

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 IPR2023-01359
Patent No. 10,933,127

REPLY DECLARATION OF DANIEL O. GRIFFIN, M.D., PH.D.

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	PERSON OF ORDINARY SKILL IN THE ART	2
III.	CLAIM CONSTRUCTION	7
1.	mRNA	8
2.	S Protein	9
3.	S Protein Subunit	11
IV.	GROUND 1: SCHRUM DISCLOSES EVERY LIMITATION OF CLAIMS 1-3, 6-9, 11-13, 17-18, AND 20	12
A.	Dr. Fuller’s Opinions Regarding Ground 1 Were Based on an Incorrect Premise	12
B.	Claim 1: “A method comprising administering to a subject a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit formulated in a lipid nanoparticle in an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit, wherein the lipid nanoparticle comprises 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid.”	15
1.	Dr. Fuller Fails to Rebut My Demonstration that Schrum Discloses Each Limitation of Claim 1	16
2.	Schrump Discloses the Elements of Claim 1 as Arranged in the Claim	24
3.	A POSA Would Readily Envisage the Limitations of Claim 1 Based upon Schrum’s Teachings	32
C.	Claim 2: “The method of claim 1, wherein the open reading frame encodes a BetaCoV S protein.”	35
D.	Claim 3: “The method of claim 2, wherein the immune response is a neutralizing antibody response specific to the BetaCoV S protein.” ..	37
E.	Claim 6: “The method of claim 1, wherein the mRNA formulated in a lipid nanoparticle is administered intramuscularly.”	40

F.	Claim 7: “The method of claim 1, wherein the mRNA further comprises a 5' untranslated region and a 3' untranslated region.”	42
G.	Claim 8: “The method of claim 1, wherein the mRNA further comprises a poly(A) tail.”	45
H.	Claim 9: “The method of claim 1, wherein the mRNA further comprises a 5' cap analog.”	48
I.	Claim 11: “The method of claim 1, wherein the mRNA comprises a chemical modification.”	50
J.	Claim 12: “The method of claim 11, wherein the chemical modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification.”	52
K.	Claim 13: “The method of claim 11, wherein at least 80% of the uracil in the open reading frame of the mRNA has a chemical modification.”	56
L.	Claim 17: “A method comprising administering to a subject an mRNA comprising a 5' cap analog, a 5' untranslated region, an open reading frame encoding a BetaCoV S protein or S protein subunit, a 3' untranslated region, and a poly(A) tail formulated in a lipid nanoparticle in an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit, wherein the lipid nanoparticle comprises 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid.....	59
	1. Dr. Fuller Fails to Rebut My Demonstration that Schrum Discloses Each Limitation of Claim 17	60
	2. Schrum discloses the elements of claim 17 as they are arranged in the claim	61
	3. A POSA would have at once envisaged the claimed arrangement of claim 17 from Schrum.	62
M.	Claim 18: “The method of claim 17, wherein the open reading frame encodes a BetaCoV S protein.”	63
N.	Claim 20: “The method of claim 18, wherein at least 80% of the uracil in the open reading frame of the mRNA has a 1-methylpseudouridine modification.”	65

V.	GROUND 2: THE COMBINATION OF SCHRUM IN VIEW OF GEALL DISCLOSES ALL OF THE LIMITATIONS OF CLAIMS 1-3, 6-9, 11-13, 17-18, AND 20	68
A.	Claim 1: “A method comprising administering to a subject a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit formulated in a lipid nanoparticle in an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit, wherein the lipid nanoparticle comprises 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid.”	69
1.	Schrum and Geall Disclose Every Element of Claim 1	69
2.	A POSA Would Have Been Motivated to Combine the Teachings of Schrum and Geall With a Reasonable Expectation of Success	73
a.	Schrum’s Teachings, Paired with the State of the Art, Would Motivate a POSA to Utilize an mRNA Vaccine with a Reasonable Expectation of Success	77
1)	No “Skepticism” of mRNA Vaccines	79
2)	Clinical Trials of mRNA Vaccines Encoding for Infectious Disease Immunogens Do Not Demonstrate Skepticism	89
3)	By October 2015, mRNA Vaccines Had Known Advantages Over Other Vaccine Modalities, Including Other Nucleic Acid Vaccines	96
b.	A POSA Would Have Been Motivated to Encode a Betacoronavirus S Protein as the Immunogen in an mRNA Vaccine with a Reasonable Expectation of Success	104
1)	The SARS-CoV S Protein Was a Known, Protective Immunogen	106
2)	By October 2015, S Protein-Based Vaccines Had Already Proven to Be Protective	112

3)	Concerns with Enhanced Disease Would Not Have Dissuaded a POSA from Using a Betacoronavirus S Protein as a Vaccine Immunogen.....	119
4)	The “Full-Length” S Protein Had Known Advantages as a Vaccine Immunogen.....	137
c.	A POSA Would Have Been Motivated to Formulate Immunogen-Encoding mRNA in Lipid Nanoparticles and Would Reasonably Expect to Do So Successfully.....	143
1)	By October 2015, Lipid Nanoparticles Were a Well-Known Delivery Approach for mRNA.....	143
2)	By October 2015, Lipid Nanoparticles Had Already Been Shown to Improve mRNA Vaccine Potency	146
d.	[REDACTED]	
	[REDACTED]	
	[REDACTED]	
	[REDACTED]	
	[REDACTED]	
B.	Claim 2: “The method of claim 1, wherein the open reading frame encodes a BetaCoV S protein.”	173
C.	Claim 3: “The method of claim 2, wherein the immune response is a neutralizing antibody response specific to the BetaCoV S protein.”	175
D.	Claim 6: “The method of claim 1, wherein the mRNA formulated in a lipid nanoparticle is administered intramuscularly.”	178
E.	Claim 7: “The method of claim 1, wherein the mRNA further comprises a 5' untranslated region and a 3' untranslated region.”	180
F.	Claim 8: “The method of claim 1, wherein the mRNA further comprises a poly(A) tail.”	182

G.	Claim 9: “The method of claim 1, wherein the mRNA further comprises a 5' cap analog.”	183
H.	Claim 11: “The method of claim 1, wherein the mRNA comprises a chemical modification.”	185
I.	Claim 12: “The method of claim 11, wherein the chemical modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification.”	190
J.	Claim 13: “The method of claim 11, wherein at least 80% of the uracil in the open reading frame of the mRNA has a chemical modification.”	193
K.	Claim 17: “A method comprising administering to a subject an mRNA comprising a 5' cap analog, a 5' untranslated region, an open reading frame encoding a BetaCoV S protein or S protein subunit, a 3' untranslated region, and a poly(A) tail formulated in a lipid nanoparticle in an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit, wherein the lipid nanoparticle comprises 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid.....	195
1.	Schrum and Geall Disclose Every Element of Claim 17	195
2.	A POSA Would Have Been Motivated to Combine the Teachings of Schrum and Geall With a Reasonable Expectation of Success	196
L.	Claim 18: “The method of claim 17, wherein the open reading frame encodes a BetaCoV S protein.”	198
M.	Claim 20: “The method of claim 18, wherein at least 80% of the uracil in the open reading frame of the mRNA has a 1-methylpseudouridine modification.”	200
VI.	GROUND 3: THE COMBINATION OF SCHRUM IN VIEW OF YANG DISCLOSES ALL OF THE LIMITATIONS OF CLAIMS 1-3, 6-9, 11-13, 17-18, AND 20	202
A.	Claim 1: “A method comprising administering to a subject a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit formulated in a lipid nanoparticle in an effective amount to	

	induce in the subject an immune response to the BetaCoV S protein or S protein subunit, wherein the lipid nanoparticle comprises 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid.”	203
1.	Schrump and Yang Disclose Every Element of Claim 1	203
2.	A POSA would have been motivated to combine the teachings of Schrump and Yang with a reasonable expectation of success	207
B.	Claim 2: “The method of claim 1, wherein the open reading frame encodes a BetaCoV S protein.”	214
C.	Claim 3: “The method of claim 2, wherein the immune response is a neutralizing antibody response specific to the BetaCoV S protein.”	215
D.	Claim 6: “The method of claim 1, wherein the mRNA formulated in a lipid nanoparticle is administered intramuscularly.”	217
E.	Claim 7: “The method of claim 1, wherein the mRNA further comprises a 5' untranslated region and a 3' untranslated region.”	217
F.	Claim 8: “The method of claim 1, wherein the mRNA further comprises a poly(A) tail.”	218
G.	Claim 9: “The method of claim 1, wherein the mRNA further comprises a 5' cap analog.”	218
H.	Claim 11: “The method of claim 1, wherein the mRNA comprises a chemical modification.”	218
I.	Claim 12: “The method of claim 11, wherein the chemical modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification.”	219
J.	Claim 13: “The method of claim 11, wherein at least 80% of the uracil in the open reading frame of the mRNA has a chemical modification.”	219
K.	Claim 17: “A method comprising administering to a subject an mRNA comprising a 5' cap analog, a 5' untranslated region, an open reading frame encoding a BetaCoV S protein or S protein subunit, a 3' untranslated region, and a poly(A) tail formulated in a lipid nanoparticle in an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit,	

wherein the lipid nanoparticle comprises 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid.....	219
1. Schrum and Yang Disclose Every Element of Claim 17	220
2. A POSA Would Have Been Motivated to Combine the Teachings of Schrum and Yang With a Reasonable Expectation of Success	220
L. Claim 18: “The method of claim 17, wherein the open reading frame encodes a BetaCoV S protein.”	222
M. Claim 20: “The method of claim 18, wherein at least 80% of the uracil in the open reading frame of the mRNA has a 1-methylpseudouridine modification.”	224
VII. GROUND 4: THE COMBINATION OF SCHRUM IN VIEW OF ALTMAYER DISCLOSES ALL OF THE LIMITATIONS OF CLAIMS 1-3, 6-9, 11-13, 17-18, AND 20	224
A. Claim 1: “A method comprising administering to a subject a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit formulated in a lipid nanoparticle in an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit, wherein the lipid nanoparticle comprises 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid.”	225
1. Schrum and Altmeyer Disclose Every Element of Claim 1 ...	225
2. A POSA would have been motivated to combine Schrum and Altmeyer with a reasonable expectation of success	230
B. Claim 2: “The method of claim 1, wherein the open reading frame encodes a BetaCoV S protein.”	234
C. Claim 3: “The method of claim 2, wherein the immune response is a neutralizing antibody response specific to the BetaCoV S protein.”	235
D. Claim 6: “The method of claim 1, wherein the mRNA formulated in a lipid nanoparticle is administered intramuscularly.”.....	237
E. Claim 7: “The method of claim 1, wherein the mRNA further comprises a 5' untranslated region and a 3' untranslated region.”	238

