As I noted above with respect to Ground 1, Schrum expressly teaches the use of lipid nanoparticle systems for the delivery of immunogen-encoding mRNA. Schrum discloses, “In one embodiment, an immune response may be elicited by delivering a lipid nanoparticle which may include . . . an immunogen.” (Ex. 1009 at ¶ 397.) Schrum identifies such “immunogen” as, inter alia, “a modified RNA described herein.” (Ex. 1009 at ¶ 397.) Consistent with Schrum’s explanation that “mRNA molecules may be used to elicit or provoke an immune response in an organism” as a vaccine, Schrum teaches that a “lipid nanoparticle may be formulated for use in a vaccine, such as, but not limited to, against a pathogen.” (Ex. 1009 at ¶¶ 340, 397.)

71. Schrum’s other teachings reinforce its express disclosures of lipid nanoparticle-mRNA vaccines. As I explained in my August 25, 2023 Declaration,

it was well-known by 2015 that exogenous nucleic acids, including immunogen-encoding mRNA molecules, are vulnerable to rapid degradation in the body and may be too large and/or negatively charged to cross the cellular membrane and be taken up by the cell. (Ex. 1004 at ¶ 20.) Protection of mRNA during circulation in the body and efficient delivery of the mRNA to the cell are necessary for a therapeutic indication, including vaccines. (Ex. 1004 at ¶ 20.) Schrum teaches that formulating mRNA in lipid nanoparticle systems may achieve both of those goals. (Ex. 1009 at ¶ 406 (“[L]ipid nanoparticles may be used to improve the efficacy of modified nucleic acid molecules or mmRNA directed protein production as these formulations may be able to increase cell transfection by the modified nucleic acid molecule or mmRNA .. [, and] may also be used to increase the stability of the modified nucleic acid molecules or mmRNA.”).)

72. Moreover, Schrum’s teachings provide a POSA with good reason to utilize a lipid nanoparticle delivery system with components within the broad ranges of 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid (as required by claims 12, 16, and 26), specifically, for the delivery of immunogen-encoding mRNA. Schrum concludes that “the LNP formulations [having 50 mol % ionizable cationic lipid, 10% neutral lipid, 38.5 mol % cholesterol, and 1.5 mol % PEG-modified lipid, i.e., the same formulations found in the examples of the ’600 patent] have

about a 10,000-100,000-fold increase in protein production compared to an administration of an intravenous (IV)-lipoplex formulation for the same dosage of modified mRNA.” (Ex. 1009 at ¶ 998.) A POSA would readily recognize that achieving such an increase in the protein expression achieved by mRNA administration would be a significant benefit, as increased immunogen expression could, in turn, improve vaccine performance. A number of additional examples in Schrum rely upon this same four component (combined at the same molar ratios) lipid nanoparticle formulation to achieve efficient protein expression in vivo. (Ex. 1009 at ¶¶ 1027 (Example 26), 1039 (Example 27), 1046 (Example 29), 1050 (Example 30), 1090 (Example 37).)

73. Based on these teachings, Schrum provides good reason to formulate immunogen-encoding mRNA, including betacoronavirus spike protein-encoding mRNA, in a lipid nanoparticle delivery system.

2. The Extensive Use of Lipid Nanoparticle Delivery Systems for the Delivery of Nucleic Acids Would Further Motivate a POSA to Use Such Systems for the Delivery of Immunogen-Encoding mRNA

74. Dr. Chan alleges that my earlier declaration, “and indeed all papers from the Petitioners, ignore the state of the art around the priority date of the ’600 patent.” (Ex. 2198 at ¶ 179.) It is Dr. Chan’s declaration, however, that does not address the decades of experience using lipid nanoparticle systems, including for the delivery of mRNA. Instead, the true “state of the art” provides further

motivation, in addition to Schrum's teachings, to use such systems for the delivery of immunogen-encoding mRNA.

75. As I explained in my August 25, 2023 Declaration, the use of nanosized lipid particles to deliver mRNA dates back as early as 1978, nearly forty years before the October 2015 provisional date of the '600 patent. (Ex. 1004 at ¶ 29.) That year, it was demonstrated that "[t]he use of liposomes enables encapsulated mRNA to be inserted into large numbers of cells, as well as cell types." (Ex. 1054 at 923.)

76. This 1978 study launched decades of further development dedicated to the use of nanosized lipid particles to deliver nucleic acids. And by 2015, four-component lipid nanoparticle systems had been used to efficiently deliver a variety of nucleic acid payloads, including antisense oligonucleotides, siRNA, plasmid DNA, self-amplifying mRNA, and non-amplifying mRNA. (Ex. 1084 at 153-54 (2001 publication describing use of four-component lipid nanoparticle systems to deliver antisense oligonucleotides); Ex. 1154 at 364 (2005 publication describing encapsulation of plasmid DNA in four-component lipid nanoparticle systems); Ex. 1082 at 8533 (2012 publication describing use of four component lipid nanoparticle systems to deliver siRNA); Ex. 2021 (2012 publication describing use of four-component lipid nanoparticle system to deliver self-amplifying mRNA

vaccine); Ex. 1009 (Schrum describing four-component lipid nanoparticle systems for delivery of modified mRNA).)

77. Further, by 2015, it was known that four-component lipid nanoparticle systems significantly improved the immunogenicity of RNA vaccines. For instance, Geall et al. published in 2012¹² that “nonviral delivery of a 9-kb self-amplifying RNA encapsulated within an LNP substantially increased immunogenicity compared with delivery of unformulated RNA.” (Ex. 2021 at 14604.) Underlying the “substantially increased immunogenicity” achieved by the immunogen-encoding RNA vaccines of Exhibit 2021 was the finding that the lipid

¹² I understand that Patent Owner’s own scientists have described Exhibit 2021 as “the first study that established amino lipid based LNPs (which had been optimized specifically for siRNA delivery to the liver) form stable particles with mRNA and effectively release the mRNA for protein translation in vivo.” (Ex. 2049 at MOD_000773688.) [REDACTED]

[REDACTED]

[REDACTED]

nanoparticle systems¹³ “protected the RNA from degradation by RNase A” and allowed “for efficient delivery of functional RNA into muscle.” (Ex. 2021 at 14605.) Similarly, in 2013, Hekele et al. showed that an RNA vaccine encoding a different infectious disease immunogen—the influenza hemagglutinin protein—achieved “significantly higher” antibody titers when formulated in a four-component lipid nanoparticle system as compared to “those elicited by the same dose of unformulated” RNA. (Ex. 1138 at 5.)

78. Armed with the knowledge that nanosized lipid particle systems had been used to deliver nucleic acids for decades, a POSA would recognize that immunogen-encoding mRNA (like betacoronavirus spike protein-encoding mRNA) must be protected from degradation during circulation and must be efficiently delivered into the body. The state of the art, in addition to Schrum, teaches that lipid nanoparticle delivery systems achieve these goals. (Ex. 2021 at 14605.) Moreover, by October 2015, lipid nanoparticle systems were already in clinical use for the delivery of RNA, which Dr. Chan grants would have made a

¹³ The lipid nanoparticle systems of Exhibit 2021 were made up of 40% ionizable cationic lipid, 10% neutral lipid, 48% cholesterol, and 2% PEG-modified lipid. (Ex. 2021 at 14605.) That is, Geall et al. described the use of lipid nanoparticles falling with the broad ranges claimed in the '600 patent.

POSA “even more confident with the safety and potential efficacy of these systems.” (Ex. 2198 at ¶ 38; Ex. 1156 (2013 article describing clinical trial using lipid nanoparticles to deliver nucleic acid to humans, specifically siRNA).) This history—the “state of the art,” as Dr. Chan states—would therefore reinforce Schrum’s teachings of formulating mRNA in lipid nanoparticle systems, including for vaccination.

3. Dr. Chan’s Opinions Fail to Account for a POSA’s Ordinary Creativity

79. In forming his opinion that “[a] POSA, based on Schrum and Geall, would not have been motivated to deliver a mRNA vaccine, let alone BetaCoV S protein mRNA in particular, using lipid nanoparticles,” Dr. Chan again fails to accurately apply a POSA’s approach. (Ex. 2198 at ¶ 196.)