F.	Claim 8: “The method of claim 1, wherein the mRNA further comprises a poly(A) tail.”	238
G.	Claim 9: “The method of claim 1, wherein the mRNA further comprises a 5' cap analog.”	238
H.	Claim 11: “The method of claim 1, wherein the mRNA comprises a chemical modification.”	238
I.	Claim 12: “The method of claim 11, wherein the chemical modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification.”	239
J.	Claim 13: “The method of claim 11, wherein at least 80% of the uracil in the open reading frame of the mRNA has a chemical modification.”	239
K.	Claim 17: “A method comprising administering to a subject an mRNA comprising a 5' cap analog, a 5' untranslated region, an open reading frame encoding a BetaCoV S protein or S protein subunit, a 3' untranslated region, and a poly(A) tail formulated in a lipid nanoparticle in an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit, wherein the lipid nanoparticle comprises 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid.”	239
1.	Schrum and Altmeyer Disclose Every Element of Claim 17	240
2.	A POSA would have been motivated to combine Schrum and Altmeyer with a reasonable expectation of success	240
L.	Claim 18: “The method of claim 17, wherein the open reading frame encodes a BetaCoV S protein.”	243
M.	Claim 20: “The method of claim 18, wherein at least 80% of the uracil in the open reading frame of the mRNA has a 1-methylpseudouridine modification.”	244
VIII.	THERE ARE NO OBJECTIVE INDICIA THAT SUPPORT THE NON-OBVIOUSNESS OF THE '127 PATENT	244
A.	Nexus.....	245
1.	Spikevax® and Comirnaty® Do Not Embody the Challenged Claims.....	245

a.	Two-Proline Mutation.....	245
b.	mRNA Structural Features.....	250
c.	Lipid Nanoparticle Composition.....	252
2.	Many features of SpikeVax®, and Comirnaty® were known in the prior art	253
a.	1-methylpseudouridine Modification	253
b.	Full-length Spike Protein	255
c.	Lipid Nanoparticle Composition.....	256
B.	No Satisfaction of a Long-Felt, Unmet Need	258
C.	Failure of Others and Skepticism Are Not Secondary Considerations Supporting the Validity of the Challenged Claims	260
1.	mRNA was viewed as a promising platform for vaccines.	260
2.	Researchers were not skeptical that the S protein could be used as an antigen in an mRNA betacoronavirus vaccine.....	261
3.	No Failure of Others Supports the Validity of the Challenged Claims.....	261
D.	No Unexpected Results.....	262
E.	No Praise	263
IX.	CONCLUSION	265

I. INTRODUCTION

1. I have previously submitted a declaration in this proceeding, relating to U.S. Patent No. 10,933,127 (“the ’127 patent”). I understand that the Board has instituted an inter partes review for the ’127 patent.

2. I further understand that Dr. Deborah H. Fuller has submitted a declaration relating to the ’127 patent. In this Declaration, I respond to the opinions she expresses in her Declaration.¹ Dr. Fuller repeats her opinions several times throughout the Declaration.² To the extent I do not address each section in which she repeats her opinion, my opinions intend to be responsive to those sections. Further, to the extent I do not address any of Dr. Fuller’s opinions expressly, it should not be taken as agreement with that opinion.

3. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

¹ Ex. 2199, IPR2023-01359, Declaration of Dr. Deborah H. Fuller.

² For example, Ex. 2199 ¶ 259 and ¶ 274.

³ Ex. 2200.

4. I am being compensated at my regular consulting rate of \$500 per hour for my time on this matter. My compensation has not changed since I submitted my previous Declaration. My compensation does not depend on the substance of my opinions or the outcome of the matter.

5. My updated CV is attached to this Declaration as Exhibit 1305. I provided a brief overview of my background in Section I of my Opening Declaration, which I incorporate by reference herein.

6. In formulating the opinions in this Declaration, I have considered my knowledge, my academic training, texts and scientific principles, and my experience in the applicable scientific disciplines, as well as the materials cited in my declarations and/or in Appendix A.

II. PERSON OF ORDINARY SKILL IN THE ART

7. I have been informed that, in its Institution Decisions in IPR2023-01359, the Board adopted—with the further detail discussed below—the definition of a person of ordinary skill in the art (“POSA”) presented in my opening declaration: “[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.”⁴ The Board further specified that “[w]here Petitioner’s definition specifies work experience, we consider the duration of such experience to be three or more years.”⁵

8. Dr. Fuller contends that “it is unclear” whether I had the requisite experience required for a POSA under that definition.⁶ In particular, Dr. Fuller states that I “did not have research experience with mRNA vaccines as of October 22, 2015.”⁷ I disagree. As stated in my prior Declaration, and as further explained below, I qualified as a part of the research team discussed in the Board’s definition of a POSA by October 2015. Further, my opinions expressed in this declaration, as well as those expressed in my prior Declaration, would remain the same regardless of which POSA definition is applied.

9. Specifically, by 2015, I had two advanced degrees with more than three years of experience with vaccines, virology, molecular medicine, and infectious diseases.

⁴ Paper No. 18 (Institution Decision IPR2023-01359) at 31-32.

⁵ Paper No. 18 (Institution Decision IPR2023-01359) at 31-32.

⁶ Ex. 2199 ¶¶ 41-45.

⁷ Ex. 2199 ¶ 41.

10. I received my M.D. in 1995 from New York University School of Medicine, where, in addition to the standard medical school curriculum, I conducted research identifying the human homolog of the murine mycobacterial resistance protein (natural resistance-associated macrophage protein 1 (NRAMP1)), which is associated with resistance to mycobacterial infection. This involved work in the field of nucleic acids, including generating and screening DNA libraries, gene sequencing, and sequence analysis. It further involved examining approaches to DNA and mRNA expression using nucleic acid-coated gold beads (gene gun), nonviral lipid-mediated gene delivery, among other techniques. I continued this work into 1995, winning the NYU School of Medicine Independent Research Project Award.

11. I acquired my Ph.D. in Molecular Medicine in 2012. This degree involved drug delivery of nucleic acid drugs (including lipid-based drug delivery systems), vaccines, virology, molecular medicine, and infectious diseases. In addition to completing a three-year categorical medicine residency, I had also completed my fellowship in infectious disease at Hofstra by October 2015.

12. I have extensive research experience involving nucleic acids, including mRNA specifically. As an associate research scientist in the Department of Biochemistry and Molecular Biophysics at Columbia University, I have conducted research on RNA, including the transduction of mRNA and siRNA into

hematopoietic stem cells. I have also researched “natural antibodies” produced by Human B1-cells, with the goal of developing novel protein-based, attenuated viral, DNA, and mRNA-based vaccines for infectious diseases, malignancies, and neurodegenerative diseases. The results of this work were presented at the 2014 Infectious Disease Society of New York Annual Meeting: Hot Topics in Infectious Diseases at the Albert Einstein College of Medicine Montefiore Medical Center, the 2017, 2018, and 2019 Cold Spring Harbor Retroviruses Meetings, and the Columbia University Stem Cell Initiative (CSCI) NY, NY presentations 2014 and 2018.⁸

13. My research produced mRNA that expressed cloned natural antibodies. As part of this research, I performed single-cell sorting of Human B1 cells, amplification of mRNA encoding natural antibody immunoglobulins, and cloning into DNA expression plasmids.

14. Starting in 2014, as part of my research, I researched stem cell latency and innate immune sensing of cytosolic nucleic acids such as foreign DNA and RNA. I also investigated how cytoskeletal trafficking impacts viral trafficking. This research involved the use of electroporation and lipid-based introduction of mRNA and small interfering RNA (siRNA) into primary human cells.⁹

⁸ Ex. 1305 at 19-21 (Abstracts and Presentations).

⁹ Ex. 1305 at 19-21 (Abstracts and Presentations).

15. Additionally, I conducted research on the phenotype of human B1 cells in umbilical cord blood and adult peripheral blood. As part of that research, I performed mRNA expression analysis and confirmed the expression of CD27 mRNA through real-time PCR.¹⁰ Similarly, I conducted research on CD11b+ human B1 cell populations and their effect on T cell stimulation, which required isolation and analysis of mRNA isolated from B cell populations to measure and compare gene expression.¹¹

16. In addition to conducting research, I am also a board-certified physician, specializing in infectious diseases and internal medicine. I work as chief of the Infectious Disease division of Optum Tristate, a health services company. I started at Optum when it was known as ProHealth in 2017 and rose to chief of the division in early 2020. As part of my practice, I provide consultations for fellow physicians and patients with infectious diseases, including COVID-19.

17. I have also been an instructor of clinical medicine at Columbia University Irving Medical Center since 2014, where I teach on infectious diseases, including SARS-CoV-2. In addition to teaching on infectious diseases, I conduct

¹⁰ Ex. 1142.

¹¹ Ex. 1141.

research on the mechanism of viral infections, including on SARS-CoV-2 and HIV-associated malignancies.¹² I have authored a book chapter on infectious disease.¹³

18. Given my extensive infectious disease expertise, various companies have sought out my input. For example, I worked as the Senior Infectious Disease Advisor at United Health Group. While working in this capacity, I advised United Health Group on mRNA and protein-based vaccines, including COVID-19 vaccines. I also provided educational programs on such vaccines.

III. CLAIM CONSTRUCTION

19. As I note in my opening Declaration,¹⁴ I applied the following claim constructions in rendering my opinions:

- “betacoronavirus” means “an enveloped, positive-sense, single stranded RNA virus of zoonotic origin that belongs to one of the four lineages of the betacoronavirus genus of the subfamily Coronavirinae (e.g., OC43, HKU1, MERS-CoV, and SARS-CoV).”
- “S protein” means a “spike protein,” which “is a structural protein forming a spike.”

¹² For example, Ex. 1103; Ex. 1143.

¹³ Ex. 1123.

¹⁴ Ex. 1002 ¶ 49.

- “open reading frame” (ORF) means “in a DNA, a continuous stretch of DNA beginning with a start codon, and ending with a stop codon and encodes a polypeptide, or, in an mRNA, a corresponding stretch of mRNA.”
- “Subject” means “a mammal”

20. In addition to the construction of the terms above, Dr. Fuller has also provided further opinions regarding the construction of the terms “mRNA,” “S Protein” and “S Protein Subunit.” As discussed below, I disagree with various statements in Dr. Fuller’s opinion. Nevertheless, my opinions, as expressed in my opening Declaration and in this reply Declaration, would not change even if Dr. Fuller’s constructions were applied.

1. mRNA

21. Dr. Fuller asserts that a POSA would have understood that the “claimed mRNA of the ’127 patent does not include and is distinct from self-amplifying RNA.”¹⁵ To the extent Dr. Fuller asserts that self-amplifying mRNA is not a type of mRNA as a scientific matter, I disagree. Self-amplifying mRNA is a specific subtype of mRNA that encodes for both the antigen as well as the proteins that form the replicon, whereas non-amplifying mRNA encodes for only the antigen. In both

¹⁵ Ex. 2199 ¶ 158.

cases, however, the RNA acts as an intermediary between DNA and protein, and is involved in translating the DNA's genetic code into amino acids that form proteins. As I explain in Section V.A.2.c.2, the scientific literature also refers to self-amplifying mRNA as a type of mRNA.

22. However, to the extent the term “mRNA” is construed to exclude self-amplifying mRNA in the specific context of the '127 patent, it would not affect the opinions I have expressed with respect to the '127 patent. As I explain below in Section IV.B, Schrum describes non-amplifying mRNA vaccines formulated in lipid nanoparticles. Schrum incorporates by reference Geall, expressly disclosing a non-amplifying mRNA vaccine encoding a betacoronavirus S protein formulated in a lipid nanoparticle. Further, Schrum in view of Geall, Schrum in view of Yang, and Schrum in view of Altmeyer similarly teach non-amplifying mRNA vaccines encoding a betacoronavirus S protein formulated in a lipid nanoparticle.