80. Dr. Chan’s deposition testimony demonstrated that, in forming his opinions, he presumed a POSA would simply read the words on the page of a prior art reference without any analysis or creativity. He testified:

As an expert, and as a scientist, as a researcher, at any level, *you read what is given to you and you do what is given to you*, right. You do not speculate because if you start to speculate beyond this, you create problems, right.

(Ex. 1152 at 78:10-15 (emphasis added).) Dr. Chan’s approach is not consistent with that of a POSA. But even if Dr. Chan’s approach to reviewing the prior art

was correct, a POSA would still have good reason to utilize lipid nanoparticle systems for the delivery of immunogen-encoding mRNA, as Schrum expressly instructs the POSA to do so in paragraph 397.

81. In any event, contrary to Dr. Chan's suggestion, a POSA would have been able to connect basic scientific concepts, such as the fact that vaccines are used to elicit an immune response. (Ex. 1009 at ¶ 340 (Activation of the Immune Response: Vaccines . . . In one embodiment of the present invention, mRNA molecules may be used to elicit or provoke an immune response in an organism.”).) Dr. Chan, however, argues that a POSA would not be capable of even this basic inference:

Q. And do you see the first sentence [of paragraph 397 of Schrum] says, “In one embodiment, an immune response may be elicited by delivering a lipid nanoparticle,” right?

A. Sure.

Q. So in the first sentence, Schrum is discussing the use of a lipid nanoparticle to elicit an immune response, right?

. . .

A. It states that an immune response may be elicited by delivering a lipid nanoparticle. Blah, blah, blah.

Q. Now, do you understand the first sentence of Schrum to be describing the use of a lipid nanoparticle in a vaccine?

A. It says, “an immune response may be elicited by delivering a lipid nanoparticle.”

Q. And you agree that in order to – *one reason why you would elicit an immune response is to make a vaccine, right?*

...

A. Again, *it just states an immune response may be elicited by delivering a lipid nanoparticle.* Then it describes the lipid nanoparticle may include a nanospecies, polymer, or immunogen.

...

[Q.] So you’re not aware of why a POSA would elicit an immune response using a lipid nanoparticle?

A. So, again, if I’m a POSA, *I just read directly what is written down here, right. And what is written down is, you know, there’s some words, right.* Immune response may be elicited by delivering a lipid nanoparticle, right.

Q. So a POSA would not – is it your opinion that a POSA would not understand why you would use a lipid nanoparticle to elicit an immune response?

A. *A POSA would just read this and look at the sentence, right.* And the sentence just says, “An immune response may be elicited by delivering a lipid nanoparticle.” And it

essentially provides that lipid nanoparticle may include a nanospecies, a polymer, and an immunogen.

Q. So it's your opinion that a POSA would read the words on a page and not make any interpretations beyond what is in the words on the page, right?

...

A. Yeah. They just read the words. A POSA, which I can tell you, I teach my students is – read the words, right.

(Ex. 1152 at 179:16-182:13 (emphasis added).)

82. I disagree with Dr. Chan that a highly educated and experienced POSA, with the qualifications of either the Board's definition or Dr. Chan's definition would be unable to recognize that "an immune response may be elicited by delivering a lipid nanoparticle" plainly refers to the use of lipid nanoparticles in a vaccine, particularly in view of Schrum's disclosures of mRNA vaccines and the history of use of lipid nanoparticle systems for the delivery of nucleic acids, as I discuss above.

**4. Other Delivery Systems Cited by
Dr. Chan Would Not Dissuade a POSA from
Using Lipid Nanoparticles to Deliver an mRNA Vaccine**

83. Dr. Chan's remaining opinions as to why a POSA would not have good reason to deliver immunogen-encoding mRNA using lipid nanoparticle delivery systems is to point to the fact that other delivery systems were also

known. He writes, “[i]f a POSA were looking to prepare a vaccine for BetaCoV as Petitioners suggests [sic], they would have recognized some of these carriers as potentially beneficial and advantageous especially in view of a potential pandemic.” (Ex. 2198 at ¶ 164.)

84. I disagree with Dr. Chan. The fact that other delivery systems may also have been known does not alter my opinion that Schrum disclosed and taught a POSA to use a four-component lipid nanoparticle system to deliver immunogen-encoding mRNA, consistent with the well-established state of the art for packaging nucleic acids in lipid nanoparticles for delivery as of October 2015.

85. One of the systems that Dr. Chan focuses on in his declaration is PLGA systems. (Ex. 2198 at ¶¶ 165-66.) However, Dr. Chan does not appear to rely on any disclosure either in Schrum or other prior art using PLGA microspheres for the delivery of RNA vaccines. Therefore, Dr. Chan’s contention that a POSA would be motivated to use PLGA microspheres to deliver an mRNA vaccine seems to be inconsistent with his own interpretation that a POSA would “read what is given to you and you do what is given to you, right.” (Ex. 1152 at 78:10-15.) In any event, Dr. Chan provides no reason for a POSA to shy away from a lipid nanoparticle delivery system as taught by Schrum simply because of the existence of PLGA microspheres.

86. Further, a POSA would have understood that PLGA presents several challenges for mRNA delivery applications. The hydrophobic property of PLGA makes it difficult to encapsulate hydrophilic molecules, including mRNA. This leads to low loading efficiency of mRNA and rapid degradation of mRNA. Additionally, PLGA is often used for slow, continuous release of small molecules. Indeed, Dr. Chan quotes a paper in which I explained how the “unique capability of PLGA particles to sustain release of antigens and adjuvant molecules for several weeks to months is thought to prolong and enhance immune stimulation.” (Ex. 2198 at ¶ 135). While this may be an attractive property for small molecules and proteins, *this is not the case for mRNA delivery*. An ideal carrier for mRNA should promote endosomal escape as well as rapid release of mRNA for efficient protein translation from the mRNA in cytosol. PLGA does not promote endosomal escape nor rapid release of mRNA. Moreover, while PLGA is generally biocompatible, its degradation products—lactic and glycolic acids—can lower pH locally, potentially compromising mRNA and reducing protein translation efficiency.

87. In addition, Dr. Chan discusses protamine and chitosan, (Ex. 2198 at ¶¶ 170-74), neither of which are disclosed in Schrum or Geall as a delivery mechanism for mRNA vaccines. Dr. Chan tries to bypass this inconsistency in his opinions with a generic statement that they are “[b]eyond the specific disclosure in

the references.” (Ex. 2198 at ¶ 170.) I disagree that a POSA would set aside the disclosures of Schrum, Geall, Yang, and Altmeyer, to only look to protamine and chitosan for delivering mRNA vaccines.

88. A POSA would have further understood that chitosan has several major limitations when it comes to mRNA delivery. One of the main challenges is its low transfection efficiency, as chitosan-based systems suffer from poor cellular uptake and limited ability to promote endosomal escape of mRNA. This makes chitosan less effective for mRNA delivery applications, compared with lipid nanoparticles that can efficiently promote endosomal escape of mRNA. Additionally, chitosan's solubility is highly pH-dependent, being soluble only in acidic conditions, which limits its application under physiological conditions at neutral pH. Further, the biomaterial properties of chitosan, such as its molecular weight and degree of deacetylation, can vary depending on its source and method of extraction, resulting in inconsistent performance in mRNA delivery.

89. Likewise, a POSA would have also understood that using protamine for mRNA-based vaccine applications is associated with several disadvantages as well. Protamine can be cytotoxic, particularly at higher concentrations, which limits its therapeutic window. This safety issue is particularly concerning for vaccine applications as vaccines often require repeat dosing. Further, protamine-

based nanoparticles may lack stability in biological fluids, which can result in aggregation, further complicating their use in mRNA delivery systems.

90. Dr. Chan also points to direct injection and cationic liposomes as delivery vehicles for an mRNA vaccine. (Ex. 2198, ¶¶ 39-41 (discussing direct injection), 175 (discussing cationic liposomes).) But Schrum discloses that mRNA delivered using lipid nanoparticles resulted in significantly higher protein expression than mRNA delivered via cationic liposomes (sometimes referred to as lipoplexes) or direct injection. (Ex. 1009 at ¶ 998) (“[T]he LNP formulations described above have about a 10,000-100,000-fold increase in protein production compared to an administration of an intravenous (IV)-lipoplex formulation for the same dosage of modified mRNA and intramuscular (IM) or subcutaneous (SC) administration of the same dose of modified mRNA in saline.”)