2. S Protein

23. Dr. Fuller contends that the “S Protein” term of the '127 patent claims necessarily refers to a full-length spike protein.¹⁶ Dr. Fuller's opinion is not the same language as Patent Owner advanced before the District Court, which I understood adopted (at Patent Owner's urging) the definition that I identified in my opening

¹⁶ Ex. 2199 ¶ 159.

declaration: “S protein” means a “spike protein,” which “is a structural protein forming a spike.”¹⁷

24. In her declaration, Dr. Fuller cites, without explanation, to several sections of the ’127 patent expressly referring to a full-length Spike protein.¹⁸ For example, Dr. Fuller refers to how the ’127 patent describes a “betacoronavirus mRNA vaccine encoding the MERS-CoV *full-length Spike protein*.”¹⁹ In my opinion, those passages do not support Dr. Fuller’s proposed construction. Instead, these passages indicate that when the patent intends to refer to a full-length spike protein, it expressly does so—by referring to it as a “full-length” spike protein. A POSA would therefore have understood that the patent uses the term “spike protein” more broadly. Again, I note that the District Court construction proposed and adopted by Patent Owner does not refer to “full-length” spike protein.

25. Dr. Fuller also alleges that the ’127 patent’s disclosure of amino acid sequences for a full-length spike protein for a vaccine support her argument.²⁰ For

¹⁷ Ex. 1002 ¶ 49.

¹⁸ Ex. 2199 ¶ 169.

¹⁹ Ex. 2199 ¶ 169 (quoting Ex. 1001) (emphases added).

²⁰ Ex. 2199 ¶¶ 164-166.

example, she points to Table 12, listing “GenBank Accession” numbers for “**Full-length** Spike Glycoprotein Amino Acid Sequences (*Homo sapiens* strains).”²¹ But Dr. Fuller fails to explain why the ’127 patent’s disclosure of amino acid sequences of a full-length spike protein necessarily requires the construction of “S protein” to mean a full-length spike protein. Instead, the portions of the specification that Dr. Fuller relies on show again that, when the patent intends to refer to a full-length spike protein, it expressly does so by referring to it as a “full length” spike protein.

26. In any event, even limiting the “S protein” to a full-length spike protein would not affect my opinion that the challenged claims of the ’127 patent were already disclosed in the prior art by October 2015. A “full-length” betacoronavirus spike protein is simply the normal, “default” version of a betacoronavirus spike protein, as had already been described in the prior art—rather than an artificially shortened version of the protein (*i.e.*, the truncated protein or a subunit thereof). As I note below, the use of the betacoronavirus spike protein (the “full length” protein, in Dr. Fuller’s terminology) as a vaccine antigen was well-known. And by 2015, the prior art had already disclosed the use of a betacoronavirus S-protein, including the “full length” S-protein, as the antigen to be encoded in an mRNA vaccine.

3. S Protein Subunit

²¹ Ex. 2199 ¶ 166 (citing Ex. 1001, Table 12) (emphasis added).

27. Dr. Fuller asserts that a POSA would understand the term “subunit” to refer only to an S1 subunit or an S2 subunit of a spike protein.²² Although Dr. Fuller does not identify any portions of the specification that define the term “subunit” as only the S1 or S2 subunit, limiting “subunit” to the S1 or S2 subunit would not affect my opinion that the challenged claims of the ’127 patent are invalid.

IV. GROUND 1: SCHRUM DISCLOSES EVERY LIMITATION OF CLAIMS 1-3, 6-9, 11-13, 17-18, AND 20

28. In Section VIII of my previous declaration, I explained that each of the limitations of claims 1-3, 6-9, 11-13, 17-18, and 20 had already been disclosed by Schrum as of its October 10, 2013 publication, which I understand is referred to as Ground 1 in this proceeding.²³ While Dr. Fuller responds to my analysis in Section X of her own declaration,²⁴ she did not consider the entirety of Schrum’s teachings, as a POSA would have done.

A. Dr. Fuller’s Opinions Regarding Ground 1 Were Based on an Incorrect Premise

29. At her deposition, Dr. Fuller explained the bases underlying her opinions with respect to Ground 1. Her testimony showed that, while she recognized

²² Ex. 2199 ¶¶ 171-186.

²³ Ex. 1002 § VIII.

²⁴ Ex. 2199 § X.

that Schrum disclosed mRNA vaccines encoding an immunogen, she set aside those teachings as “not something that . . . [she] would take actually seriously” on account of Schrum not including working examples of an mRNA vaccine encoding a betacoronavirus S protein.²⁵ She testified:

Q. Okay. You don’t dispute that Schrum discloses an mRNA vaccine encoding an immunogen, do you?

. . .

A. So *what Schrum describes is the potential to use mRNA vaccines, mRNA, to encode – deliver an immunogenic peptide or polypeptide.*

But what Schrum doesn’t do is provide any examples of or any data supporting that statement anywhere in the patent application.

Q. You don’t dispute that Schrum discloses an mRNA vaccine to elicit or provoke an immune response. Right?

. . .

A. By 2013 it was pretty well known that you could do different nucleic acids, inject those into cells, those nucleic acids could express something and maybe provoke an immune response.

So, in generic language, I think to include if you’re going to work on any sort of mRNA, to mention that even though there’s no specific examples or data to support that.

²⁵ Ex. 1104 at 213:10-12.

I see that as – as a POSA, I see that as a generic statement,
***not something that is actually being – that I would take
actually seriously.***²⁶

30. At her deposition, Dr. Fuller repeated that her primary basis for concluding that Schrum did not disclose the claims of the '127 patent was based on what Schrum “focuses on” and exemplifies:

So my opinion is that ***Schrum is not anticipatory because it focuses on methods and technologies to – for mRNA as a therapeutic, not as a vaccine.*** So it’s not anticipatory for vaccines. It has only examples that are specific towards production of protein and the amount of protein in vivo but not any examples that show vaccines that relate in any way to vaccines.²⁷

31. I disagree that a POSA would set aside Schrum’s teachings of mRNA vaccines in such a manner—particularly where, as Dr. Fuller recognized, “[b]y 2013 it was pretty well known that you could do different nucleic acid[] [vaccines], []

²⁶ Ex. 1104 at 212:8-213:12 (emphases added).

²⁷ Ex. 1104 at 218:17-219:3 (emphases added). Ex. 1104 at 216:16-20 (“My opinion on Schrum is that Schrum is a document that describes the use of mRNA for therapeutics, and it doesn’t anticipate mRNA for vaccines. It offers examples on using mRNA for therapeutics.”).

inject those into cells, and those nucleic acids could express something and maybe provoke an immune response.”²⁸

32. Instead, a POSA would consider the entirety of Schrum’s teachings. Considered under that proper framework, Schrum discloses each limitation of the ’127 patent at issue in this proceeding, as I previously explained²⁹ and reiterate in response to Dr. Fuller’s opinions below.

B. Claim 1: “A method comprising administering to a subject a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit formulated in a lipid nanoparticle in an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit, wherein the lipid nanoparticle comprises 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid.”

33. As explained in my opening declaration, Schrum discloses each limitation of claim 1, as arranged in the claim.³⁰

34. Dr. Fuller does not dispute the majority of my explanation of Schrum’s disclosures. That is, Dr. Fuller does not dispute that Schrum teaches administering

²⁸ Ex. 1104 at 213:1-4.

²⁹ Ex. 1002 § VIII.

³⁰ Ex. 1002 § VIII.1.

mRNA encoding an immunogen (like the BetaCoV S protein), as a vaccine.³¹ Nor does Dr. Fuller dispute that Schrum teaches encapsulating mRNA in lipid nanoparticle systems, including for mRNA vaccine applications.³²

35. Instead, Dr. Fuller argues that Schrum does not disclose the immunogen of the claims of the '127 patent—a BetaCoV S protein administered in an effective amount to induce an immune response.³³ As explained below, I disagree.

36. Dr. Fuller further alleges that Schrum does not disclose the elements of claim 1 as they are arranged in the claim, and that a POSA would not have at once envisaged the claimed arrangement of claim 1 from Schrum.³⁴ I disagree with Dr. Fuller's opinions for the reasons below.

**1. Dr. Fuller Fails to Rebut My Demonstration
that Schrum Discloses Each Limitation of Claim 1**

37. As discussed above, the only limitation of claim 1 of the '127 patent that Dr. Fuller contends to not be disclosed by Schrum is the BetaCoV S protein antigen that induces an immune response to the BetaCoV S protein. Contrary to Dr.

³¹ Ex. 2199 ¶¶ 237-275.

³² Ex. 2199 ¶¶ 237-275.

³³ Ex. 2199 ¶¶ 237-275.

³⁴ Ex. 2199 ¶¶ 276-322.

Fuller's opinion, Schrum discloses "a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (betacov) S protein or S protein subunit" that induces a specific immune response, including through its express incorporation of Geall, which specifically identifies the SARS-CoV S protein as the antigen to be encoded by an RNA vaccine.³⁵ Schrum therefore discloses each limitation of claim 1, as I have previously explained.³⁶ Dr. Fuller's arguments are without merit.

38. *First*, Dr. Fuller asserts that Schrum does not incorporate Geall's teaching of the SARS-CoV spike protein as an RNA vaccine antigen. Specifically, she contends that "Schrum only incorporates Geall for its **dose amounts**."³⁷ Dr. Fuller's opinion is contrary to the plain text of Schrum, which states that Geall is "herein incorporated by reference in [its] *entirety*."³⁸ A POSA would understand and credit the applicant's own words, understanding that the "entire[]" disclosure of Geall was incorporated into the text of Schrum, including Geall's disclosure of the

³⁵ Ex. 1002 ¶¶ VIII.1.

³⁶ Ex. 1002 ¶¶ VIII.1.

³⁷ Ex. 2199 ¶¶ 240-244.

³⁸ Ex. 1009 ¶ 342.

use of the SARS-CoV S protein as an RNA vaccine antigen. Given Schrum's instruction, a POSA would not look to Geall only for its disclosure of dosage levels.

39. Dr. Fuller's opinion is also inconsistent with the context in which Schrum incorporates Geall. In particular, paragraph 342 of Schrum (in which Schrum incorporates Geall) focuses on immunogens, beginning "[t]he modified nucleic acid molecules and/ or mmRNA of the invention may encode an immunogen. The delivery of modified nucleic acid molecules and/or mmRNA encoding an immunogen may activate the immune response."³⁹ Schrum's reference to dosage levels in the precise sentence of paragraph 342 incorporating Geall is consistent with the fact that, as Dr. Fuller recognized at deposition, the choice of immunogen influences the dosage level at which a vaccine will be given.⁴⁰ Given that interrelatedness, a POSA would not consider Geall's teachings of dosage levels

³⁹ Ex. 1009 ¶ 342.

⁴⁰ Ex. 1104 at 119:22-120:5 ("[R]egardless of what vaccine that you have . . . multiple things can influence a dose. So that can be the immunogen that you use. Some immunogens are more immunogenic than others.").

without also considering its discussion of immunogens, particularly where Geall is expressly incorporated “in [its] entirety.”⁴¹

40. *Second*, Dr. Fuller asserts that Schrum—through its incorporation of Geall—does not teach an “S protein,” *i.e.*, a “structural protein forming a spike.”⁴² Dr. Fuller is mistaken.

41. Dr. Fuller principally relies on the fact that Schrum (and Geall, incorporated into Schrum) “has **no working example** with a betacoronavirus immunogen, let alone a betacoronavirus S protein or S protein subunit.”⁴³ This argument seems to flow from Dr. Fuller’s faulty premise that the prior art patent cannot disclose each limitation of a patent claim without including a working example.⁴⁴

⁴¹ Ex. 1009 ¶ 342.

⁴² Ex. 2199 ¶¶ 245-252.

⁴³ Ex. 2199 ¶ 247.

⁴⁴ Ex. 2199 ¶ 247; Ex. 1104 at 216:16-20 (“My opinion on Schrum is that Schrum is a document that describes the use of mRNA for therapeutics, and it doesn’t anticipate mRNA for vaccines. It offers examples on using mRNA for therapeutics.”).

42. I disagree with Dr. Fuller’s assertion that a POSA would have required a working example to conclude that Geall’s disclosure of a “spike polypeptide”⁴⁵ would result in a structural protein forming a spike. By the priority date of the challenged patents, it was well known “[t]he spikes of SARS-CoV are composed of trimers of S protein” and that an expressed S protein folds into the figurative “spike” for which these proteins are named.⁴⁶ Therefore, as I explained in my initial declaration, “[a] POSA would have understood [Geall’s] disclosure of ‘spike polypeptide’ from a SARS coronavirus . . . as referring to a structural protein forming a spike.”⁴⁷

43. I also note that Dr. Fuller’s opinion is inconsistent with the specification of the ’127 patent, which does not provide any data showing that any of the contemplated BetaCoV S proteins “actually result[] in a ‘structural protein **forming**

⁴⁵ The term “polypeptide” may be used interchangeably with the term “protein.”

⁴⁶ Ex. 1031 at 227.

⁴⁷ Ex. 1002 ¶ 72 n.120; Ex. 1002 ¶ 73 (“A POSA would understand that mRNA encoding the spike protein of a SARS-CoV would necessarily disclose an open reading frame, which is the portion of the mRNA that encodes the protein/polypeptide of interest.”).

a spike.”⁴⁸ Instead, the specification of the ’127 patent—like Geall—simply refers to vaccines encoding “at least one antigenic polypeptide [that] is a MERS-CoV Structural protein. For example, a MERS-CoV structural protein may be a spike protein (S).”⁴⁹ The ’127 patent does not provide data showing that each such S protein “actually” forms a spike, consistent with a POSA’s understanding that the spike protein (or, spike polypeptide) is a structural protein that forms a spike. And the ’127 patent further does not even disclose the complete mRNA sequence of the MERS vaccine used in the example. In fact, the patent only tests an mRNA vaccine encoding for a single betacoronavirus spike protein vaccine (MERS-CoV S), and Dr. Fuller simply infers that the expressed proteins formed a spike.⁵⁰

44. Dr. Fuller also argues that “[e]ven if mRNA was synthesized to include the sequence for a betacoronavirus full-length spike protein . . . that does not mean that a full-length spike protein would ‘form’” because, in Dr. Fuller’s opinion, “large proteins are difficult to express.”⁵¹ I disagree with this assertion, as by October 2015,

⁴⁸ Ex. 2199 ¶ 246.

⁴⁹ Ex. 1001 at 8:5-7.

⁵⁰ Ex. 2199 ¶ 313.

⁵¹ Ex. 2199 ¶ 252.

it had already been shown that betacoronavirus spike proteins could be expressed using nucleic acid vaccines to induce a protective immune response.⁵² Further, it was well-known by 2015 that “any protein can be expressed from mRNA without the need to adjust the production process,”⁵³ and that 9-10 kb nucleotide RNA vaccines could express protective antigens *in vivo* to induce a protective immune response (around three-times the size of a betacoronavirus spike protein).⁵⁴

45. **Third**, Dr. Fuller asserts that neither Schrum nor Geall disclose a full-length spike protein.⁵⁵ This argument, also, is incorrect.

46. Geall discloses the use of a SARS-CoV “spike polypeptide” as a vaccine immunogen.⁵⁶ A POSA would understand the disclosure of a “spike polypeptide” to refer to (or, at the very least, include) the disclosure of a full-length

⁵² Ex. 1031 at 226-236.

⁵³ Ex. 1019 at 1.

⁵⁴ Ex. 2021 at 14604 (9-kb nucleotide RNA vaccine delivered via lipid nanoparticles used to induce immune response against respiratory syncytial virus).

⁵⁵ Ex. 2199 ¶¶ 253-260.

⁵⁶ Ex. 1010 at 19:26-29 (“The coronavirus immunogen may be a spike polypeptide”).

S protein. As I note above, a “full-length” spike protein is simply the naturally occurring spike protein, itself, as opposed to a truncated form or a subunit thereof. So, by referring to just the “spike” polypeptide (or protein), without identifying modifications or truncations, a POSA would understand Geall to be disclosing the use of the SARS-CoV spike protein (without alteration) as an RNA vaccine antigen, *i.e.*, the “full-length” spike protein.

47. **Fourth**, Dr. Fuller asserts that Schrum does not disclose administering an mRNA encoding a betacoronavirus S protein in an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit.”⁵⁷ More specifically, Dr. Fuller criticizes Schrum for “discussing an immune response generally” and not showing “working examples.”⁵⁸ As an initial matter, as explained above, this argument seems to flow from Dr. Fuller’s faulty premise that the prior art cannot disclose each limitation of a patent claim without such working examples.

48. Regardless, I disagree. As explained in my opening declaration, Schrum discloses that the administered mRNA may encode an “immunogen[]” that

⁵⁷ Ex. 2199 ¶¶ 261-275.

⁵⁸ Ex. 2199 ¶¶ 263, 270.

“elicit[s] or provoke an immune response in an organism.”⁵⁹ Schrum additionally teaches that such an immunogen may “be delivered to a vertebrate in a dose amount large enough to be immunogenic to the vertebrate.”⁶⁰ Moreover, in that same section, Schrum incorporates by reference Geall (Ex. 1010), which in turn, discloses a spike polypeptide.⁶¹ As further explained in my opening declaration, Geall elaborates that delivery of the immunogen will “elicit[] an immune response *in vivo* against an immunogen of interest” and that the response “is preferably protective and preferably involves antibodies and/or cell-mediated immunity.”⁶² As a result “the mammal can be protected against various diseases and/or infections *e.g.* against bacterial and/or viral diseases.”⁶³ Based on Schrum’s disclosure, a POSA would understand the spike protein to induce an immune response specific to the BetaCoV S protein.

2. Schrum Discloses the Elements of Claim 1 as Arranged in the Claim

⁵⁹ Ex. 1002 ¶¶ VIII.1 (quoting Ex. 1009 ¶¶ 340, 342).

⁶⁰ Ex. 1002 ¶¶ VIII.1 (quoting Ex. 1009 ¶ 340, 342).

⁶¹ Ex. 1002 ¶¶ VIII.1 (quoting Ex. 1009 ¶ 342; Ex. 1010 at 16:6-7; 19:26-29).

⁶² Ex. 1002 ¶¶ VIII.3 (quoting Ex. 1010 at 24:15-17).

⁶³ Ex. 1002 ¶¶ VIII.3 (quoting Ex. 1010 at 24:15-17).

49. Dr. Fuller also asserts that Schrum does not disclose every element of claim 1 as arranged in the claim.⁶⁴ Contrary to Dr. Fuller's opinion, Schrum does so.

50. As I explain in my opening declaration, Schrum discloses a vaccine made up of mRNA encoding an immunogen that induces an immune response.⁶⁵ As discussed above, in a paragraph describing such immunogens to be encoded by the disclosed mRNA vaccine and the dosage for such a vaccine, Schrum incorporates Geall in its entirety.⁶⁶ Thus, a POSA reading Schrum would be directed to Geall's disclosure of immunogens, which includes the SARS-CoV S protein.⁶⁷

51. I explained just as much in my deposition in response to Patent Owner's questioning:

[R]ight above paragraph 340, and it says, you can use this technology to make vaccines . . . and we are then directed to look at Geall, and then, Geall gives us a list of

⁶⁴ Ex. 2199 ¶¶ 276-316.

⁶⁵ Ex. 1002 § VIII.1 (citing Ex. 1009 ¶ 342).

⁶⁶ Ex. 1002 § VIII.1 (citing Ex. 1009 ¶ 342). And for the reasons explained above in Section IV.B.1, the incorporation includes dosages and the spike protein.

⁶⁷ Ex. 1002 ¶ 72 (citing Ex. 1010 at 16:6-7; 19:26-29).

pathogens that we might want to make a vaccine for.
And while there is a rather long list of pathogens, in that list are the top ten emerging -- some of the top ten emerging pathogens of pandemic potential, including at the very bottom of page 19, Coronavirus in the very last sentence, the spike protein.⁶⁸

52. Further, Schrum teaches formulating the immunogen-encoding mRNA vaccines, such as a betacoronavirus S protein-encoding mRNA vaccine, in a lipid nanoparticle system. Specifically, Schrum explains in paragraph 397:

In one embodiment, *an immune response may be elicited by delivering a lipid nanoparticle* which may include a nanospecies, a polymer and an immunogen. . . The polymer may encapsulate the nanospecies or partially encapsulate the nanospecies. *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.”⁶⁹

This paragraph of Schrum, paragraph 397, therefore teaches a vaccine formulated using a lipid nanoparticle (*i.e.*, that “an immune response may be elicited by

⁶⁸ Ex. 2114 at 68:3-20.

⁶⁹ Ex. 1002 ¶¶ 74-75 (citing Ex. 1009 ¶ 397) (emphases added).

delivering a lipid nanoparticle”) to encapsulate mRNA encoding an antigen (“[t]he immunogen may be a recombinant protein, *a modified RNA* described herein”). Consistent with the lipid nanoparticle’s intended purpose to elicit “an immune response,” the last sentence of paragraph 397 confirms that “the lipid nanoparticle may be formulated for use in a vaccine.” Thus, Schrum discloses the elements of claim 1 precisely as they are arranged in the claim.

53. Schrum’s express linking of mRNA vaccines and lipid nanoparticles in paragraph 397 is further consistent with the context of the reference. Schrum’s disclosures of mRNA vaccines and lipid nanoparticle delivery systems also appear closely together in Schrum. The very first application of the mRNA technology in Schrum is for vaccine applications under the heading “Activation of the Immune Response: Vaccines.”⁷⁰ Then, just three pages later, in one of the first mRNA formulation approaches identified, Schrum teaches formulating mRNA in lipid nanoparticle delivery systems under the heading “Liposomes, Lipoplexes, and Lipid Nanoparticles.”⁷¹ Paragraph 397 then expressly knits together these two closely related sections.

⁷⁰ Ex. 1009 ¶ 340.

⁷¹ Ex. 1009 ¶ 378.