91. And although Dr. Chan asserts in his declaration that a POSA would have selected cationic liposomes over lipid nanoparticles in 2015 (Ex. 2198 at ¶ 175), Dr. Chan refused to stand by this opinion. In his declaration, Dr. Chan states that “[t]o the extent a POSA was looking to construct an mRNA vaccine before October 2015, cationic liposomes would have been a more attractive option than lipid nanoparticles to deliver that mRNA vaccine.” (Ex. 2198 at ¶ 175.) By contrast, when asked about this opinion at deposition, Dr. Chan became critical of his own generalization:

Q. I'm just going to ask you if this is a true statement or not. Okay?

A. Okay.

Q. *If a POSA was looking to construct an mRNA vaccine before October 2015, cationic liposomes would have been a more attractive option than lipid nanoparticles to deliver that mRNA vaccine?*

. . . .

A. *Again, it's not specific enough, right, for me to be able to address that particular question,* considering that there's a huge sea of nanoparticle formulation designs, right. And there's also lots of permutations of the cationic as well as the lipid nanoparticles, right.

(Ex. 1152 at 254:17-255:19 (emphasis added).) In any event, Dr. Chan's declaration opinion contradicts the literature already published by October 2015, as it was well understood by that point that cationic liposomes (which generally include permanently charged cationic lipids), unlike lipid nanoparticles, posed significant toxicity risks. A POSA would therefore have good reason to select lipid nanoparticles to avoid such toxicity concerns. (Ex. 1083 at 82 ("Because most permanently charged cationic lipids are highly toxic, this has severely limited their in vivo application.").)

5. The Differences Between Self-Amplifying mRNA and Non-Amplifying mRNA Would Not Have Dissuaded a POSA from Using Lipid Nanoparticle Delivery Systems

92. In his declaration, Dr. Chan contends that, in “the context of saRNA and mRNA, a POSA would not have been motivated to formulate an mRNA vaccine using a carrier that had been used for saRNA vaccine with reasonable expectation of success.” (Ex. 2198 at ¶ 198.) I disagree, but whether a POSA would have used the lipid nanoparticles disclosed in Geall—which exemplifies the use of lipid nanoparticles to deliver self-amplifying mRNA—however, is beside the point. That is because Schrum expressly discloses lipid nanoparticles for use in non-amplifying mRNA vaccines, and further provides specific lipid nanoparticle formulations for the delivery of non-amplifying mRNA that achieved high protein expression for multiple proteins. (*See* Section V.A-C.) A POSA would have thus relied on the lipid nanoparticles disclosed in Schrum as a delivery vehicle for mRNA vaccines.

93. The differences between self-amplifying mRNA and non-amplifying mRNA would not have dissuaded a POSA from following Schrum’s teachings to use a lipid nanoparticle to deliver a mRNA vaccine. For example, Dr. Chan contends that “[i]t was also very difficult for a POSA to address the low efficacy of endosomal escape” for mRNA, and “a POSA would not have been motivated to use the carrier system of a saRNA vaccine for a mRNA vaccine with reasonable

expectation of success.” (Ex. 2198 at ¶¶ 203-04.) This opinion ignores the teachings of Schrum, which demonstrates that mRNA delivered through lipid nanoparticles is entirely capable of endosomal escape. In particular, Schrum demonstrates that non-amplifying mRNA delivered through lipid nanoparticles result in high protein expression *in vivo*. (Ex. 1009 at ¶¶ 999-1000 (Example 17), 1010-20 (Examples 21-22), 1032-36 (Example 27).) This is only possible if the non-amplifying mRNA delivered via lipid nanoparticle escaped the endosome, as the mRNA is translated in the cytoplasm and not the endosome.

94. Dr. Chan also asserts that “a higher immunity may be expected from a saRNA vaccine than from an mRNA vaccine, because the higher innate immunity may help prime a higher adaptive immune response to the saRNA vaccine.” (Ex. 2189 at ¶ 206). Dr. Chan, however, does not address the teachings in Schrum, which state that non-amplifying modified mRNA can be used in a vaccine, and can be expected to trigger the innate immune response. (Ex. 2189 at ¶¶ 341-42)

95. Finally, Dr. Chan speculates that “characteristics of saRNA and mRNA—such as their size and folding pattern—may differ, which would in turn affect the relative thermodynamics of LNP-saRNA formulations and LNP-mRNA formulations, respectively.” (Ex. 2198 at ¶ 207.) Dr. Chan provides no support for this statement, and in fact carefully avoids saying that any such differences would in fact translate to differences in a lipid nanoparticle formulation. Schrum and

Geall show that the same lipid nanoparticle formulation can effectively deliver both non-amplifying mRNA (as shown in Schrum) as well as self-amplifying mRNA (as shown in Geall).