54. Despite these teachings, Dr. Fuller asserts in her declaration that Schrum fails to link how the mRNA vaccines disclosed in paragraph 342 would be encapsulated in lipid nanoparticles.⁷² I disagree with Dr. Fuller's opinion. The first sentence of paragraph 397 refers to the use of a lipid nanoparticle in a vaccine, as a POSA would have understood that the term "an immune response may be elicited" refers to a vaccine. Schrum, in fact, uses just that language in its section describing mRNA vaccines.

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*. The mRNA molecules to be delivered may encode an immunogenic peptide or polypeptide and may encode more than one such peptide or polypeptide.⁷³

A POSA would therefore have understood that paragraph 397 describes the use of lipid nanoparticles to deliver a mRNA vaccine.

⁷² Ex. 2199 ¶ 278.

⁷³ Ex. 1009 ¶ 340 (emphases added).

55. Schrum reinforces that immunogen-encoding mRNA may be formulated in a lipid nanoparticle for use as a vaccine.⁷⁴ Schrum echoes that “[t]he modified nucleic acid molecules and *mmRNA of the invention* can be formulated using one or more liposomes, lipoplexes, or *lipid nanoparticles*.”⁷⁵ And, Schrum provides that in one such “*embodiment of the present invention*, mRNA molecules may be used to *elicit or provoke an immune response in an organism*.”⁷⁶ A POSA would have understood therefore that mRNA encoding an immunogen—an “mmRNA of the invention”—can be formulated using lipid nanoparticles, as Paragraph 378 of Schrum instructs.

56. Building on its disclosures of mRNA vaccines encapsulated by lipid nanoparticles, Schrum further provides concrete examples of lipid nanoparticles comprising 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid.”⁷⁷ A POSA would have understood that the mRNA vaccines disclosed in Schrum could be delivered using the lipid nanoparticles disclosed in the examples. Given that Schrum expressly

⁷⁴ Ex. 1002 ¶¶ 74-75 (citing Ex. 1009 ¶ 397).

⁷⁵ Ex. 1002 ¶ 56 (citing Ex. 1009 ¶ 378) (emphases added).

⁷⁶ Ex. 1009 ¶ 340 (emphases added).

⁷⁷ Ex. 1002 § VIII.1 (citing Ex. 1009 ¶¶ 995, 999).

states that mRNA vaccines can be encapsulated in a lipid nanoparticle *and* provides specific examples of lipid nanoparticle compositions, a POSA would have understood that the lipid nanoparticle compositions are to be used in mRNA vaccines.

57. Dr. Fuller also argues that Schrum does not disclose the elements of claim 1 as they are arranged in the claim because Schrum discloses both self-amplifying mRNA and non-amplifying mRNA.⁷⁸ There is no question, however, that Schrum discloses non-amplifying mRNA, including non-amplifying mRNA encoding an immunogen for use as a vaccine.⁷⁹ That other mRNA vaccine modalities (*i.e.*, self-amplifying mRNA) are *also* disclosed does not alter my conclusion that Schrum discloses each limitation of claim 1 as arranged in the claim.

58. In her declaration, Dr. Fuller further argues that Geall discloses “hundreds of immunogens [that] cover a wide variety of targets.”⁸⁰ Geall, however, includes a discrete section on coronaviruses, and within that section, discloses only

⁷⁸ Ex. 2199 ¶¶ 283-284.

⁷⁹ Ex. 1009 ¶ 342 (“[The] . . . mmRNA of the invention may encode an immunogen.”).

⁸⁰ Ex. 2199 ¶ 288.

one immunogen: a spike protein (as shown below).⁸¹ Thus, a POSA looking to develop an mRNA vaccine for a betacoronavirus would have only *one* option for the immunogen. Here also, the fact that Schrum *also* discloses other vaccine immunogens does not alter the fact that Schrum discloses each limitation of claim 1 as arranged therein.

59. Dr. Fuller criticizes both Schrum and Geall for lacking working examples or “data” regarding mRNA encoding betacoronavirus immunogens.⁸² A POSA, however, would have readily understood that Schrum discloses each limitation of claim 1 as arranged therein without such data. And in any event, Schrum discloses numerous working examples of mRNA encapsulated in lipid nanoparticles that result in high expression of the encoded protein.⁸³ By 2015, it was known that “[b]ecause any protein can be expressed from mRNA without the need to adjust the production process, mRNA vaccines also offer maximum flexibility with respect to development.”⁸⁴ Because Schrum discloses that “an

⁸¹ Ex. 1010 at 19:26-29.

⁸² Ex. 2199 ¶¶ 290-293.

⁸³ Ex. 1009 ¶¶ 6-8, ¶ 995.

⁸⁴ Ex. 1019 at 1319.

immune response may be elicited by delivering a lipid nanoparticle,” and “the lipid nanoparticle may be formulated for use in a vaccine,”⁸⁵ Schrum’s examples reinforce its express disclosure of formulating immunogen-encoding mRNA formulated in a lipid nanoparticle, as well as using those compositions to induce an immune response. Particularly so, since claim 1 of the ’127 patent (as well as claim 1 of the related ’600 patent) does not require any threshold level of immune response.

3. A POSA Would Readily Envisage the Limitations of Claim 1 Based upon Schrum’s Teachings

60. Dr. Fuller writes that “a POSA would not have at once envisaged the claimed arrangement of claim 1 of the ’127 patent from Schrum (including via any alleged incorporation of Geall) for at least the reasons discussed above in Section X.A.3 [*i.e.*, Dr. Fuller’s opinion that Schrum does not disclose the limitations of Claim 1 as arranged].”⁸⁶ I disagree, as, in my opinion, a POSA would have envisaged the arrangement of Claim 1 based on Schrum’s teachings.

61. As an initial matter, I note that Dr. Fuller refers back to her opinions relating to Schrum’s disclosure of each limitation of claim 1, as arranged therein. I disagree with her opinions in that section for the reasons discussed above in Section IV.B.2.

⁸⁵ Ex. 1009 ¶ 397.

⁸⁶ Ex. 2199 ¶ 317-322.

62. The remainder of Dr. Fuller’s opinions as to whether a POSA would envisage the claimed combination largely repeat that Schrum—in her eyes—discloses too much, specifically multiple immunogens that could be encoded, and multiple delivery systems.⁸⁷ I disagree. The only “selection” the POSA must make from Schrum’s disclosure is which immunogen to incorporate into the LNP-encapsulated mRNA vaccine it describes.

63. As to the selection of the SARS-CoV S protein from Geall’s list of immunogens, Dr. Fuller asserts that Geall’s list of immunogens does not contain “a small recognizable class with common properties.”⁸⁸ In my opinion, a POSA would not agree with Dr. Fuller’s interpretation. Geall discloses different classes of viruses, and within each class, Geall discloses immunogens for use against those viruses.⁸⁹ Geall discloses the small recognizable class of coronaviruses and *only* one immunogen within that class:

Coronavirus: Viral immunogens include, but are not limited to, those derived from a SARS coronavirus, avian infectious bronchitis (IBV), Mouse hepatitis virus

⁸⁷ Ex. 2199 ¶¶ 319-322.

⁸⁸ Ex. 2199 ¶ 320.

⁸⁹ For example, Ex. 1010 at 19:1-29.

(MHV), and Porcine transmissible gastroenteritis virus (TGEV). *The coronavirus immunogen may be a spike polypeptide.*⁹⁰

With respect to coronavirus, there are no other immunogens listed, and a POSA would at once envisage a mRNA vaccine encoding the betacoronavirus spike polypeptide. Further, as I explained above and at deposition, a POSA would recognize that coronaviruses remained in the list of pathogens with pandemic potential, and would therefore have selected that limited class of viruses from Geall's identified immunogens.

64. Dr. Fuller asserts that a POSA would have no reason to focus on lipid nanoparticles as delivery systems for mRNA.⁹¹ But, Schrum expressly states that “an immune response may be elicited *by delivering a lipid nanoparticle* which may include a nanospecies, a polymer and an immunogen” and “the lipid nanoparticle may be formulated for use in a vaccine such as, but not limited to, against a pathogen.”⁹² Certainly, a POSA would have at once envisaged what Schrum discloses expressly in combination – i.e., the use of lipid nanoparticles to deliver the

⁹⁰ Ex. 1010 at 19:26-29 (emphases added).

⁹¹ Ex. 2199 ¶ 321.

⁹² Ex. 1009 ¶ 397 (emphases added).

mRNA vaccine.

65. Moreover, as discussed above, in a paragraph describing an mRNA vaccine that can invoke an immune response and the dosage for such a vaccine, Schrum incorporates Geall in its entirety.⁹³ Geall elaborates that delivery of the immunogen will “elicit[] an immune response *in vivo* against an immunogen of interest” and that the response “is preferably protective and preferably involves antibodies and/or cell-mediated immunity.”⁹⁴ Specifically, it “may comprise an antibody response (usually including IgG) and/or a cell-mediated immune response.”⁹⁵ Thus, a POSA reading Schrum would be directed to Geall’s disclosure of immunogens that invoke an immune response, which includes the SARS-CoV S protein.

C. Claim 2: “The method of claim 1, wherein the open reading frame encodes a BetaCoV S protein.”

66. As I explained in my opening declaration⁹⁶ and for the reasons

⁹³ Ex. 1002 ¶ 72 (citing Ex. 1009 ¶ 342). And for the reasons explained above in Section IV.B.1, the incorporation includes dosages and the spike protein.

⁹⁴ Ex. 1002 ¶¶ VIII.3 (quoting Ex. 1010 at 24:15-17).

⁹⁵ Ex. 1002 ¶¶ VIII.3 (quoting Ex. 1010 at 16:1-3).

⁹⁶ Ex. 1002 § VIII.2.

explained in claim 1, Section IV.B, Schrum discloses each limitation of claim 2. In response, Dr. Fuller makes four arguments. I disagree with each.

67. **First**, Dr. Fuller asserts that Schrum does not anticipate claim 2 for the same reason that it does not anticipate claim 1.⁹⁷ For the reasons explained in claim 1, Section IV.B, I disagree.

68. **Second**, Dr. Fuller asserts that Schrum does not disclose the requirement of “wherein the open reading frame encodes a BetaCoV S protein.”⁹⁸ For the reasons explained in claim 1, Section IV.B, I disagree with Dr. Fuller’s opinion, as Schrum incorporates Geall, which expressly discloses an open reading frame encoding the use of the S-protein as an immunogen for a betacoronavirus vaccine.⁹⁹

⁹⁷ Ex. 2199 ¶ 325.

⁹⁸ Ex. 2199 ¶ 326.

⁹⁹ A POSA would understand that mRNA encoding the spike protein of SARS-CoV-2 would necessarily disclose an open reading frame, which is the portion of the mRNA that encodes the protein/polypeptide of interest. Ex. 1002 ¶ 73.

69. **Third**, Dr. Fuller asserts that I cannot show that Schrum discloses every element of claim 2 arranged in the same way as claim 2.¹⁰⁰ For the reasons explained in claim 1, Section IV.B, I disagree. Schrum discloses a LNP-mRNA vaccine and incorporates Geall by reference, which teaches the S-protein as an immunogen for a betacoronavirus vaccine, that can elicit an immune response.¹⁰¹

70. **Fourth**, Dr. Fuller asserts that a POSA would not have at once envisaged claim 2 for at least the reasons discussed regarding why Schrum does not disclose each element of claim 2 as arranged in the claim.¹⁰² For the reasons laid out above, and with respect to claim 1, I disagree.

D. Claim 3: “The method of claim 2, wherein the immune response is a neutralizing antibody response specific to the BetaCoV S protein.”

71. As I explained in my opening declaration¹⁰³ and for the reasons explained in Section IV.B and Section IV.C, for claims 1 and 2, Schrum discloses this limitation. I thus disagree with Dr. Fuller’s opinions to the contrary.

¹⁰⁰ Ex. 2199 ¶¶ 327-329.

¹⁰¹ Ex. 1009 ¶¶ 342, 397.

¹⁰² Ex. 2199 ¶ 330-331.

¹⁰³ Ex. 1002 § VIII.3.

72. **First**, Dr. Fuller asserts that I do not address how claims 1 and 2, from which claim 3 depends, is met.¹⁰⁴ For the reasons explained in my opening declaration,¹⁰⁵ I disagree.

73. **Second**, Dr. Fuller asserts that Schrum does not disclose a “neutralizing antibody response specific to the BetaCoV S protein,” recycling her arguments from claim 1, including that Geall does not disclose a structural protein forming a spike, a full-length spike protein, or working examples.¹⁰⁶ For the reasons explained in claim 1, Section IV.B, I disagree.

74. **Third**, Dr. Fuller asserts that I do not explain how Schrum discloses every element of claim 3 as arranged in the claim.¹⁰⁷ I disagree. As explained in my opening declaration with respect to claims 1-2, Sections IV.B and Section IV.C, Schrum discloses that the administered mRNA may encode an “immunogen[]” that “elicit[s] or provoke an immune response in an organism.”¹⁰⁸ Schrum additionally

¹⁰⁴ Ex. 2199 ¶¶ 335-336.

¹⁰⁵ Ex. 1002 §§ VIII.1-3.

¹⁰⁶ Ex. 1002 ¶¶ 337-339.

¹⁰⁷ Ex. 2199 ¶¶ 340-342.

¹⁰⁸ Ex. 1002 ¶¶ VIII.1 (quoting Ex. 1009 ¶¶ 340, 342).

teaches that such an immunogen may “be delivered to a vertebrate in a dose amount large enough to be immunogenic to the vertebrate.”¹⁰⁹

75. And as explained for claim 3 of my opening declaration, Geall elaborates that delivery of the immunogen will “elicit[] an immune response *in vivo* against an immunogen of interest” and that the response “is preferably protective and preferably involves antibodies and/or cell-mediated immunity.”¹¹⁰ Specifically, it “may comprise an antibody response (usually including IgG) and/or a cell-mediated immune response.”¹¹¹

76. Thus, given that Schrum (incorporating Geall) discloses administering mRNA encoding a spike protein and encapsulated in a lipid nanoparticle to induce an immune response, and Geall discloses that the response includes a neutralizing

¹⁰⁹ Ex. 1002 ¶¶ VIII.1 (quoting Ex. 1009 ¶ 340, 342).

¹¹⁰ Ex. 1002 §§ VIII.3 (quoting Ex. 1010 at 24:15-17); By 2015, the POSA would have recognized that Geall’s teaching that the immune response is “preferably protective” and may comprise “an antibody response (usually including IgG)” would encompass a neutralizing antibody response specific to the Beta-Cov S protein. Ex. 1002 ¶ 87.

¹¹¹ Ex. 1002 §§ VIII.3 (quoting Ex. 1010 at 15:33-16:3).

antibody response, a POSA would have further understood Schrum to disclose the additional limitation of claim 3.

77. **Fourth**, Dr. Fuller asserts that I do not explain how a POSA would have at once envisaged the claimed arrangement of claim 3.¹¹² As explained in Section IV.B and Section IV.C, a POSA would have at once envisaged the elements of claims 1 and 2. Moreover, for the reasons explained in the paragraph above, the POSA would have further understood that the mRNA in Schrum (incorporating Geall) encoding a spike protein, induces an immune response, including neutralizing antibodies. Thus, a POSA would have at once envisaged that the mRNA utilized in Schrum's disclosure of a mRNA encoding a betacoronavirus S protein and encapsulated in a lipid nanoparticle would induce a neutralizing antibody response, consistent with the additional limitation of claim 3.

E. Claim 6: "The method of claim 1, wherein the mRNA formulated in a lipid nanoparticle is administered intramuscularly."

78. As I explained in my opening declaration¹¹³ and for the reasons explained in claim 1, Section IV.B, Schrum discloses this limitation.

79. **First**, Dr. Fuller asserts that I do not address how claim 1, from which

¹¹² Ex. 2199 ¶¶ 343-344.

¹¹³ Ex. 1002 § VIII.4.

claim 6 depends, is met.¹¹⁴ For the reasons explained in my opening declaration,¹¹⁵ and in claim 1, Section IV.B, I disagree.

80. *Second*, Dr. Fuller asserts that I do not explain how Schrum discloses every element of claim 6, as arranged in the claim.¹¹⁶ As explained in my opening declaration with respect to claim 1, Schrum (incorporating Geall) discloses administering mRNA encoding a spike protein and encapsulated in a lipid nanoparticle to induce an immune response.¹¹⁷ And, as explained in my opening declaration with respect to claim 6, Schrum discusses specific examples where the lipid nanoparticle-encapsulated mRNA of the invention can be administered intramuscularly.¹¹⁸ Thus, given that Schrum discloses that the mRNA encoding a spike protein and encapsulated in a lipid nanoparticle can be administered intramuscularly, and further provides specific examples of intramuscular delivery, POSA would have understood that Schrum discloses the additional limitation of

¹¹⁴ Ex. 2199 ¶¶ 348-349.

¹¹⁵ Ex. 1002 § VIII.1, 4.

¹¹⁶ Ex. 2199 ¶¶ 350-351.

¹¹⁷ Ex. 1002 §§ VIII.1.

¹¹⁸ Ex. 1002 § VIII.4 (citing ¶¶ 999-1000; *see also* ¶¶ 1046-1049 (Example 29)).

claim 6. Still, Dr. Fuller attempts to negate Schrum's teachings by pointing to *other* options for delivery.¹¹⁹ Dr. Fuller, however, does not address Schrum's express disclosure that the mRNA can be administered intramuscularly, and that it results in successful protein expression.

81. **Third**, Dr. Fuller asserts that I do not explain how a POSA would have at once envisaged the claimed arrangement of claim 6.¹²⁰ As explained in Section IV.B.3, a POSA would have at once envisaged the elements of claim 1. Moreover, for the reasons explained in the paragraph above, given that Schrum discloses administering mRNA encoding a spike protein and encapsulated in a lipid nanoparticle, and provides examples where such mRNA is administered intramuscularly, a POSA would have further understood that the mRNA in Schrum could be administered intramuscularly. Thus, a POSA would have at once envisaged that the mRNA utilized in Schrum's disclosure of a mRNA encapsulated in a lipid nanoparticle could also be administered intramuscularly, consistent with the additional limitation of the additional limitation of claim 6.

F. Claim 7: "The method of claim 1, wherein the mRNA further comprises a 5' untranslated region and a 3' untranslated region."

¹¹⁹ Ex. 2199 ¶¶ 352-356.

¹²⁰ Ex. 2199 ¶¶ 357-358.

82. As I explained in my opening declaration¹²¹ and for the reasons explained in claim 1, Section IV.B, Schrum discloses this limitation. I thus disagree with Dr. Fuller's opinions to the contrary.

83. **First**, Dr. Fuller asserts that I do not address how claim 1, from which claim 7 depends, is met.¹²² For the reasons explained in my opening declaration,¹²³ I disagree.

84. **Second**, Dr. Fuller asserts that I do not explain how Schrum discloses every element of claim 7 as arranged in the claim.¹²⁴ I disagree. As explained in my opening declaration with respect to claim 1, Schrum (incorporating Geall) discloses administering mRNA encoding a spike protein and encapsulated in a lipid nanoparticle to induce an immune response.¹²⁵ And as further explained in my opening declaration, a POSA would have understood that mature eukaryotic mRNA transcripts contain a 5' UTR and a 3' UTR, which regulate translation of the mRNA

¹²¹ Ex. 1002 § VIII.5.

¹²² Ex. 2199 ¶¶ 362-363.

¹²³ Ex. 1002 §§ VIII.1, 5.

¹²⁴ Ex. 2199 ¶¶ 364-365.

¹²⁵ Ex. 1002 § VIII.1.

into polypeptide and can contain signal sequences directing the mRNA to certain locations within a cell so that it is translated in the appropriate cellular location.¹²⁶ Schrum further confirms that “[t]here is a growing body of evidence about the regulatory roles played by the UTRs in terms of stability of the nucleic acid molecule and translation.”¹²⁷ The ’127 patent itself confirms that “[t]he *basic components of an mRNA molecule typically include* at least one coding region, *a 5’ untranslated region (UTR), a 3’ UTR*, a 5’ cap and a poly(A) tail.”¹²⁸ Indeed, as explained in my opening declaration with respect to claim 7, Schrum discusses several such examples of mRNA comprising UTRs.¹²⁹ Thus, given that Schrum discloses mRNA, a POSA would have understood that the mRNA further comprises a 5’ UTR and 3’ UTR, as arranged in the claim.

¹²⁶ Ex. 1002 ¶¶ 26-27.

¹²⁷ Ex. 1009 ¶ 61. *See also* Ex. 1009 ¶ 904 (method for making modified mRNA including 5’ and 3’ UTRs).

¹²⁸ Ex. 1001 at 41:65-67 (emphases added).

¹²⁹ Ex. 1002 § VIII.5.

85. **Third**, Dr. Fuller asserts that I do not explain how a POSA would have at once envisaged the claimed arrangement of claim 7.¹³⁰ As explained in Section IV.B.3, a POSA would have at once envisaged the elements of claim 1. Moreover, for the reasons explained in the paragraph above, given that Schrum discloses mRNA, a POSA would have further understood that Schrum discloses a mRNA comprising a 5' untranslated region (UTR) and a 3' UTR.¹³¹ Thus, a POSA would have at once envisaged that the mRNA utilized in Schrum's disclosure of a LNP-encapsulated mRNA vaccine encoding a betacoronavirus S protein would comprise 5' and 3' UTRs, consistent with the additional limitation of claim 7.

G. Claim 8: "The method of claim 1, wherein the mRNA further comprises a poly(A) tail."

86. As I explained in my opening declaration¹³² and for the reasons explained in claim 1, Section IV.B, Schrum discloses this limitation. I thus disagree with Dr. Fuller's opinions to the contrary.

¹³⁰ Ex. 2199 ¶¶ 366-367.

¹³¹ Ex. 1002 ¶¶ 26-27.

¹³² Ex. 1002 § VIII.6.

87. **First**, Dr. Fuller asserts that I do not address how claim 1, from which claim 8 depends, is met.¹³³ For the reasons explained in my opening declaration,¹³⁴ I disagree.