B. By October 2015, a POSA Would Have Had a Reasonable Expectation of Success of Formulating Immunogen-Encoding mRNA in a Lipid Nanoparticle Delivery System

96. I understand that a POSA requires only a reasonable expectation of success, and not proof of actual success.

97. In his declaration, Dr. Chan applies a different standard. Dr. Chan concludes that “[t]he references also do not provide any data on an RNA vaccine encoding a BetaCoV S protein or S protein subunit, let alone an mRNA vaccine encoding a BetaCoV S protein or S protein subunit formulated in a lipid nanoparticle. A POSA would have had no motivation to make or use such a vaccine with a reasonable expectation of success.” (Ex. 2198 at ¶ 189.) This appears to be the application of Dr. Chan’s procedure whereby a POSA would “read what is given to [them] . . . and not speculate because if you start to speculate beyond this, you create problems, right.” (Ex. 1152 at 78:10-15.) I disagree with Dr. Chan’s approach, as well as his conclusion.

98. Instead, a POSA would have reasonably expected to formulate immunogen-encoding mRNA in a lipid nanoparticle delivery system, as the claims require. As I have stated above, Schrum demonstrates formulating mRNA in a

lipid nanoparticle delivery system, as well as the use of such compositions to achieve efficient expression of the encoded protein. I understand that Dr. Griffin has explained that the betacoronavirus spike protein was a known immunogen. Based on that, a POSA would reasonably expect that mRNA encoding for a betacoronavirus spike protein could be formulated in lipid nanoparticle system, such as those disclosed in Schrum. Moreover, a POSA would reasonably expect that administration of such a composition would result in expression of the betacoronavirus spike protein, which would induce some level of an immune response to that encoded immunogen. The testimony of Dr. Deborah Fuller, another of Patent Owner's declarants, is consistent with my opinions:

[Q.] Once you know that the spike protein is expressing, you would expect that the vaccine candidate would induce an immune response. Is that fair?

...

Q. That was your expectation?

A. Yes.

Q. And once you knew that the spike protein was expressing, you would expect that the vaccine candidate would have some level of a neutralizing antibody response. Is that fair?

...

A. We had hypotheses that it was able to induce an immune response.

Q. What was the basis for that hypothesis?

A. Could you elaborate a little bit?

Q. I don't think so. I think you said that you had hypotheses that it was able to induce an immune response. I think that was your testimony. I just want to understand what you meant when you said "hypotheses."

A. Right. *So it's just basic fundamental nucleic acid vaccine biology that when you have a DNA or an RNA vaccine and you could validate that it expresses a protein in vitro, then the hypothesis is that if you inject that DNA or RNA vaccine into an animal, the muscle cell, or in the case of gene gun delivery, the skin cell, will express that antigen. You can give that antigen to express in animal, and the hypothesis is that it will [e]licit an immune response.*

(Ex. 1104 at 50:21-52:9 (emphasis added).)

99. The teachings of the prior art using RNA vaccines formulated in four-component lipid nanoparticle delivery systems reinforces this reasonable expectation of success. For example, Exhibit 2021 (Geall et al., 2012) teaches that "nonviral delivery of a 9-kb self-amplifying RNA encapsulated within an LNP substantially increased immunogenicity compared with delivery of unformulated

RNA” and that “[t]he LNP/RNA formulation boosted F-specific IgG titers approximately 8-fold (GMTs 4,355) and neutralization titers 10-fold (GMTs 1,493) relative to the same dose of naked RNA.” (Ex. 2021 at 14604, 14606.) Likewise, literature from 2013 reaffirmed that a self-amplifying mRNA vaccine encoding for the hemagglutinin influenza protein formulated in a four-component lipid nanoparticle system elicited antibody titers “significantly higher than those elicited by the same dose of unformulated” RNA encoding the same protein. (Ex. 1138 at 5.)