88. **Second**, Dr. Fuller asserts that I do not explain how Schrum discloses every element of claim 8 as arranged in the claim.¹³⁵ I disagree. As explained in my opening declaration with respect to claim 1, Schrum (incorporating Geall) discloses administering mRNA encoding a spike protein and encapsulated in a lipid nanoparticle to induce an immune response.¹³⁶ And as further explained in my opening declaration, a POSA would have understood that mature eukaryotic mRNA transcripts contain a poly A tail that plays a role in mRNA stability and the regulation of protein translation.¹³⁷ The '127 patent itself confirms that “[t]he *basic components of an mRNA molecule typically include* at least one coding region, a

¹³³ Ex. 2199 ¶¶ 371-372.

¹³⁴ Ex. 1002 §§ VIII.1, 6.

¹³⁵ Ex. 2199 ¶¶ 373-374.

¹³⁶ Ex. 1002 § VIII.1.

¹³⁷ Ex. 1002 ¶¶ 26-27.

5' untranslated region (UTR), a 3' UTR, a 5' cap and *a poly(A) tail*.”¹³⁸ Indeed, as explained in my opening declaration with respect to claim 8, Schrum discusses such examples of mRNA comprising poly(A) tails.¹³⁹ Thus, given that Schrum discloses mRNA, a POSA would have understood that the mRNA comprises a poly(A) tail as arranged in the claim.

89. *Third*, Dr. Fuller asserts that I do not explain how a POSA would have at once envisaged the claimed arrangement of claim 8.¹⁴⁰ As explained in Section IV.B.3, a POSA would have at once envisaged the elements of claim 1. Moreover, for the reasons explained in the paragraph above, given that Schrum discloses mRNA, a POSA would have further understood that Schrum discloses a mRNA comprising a poly(A) tail. Thus, given that Schrum discloses mRNA, a POSA would have at once envisaged that the mRNA utilized in Schrum’s disclosure of a LNP-encapsulated mRNA vaccine encoding a betacoronavirus S protein would comprise a poly-A tail, consistent with the additional limitation of the additional limitation of claim 8.

¹³⁸ Ex. 1001 at 41:65-67 (emphases added).

¹³⁹ Ex. 1002 § VIII.6.

¹⁴⁰ Ex. 2199 ¶¶ 375-376.

H. Claim 9: “The method of claim 1, wherein the mRNA further comprises a 5' cap analog.”

90. As I explained in my opening declaration¹⁴¹ and for the reasons explained in claim 1, Section IV.B, Schrum discloses this limitation. I thus disagree with Dr. Fuller’s opinions to the contrary.

91. *First*, Dr. Fuller asserts that I do not address how claim 1, from which claim 9 depends, is met.¹⁴² For the reasons explained in my opening declaration,¹⁴³ I disagree.

92. *Second*, Dr. Fuller asserts that I do not explain how Schrum discloses every element of claim 9 as arranged in the claim.¹⁴⁴ I disagree. As explained in my opening declaration with respect to claim 1, Schrum (incorporating Geall) discloses administering mRNA encoding a spike protein and encapsulated in a lipid nanoparticle to induce an immune response.¹⁴⁵ And as further explained in my opening declaration, a POSA would have understood that mature eukaryotic mRNA

¹⁴¹ Ex. 1002 § VIII.7.

¹⁴² Ex. 2199 ¶¶ 380-381.

¹⁴³ Ex. 1002 §§ VIII.1, 7.

¹⁴⁴ Ex. 2199 ¶¶ 382-383.

¹⁴⁵ Ex. 1002 § VIII.1.

transcripts contain a 5' cap, which stabilize mRNA and align it on the ribosome appropriately for translation.¹⁴⁶ The '127 patent itself confirms that “[t]he *basic components of an mRNA molecule typically include* at least one coding region, a 5' untranslated region (UTR), a 3' UTR, a *5' cap* and a poly(A) tail.”¹⁴⁷ Indeed, as explained in my opening declaration with respect to claim 9, Schrum discusses such examples of mRNA comprising 5' cap analog.¹⁴⁸ Thus, given that Schrum discloses mRNA, a POSA would have understood the mRNA to further comprise a 5' cap analog, as arranged in the claim.

93. *Third*, Dr. Fuller asserts that I do not explain how a POSA would have at once envisaged the claimed arrangement of claim 9.¹⁴⁹ I disagree. As explained in Section IV.B.3, a POSA would have at once envisaged the elements of claim 1. Moreover, for the reasons explained in the paragraph above given that Schrum discloses mRNA, a POSA would have further understood that Schrum discloses a mRNA comprising a 5' cap analog. Thus, given that Schrum discloses mRNA, a POSA would have at once envisaged that the mRNA used in Schrum's disclosure pf

¹⁴⁶ Ex. 1002 ¶¶ 26-27.

¹⁴⁷ Ex. 1001 at 41:65-67 (emphases added).

¹⁴⁸ Ex. 1002 § VIII.7.

¹⁴⁹ Ex. 2199 ¶¶ 384-385.

the a LNP-encapsulated mRNA vaccine encoding a betacoronavirus S protein would comprise a comprise a 5' cap analog, consistent with the additional limitation of claim 9.

I. Claim 11: “The method of claim 1, wherein the mRNA comprises a chemical modification.”

94. As I explained in my opening declaration¹⁵⁰ and for the reasons explained for claim 1, Section IV.B, Schrum discloses this limitation. I thus disagree with Dr. Fuller’s opinions to the contrary.

95. *First*, Dr. Fuller asserts that I do not address how claim 1, from which claim 11 depends, is met.¹⁵¹ For the reasons explained in my opening declaration,¹⁵² I disagree.

96. *Second*, Dr. Fuller asserts that I do not explain how Schrum discloses every element of claim 11 as arranged in the claim.¹⁵³ I disagree. As explained in my opening declaration with respect to claim 1, Schrum (incorporating Geall) discloses administering mRNA encoding a spike protein and encapsulated in a lipid

¹⁵⁰ Ex. 1002 § VIII.8.

¹⁵¹ Ex. 2199 ¶¶ 389-390.

¹⁵² Ex. 1002 §§ VIII.1, 8.

¹⁵³ Ex. 2199 ¶¶ 391-392.

nanoparticle to induce an immune response, and that the mRNA may be modified.¹⁵⁴ And, as explained in my opening declaration with respect to claim 11, Schrum discusses examples of chemically modified mRNA resulting in successful protein expression.¹⁵⁵ Thus, given that Schrum discloses modified mRNA, and examples of modified mRNA resulting in successful protein expression, a POSA would understand that Schrum discloses the additional limitation of claim 11. Moreover, the examples of the '127 patent itself did not disclose whether or not the mRNA comprises a chemical modification, and the specification expressly states that “[b]oth chemically modified and unmodified RNA vaccines are useful according to the invention.”¹⁵⁶ Dr. Fuller further states that Geall reported ineffective results when using chemical modifications for self-amplifying mRNA.”¹⁵⁷ Irrespective of Geall’s disclosure, a POSA still would have understood that Schrum discloses that

¹⁵⁴ Ex. 1002 § VIII.1; Ex. 1009 ¶ 586.

¹⁵⁵ Ex. 1002 § VIII.8.

¹⁵⁶ Ex. 1001 at 21:8-9.

¹⁵⁷ Ex. 2199 ¶¶ 393-395, 398.

non-amplifying mRNA achieved high levels of protein expression with modified nucleotides, as explained in my opening declaration.¹⁵⁸

97. *Third*, Dr. Fuller asserts that I do not explain how a POSA would have at once envisaged the claimed arrangement of claim 11.¹⁵⁹ I disagree. As explained in Section IV.B.3, a POSA would have at once envisaged the elements of claim 1. Moreover, for the reasons explained in the paragraph above, given that Schrum discloses mRNA encoding a betacoronavirus spike protein encapsulated in a lipid nanoparticle (which has lipid components within the claimed ranges) for use in a vaccine to induce an immune response, and also discloses chemical modifications of mRNA, including examples of chemically-modified mRNA successfully expressing proteins, a POSA would have at once envisaged that Schrum's disclosure of a LNP-encapsulated mRNA encoding a betacoronavirus S protein would use the modified mRNA Schrum exemplifies, consistent with the additional limitation of claim 11.

J. Claim 12: "The method of claim 11, wherein the chemical modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification."

¹⁵⁸ Ex. 1002 § VIII.8.

¹⁵⁹ Ex. 2199 ¶¶ 396-398.

98. As I explained in my opening declaration¹⁶⁰ and for the reasons explained in claims 1 and 11, Sections IV.B and IV.I, Schrum discloses this limitation. I thus disagree with Dr. Fuller's opinions to the contrary.

99. **First**, Dr. Fuller asserts that I do not address how claims 1 and 11, from which claim 12 depends, are met.¹⁶¹ For the reasons explained in my opening declaration,¹⁶² I disagree.

100. **Second**, Dr. Fuller asserts that I do not explain how Schrum discloses every element of claim 12 as arranged in the claim.¹⁶³ As explained in my opening declaration with respect to claim 1, Schrum (incorporating Geall) discloses administering mRNA encoding a spike protein and encapsulated in a lipid nanoparticle to induce an immune response, and that the mRNA may be modified.¹⁶⁴ And, as explained in my opening declaration with respect to claim 11, Schrum

¹⁶⁰ Ex. 1002 § VIII.9.

¹⁶¹ Ex. 2199 ¶¶ 402-403.

¹⁶² Ex. 1002 §§ VIII.1, 8-9.

¹⁶³ Ex. 2199 ¶¶ 404-405.

¹⁶⁴ Ex. 1002 § VIII.1; Ex. 1009 ¶ 586.

discusses examples of modified mRNA resulting in successful protein expression.¹⁶⁵ Moreover, as I explained with respect to claim 12 of my opening declaration, Schrum provides examples of successful production of protein *in vitro* and *in vivo* after administration of N1-methylpseudouridine-modified mRNA.¹⁶⁶ Indeed, Schrum notes that “exemplary nucleobases and nucleosides having a modified uracil include . . . N1-methyl-pseudouridine.”¹⁶⁷ Thus, given Schrum’s disclosure of modified mRNA encoding a spike protein encapsulated in a lipid nanoparticle for use in a vaccine to induce an immune response, its instruction that modified mRNA can include 1-methylpseudouridine or 1-ethylpseudouridine, and its disclosure of several examples using 1-methylpseudouridine, a POSA would understand that Schrum discloses the additional limitation of claim 12. Moreover, the examples of the ’127 patent itself do not disclose whether or not the mRNA comprises a chemical modification, and the specification expressly states that “[b]oth chemically modified and unmodified RNA vaccines are useful according to the invention.”¹⁶⁸

¹⁶⁵ Ex. 1002 § VIII.8.

¹⁶⁶ Ex. 1002 § VIII.9.

¹⁶⁷ Ex. 1009 ¶ 283.

¹⁶⁸ Ex. 1001 at 21:8-9.