VII. CONCLUSION

100. I declare that all statements made herein to my knowledge are true, that all statements made on information and belief are believed to be true, and 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: August 30, 2024

By: 
James J. Moon, Ph.D.

APPENDIX A

APPENDIX A – LIST OF MATERIALS CONSIDERED

Exhibit No.	Document
Ex. 1001	U.S. Patent No. 10,702,600
Ex. 1004	Declaration of James J. Moon, Ph.D.
Ex. 1009	U.S. Patent App. Publication 2013/0266640 (“Schrum”)
Ex. 1010	International Patent App. Pub. No. WO 2012/006369 (“Geall”)
Ex. 1054	Marc J. Ostro et al., <i>Evidence for translation of rabbit globin mRNA after liposome-mediated insertion into a human cell line</i> , 274 NATURE 921 (1978)
Ex. 1082	Muthusamy Jayaraman et al., <i>Maximizing the potency of siRNA lipid nanoparticles for hepatic gene silencing in vivo</i> , 51 ANGEW. CHEM. INT. ED. 8259 (2012)
Ex. 1083	Alex K. K. Leung et al., <i>Chapter Four – Lipid nanoparticles for short interfering RNA delivery</i> , in ADVANCES IN GENETICS, Vol. 88, (2014)
Ex. 1084	Sean C. Semple et al., <i>Efficient encapsulation of antisense oligonucleotides in lipid vesicles using ionizable aminolipids: Formation of novel small multilamellar vesicle structures</i> , 1510 BIOCHIMICA ET BIOPHYSICA ACTA 152 (2001)
Ex. 1138	Armin Hekele et al., <i>Rapidly produced SAM® vaccine against H7N9 influenza is immunogenic in mice</i> , 2(8) Emerging Microbes and Infections (2013)
Ex. 1151	Yahua Hu et al., <i>Cytosolic delivery mediated via electrostatic surface binding of protein, virus, or siRNA cargos to pH-responsive core-shell gel particles</i> , 10(4) Biomacromolecules 756 (2009)
Ex. 1152	Deposition of Warren C.W. Chan Ph.D., dated July 30, 2024

Exhibit No.	Document
Ex. 1153	Akin Akinc et al., <i>Targeted Delivery of RNAi Therapeutics With Endogenous and Exogenous Ligand-Based Mechanisms</i> , 18(7) MOLECULAR THERAPY 1357 (2010)
Ex. 1154	Lloyd B. Jeffs et al., <i>A Scalable, Extrusion-Free Method for Efficient Liposomal Encapsulation of Plasmid DNA</i> , 22 PHARMACEUTICAL RESEARCH 362 (2005)
Ex. 1156	Teresa Coelho, M.D., et al., <i>Safety and Efficacy of RNAi Therapy for Transthyretin Amyloidosis</i> , 369(9) New England J. Med. 819 (2013)
Ex. 2021	Andrew J. Geall, Nonviral Delivery of Self-Amplifying RNA Vaccines, 109 Proceedings of the Nat'l Acad. of Sci. 14604 (2012) ("Geall 2012")
Ex. 2049	Excerpts from Matthew G. Stanton & Kerry E. Murphy-Benenato, <i>Messenger RNA as a Novel Therapeutic Approach</i> , Topics in Medicinal Chemistry RNA Therapeutics 237 (2017); MOD_000773684-MOD_000773700 at MOD_000773688
Ex. 2050	Excerpts from Investigator's Brochure mRNA-1325 (Sept. 23, 2016) (PROTECTIVE ORDER MATERIAL); MOD_001416753-MOD_001416784 at MOD_001416764-MOD_001416765
Ex. 2077	Preety Sahdev et al., <i>Biomaterials for Nanoparticle Vaccine Delivery Systems</i> , 31 Pharmaceutical Research 2563 (2014)
Ex. 2189	Sebastian Kreiter et al., <i>Intranodal Vaccination with Naked Antigen-Encoding RNA Elicits Potent Prophylactic and Therapeutic Antitumoral Immunity</i> , 70 Cancer Research 9031 (2010)
Ex. 2198	Declaration of Warren C.W. Chan, Ph.D.