101. Dr. Fuller further states that Geall reported ineffective results when using chemical modifications for self-amplifying mRNA.”¹⁶⁹ Irrespective of Geall’s disclosure, a POSA still would have understood that Schrum discloses that non-amplifying mRNA achieved high levels of protein expression with modified nucleotides, as explained in my opening declaration.¹⁷⁰

102. *Third*, Dr. Fuller asserts that I do not explain how a POSA would have at once envisaged the claimed arrangement of claim 12 from Schrum.¹⁷¹ As explained in Sections IV.B.3 and IV.I, a POSA would have at once envisaged the elements of claims 1 and 11, Moreover, for the reasons explained in the paragraph above, given that Schrum discloses modified mRNA encoding a spike protein and encapsulated in a lipid nanoparticle (which has lipid components within the claimed ranges) for use in a vaccine to induce an immune response, and examples of modified mRNA (with 1-methylpseudouridine) successfully expressing proteins, a POSA would have at once envisaged that the mRNA utilized in Schrum’s disclosure of a LNP encapsulated mRNA vaccine encoding a betacoronavirus S protein that induces an immune response could contain the 1-methylpseudouridine modification Schrum

¹⁶⁹ Ex. 2199 ¶¶ 406, 409.

¹⁷⁰ Ex. 1002 § VIII.9.

¹⁷¹ Ex. 2199 ¶¶ 407-409.

exemplifies, consistent with the additional limitation of claim 12.

K. Claim 13: “The method of claim 11, wherein at least 80% of the uracil in the open reading frame of the mRNA has a chemical modification.”

103. As I explained in my opening declaration¹⁷² and for the reasons explained in claims 1 and 11, Sections IV.B and IV.I, Schrum discloses this limitation. I thus disagree with Dr. Fuller’s opinions to the contrary.

104. *First*, Dr. Fuller asserts that I do not address how claims 1 and 11, from which claim 13 depends, are met.¹⁷³ For the reasons explained in my opening declaration,¹⁷⁴ I disagree.

105. *Second*, Dr. Fuller asserts that I do not explain how Schrum discloses every element of claim 13 as arranged in the claim.¹⁷⁵ As explained in my opening declaration with respect to claim 1, Schrum (incorporating Geall) discloses administering mRNA encoding a spike protein and encapsulated in a lipid nanoparticle to induce an immune response and that the mRNA may be modified.¹⁷⁶

¹⁷² Ex. 1002 § VIII.10.

¹⁷³ Ex. 2199 ¶¶ 413-414.

¹⁷⁴ Ex. 1002 § VIII.1, 8, 10.

¹⁷⁵ Ex. 2199 ¶¶ 415-416.

¹⁷⁶ Ex. 1002 § VIII.1; Ex. 1009 ¶ 586.

And, as explained in my opening declaration with respect to claim 11, Schrum discusses examples of modified mRNA resulting in successful protein expression.¹⁷⁷ Moreover, as I explain with respect to claim 13 of my opening declaration, Schrum further explains that in the disclosed mRNA, “at least 80%, at least 90%, or 100% of the uracil in the nucleic acid may be replaced with a modified uracil.”¹⁷⁸ Thus, given that Schrum discloses modified mRNA, including examples in which at least 80%, at least 90%, or 100% of the uracil in the nucleic acid such as mRNA may be replaced with a modified uracil, a POSA would have understood that the mRNA disclosed in Schrum comprises the additional limitation in claim 13. Additionally, the examples of the ’127 patent itself did not disclose whether or not the mRNA comprises a chemical modification, and the specification expressly states that “[b]oth chemically modified and unmodified RNA vaccines are useful according to the invention.”¹⁷⁹

¹⁷⁷ Ex. 1002 § VIII.8.

¹⁷⁸ Ex. 1002 § VIII.10.

¹⁷⁹ Ex. 1001 at 21:8-9.

106. Dr. Fuller further states that Geall reported ineffective results when using chemical modifications for self-amplifying mRNA.”¹⁸⁰ Irrespective of Geall’s disclosure, a POSA still would have understood that Schrum discloses that non-amplifying mRNA achieved high levels of protein expression with modified nucleotides, as explained in my opening declaration.¹⁸¹

107. *Third*, Dr. Fuller asserts that I do not explain how a POSA would have at once envisaged the claimed arrangement of claim 13 from Schrum.¹⁸² As explained in Section IV.B.3 and IV.I, a POSA would have at once envisaged the elements of claims 1 and 11. Moreover, for the reasons explained in the paragraph above, given that Schrum discloses modified mRNA encoding a spike protein encapsulated in a lipid nanoparticle (which has lipid components within the claimed ranges) for use in a vaccine that induces an immune response, and that the mRNA can be modified from at least 80%, a POSA would have at once envisaged that the mRNA utilized in Schrum’s disclosure of a LNP-encapsulated mRNA vaccine encoding a betacoronavirus S protein to induce an immune response, would contain at least 80%, modified uracil consistent with claim 13.

¹⁸⁰ Ex. 2199 ¶ 417.

¹⁸¹ Ex. 1002 § VIII.10.

¹⁸² Ex. 2199 ¶¶ 418-420.

- L. Claim 17: “A method comprising administering to a subject an mRNA comprising a 5' cap analog, a 5' untranslated region, an open reading frame encoding a BetaCoV S protein or S protein subunit, a 3' untranslated region, and a poly(A) tail formulated in a lipid nanoparticle in an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit, wherein the lipid nanoparticle comprises 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid.”**

108. As explained in my opening declaration, Schrum discloses each limitation of claim 17.¹⁸³

109. Dr. Fuller does not dispute the majority of my explanation of Schrum's disclosures. That is, Dr. Fuller does not dispute that Schrum teaches administering mRNA encoding an immunogen (like the BetaCoV S protein), for vaccination.¹⁸⁴ Nor does Dr. Fuller dispute that Schrum teaches encapsulating mRNA in lipid nanoparticle systems in the claimed composition and ranges, including for mRNA vaccine applications, and that the mRNA comprises the 3' and 5' UTR, and a poly(A) tail.¹⁸⁵

110. Instead, Dr. Fuller argues that Schrum does not disclose the immunogen of the claims of the '127 patent—a BetaCoV S protein in an effective amount to

¹⁸³ Ex. 1002 § VIII.11.

¹⁸⁴ Ex. 2199 ¶¶ 422-428.

¹⁸⁵ Ex. 2199 ¶¶ 422-428.

induce in the subject an immune response to the BetaCoV S protein.¹⁸⁶ As explained below, I disagree.

111. Dr. Fuller further alleges that Schrum does not disclose the elements of claim 17 as they are arranged in the claim, and that a POSA would not have at once envisaged the claimed arrangement of claim 17 from Schrum.¹⁸⁷ I disagree with Dr. Fuller's opinions for the reasons below.

**1. Dr. Fuller Fails to Rebut My Demonstration
that Schrum Discloses Each Limitation of Claim 17**

112. As discussed above, the only limitation of claim 17 that Dr. Fuller contends to be not disclosed by Schrum is the BetaCoV S protein antigen that induces in the subject an immune response to the BetaCoV S protein or S protein subunit. For the reasons explained in claim 1, Section IV.B, I disagree. Schrum discloses “a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (betacov) S protein or S protein subunit,” that is administered in “an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit” including through its express incorporation of Geall, which specifically identifies the SARS-CoV S protein as the

¹⁸⁶ Ex. 2199 ¶¶ 422-428.

¹⁸⁷ Ex. 2199 ¶¶ 429-440.

antigen to be encoded by an RNA vaccine.¹⁸⁸

2. Schrum discloses the elements of claim 17 as they are arranged in the claim

113. Dr. Fuller also asserts that Schrum does not disclose every element of claim 17 as arranged in the claim.¹⁸⁹ Contrary to Dr. Fuller's opinion, Schrum does so.

114. As explained in my opening declaration,¹⁹⁰ Schrum (incorporating Geall) discloses administering a vaccine made up of mRNA with a 3' and 5' UTR, and a poly(A) tail encoding an immunogen that induces an immune response to the S protein, and formulating the mRNA vaccine in a lipid nanoparticle system that encompasses the claimed composition and ranges, as arranged in the claim.

115. In particular, building on its disclosures of mRNA vaccines encapsulated by lipid nanoparticles, Schrum provides concrete examples of lipid

¹⁸⁸ Ex. 1002 § VIII.11; A POSA would understand that mRNA encoding the spike protein of SARS-CoV-2 would necessarily disclose an open reading frame, which is the portion of the mRNA that encodes the protein/polypeptide of interest. Ex. 1002 ¶ 73.

¹⁸⁹ Ex. 2199 ¶¶ 429-436.

¹⁹⁰ Ex. 1002 ¶ VIII.11.

nanoparticles comprising 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid.”¹⁹¹ A POSA would have understood that the mRNA vaccines disclosed in Schrum could be delivered using the lipid nanoparticles disclosed in the examples.

116. Moreover, as explained in my opening declaration, a POSA would have understood that mature eukaryotic mRNA transcripts contain a 5' UTR and a 3' UTR, and a poly(A) tail.¹⁹² Indeed, the '127 patent itself confirms that “[t]he basic components of an mRNA molecule typically include at least one coding region, a 5' untranslated region (UTR), a 3' UTR, a 5' cap and a poly(A) tail.”¹⁹³ And, as explained in my opening declaration, Schrum discusses examples of mRNA comprising those components resulting in successful protein expression.¹⁹⁴ Thus, a POSA would further understand that Schrum discloses these mRNA components, as arranged in the claim.

3. A POSA would have at once envisaged the claimed arrangement of claim 17 from Schrum.

¹⁹¹ Ex. 1002 ¶ VIII.11.

¹⁹² Ex. 1002 ¶ VIII.11.

¹⁹³ Ex. 1001 at 41:65-67 (emphases added).

¹⁹⁴ 1002 § VIII.11.

117. Dr. Fuller writes that “a POSA would not have at once envisaged the claimed arrangement of claim 17 of the ’127 patent from Schrum (including via any alleged incorporation of Geall)” for at least the reasons discussed above in Section X.K.3 [*i.e.*, Dr. Fuller’s opinion that Schrum does not disclose the limitations of Claim 17 as arranged].¹⁹⁵ In particular, Dr. Fuller refers back to her opinions relating to Schrum’s disclosure of each limitation of claim 17, as arranged therein, including the SARS-CoV S protein and the lipid nanoparticle composition and ranges. I disagree with her opinions in that section for the reasons discussed in Section IV.L.2.

M. Claim 18: “The method of claim 17, wherein the open reading frame encodes a BetaCoV S protein.”

118. As I explained in my opening declaration¹⁹⁶ and for the reasons explained in claim 17, Section IV.L, Schrum discloses each limitation of claim 18. In response, Dr. Fuller makes four arguments. I disagree with each.

119. **First**, Dr. Fuller asserts that Schrum does not anticipate claim 18 for the same reason that it does not anticipate claim 17.¹⁹⁷ For the reasons explained in claim 17, Section IV.L, I disagree.

¹⁹⁵ Ex. 2199 ¶¶ 437-439

¹⁹⁶ Ex. 1002 § VIII.12.

¹⁹⁷ Ex. 2199 ¶¶ 443-444.

120. **Second**, Dr. Fuller asserts that Schrum does not disclose the requirement of “wherein the open reading frame encodes a BetaCoV S protein.”¹⁹⁸ For the reasons explained in claim 17, Section IV.L, I disagree with Dr. Fuller’s opinion, as Schrum incorporates Geall, which expressly discloses the use of the S-protein as an immunogen for a betacoronavirus vaccine.¹⁹⁹

121. **Third**, Dr. Fuller asserts that I cannot show that Schrum discloses every element of claim 18 arranged in the same way as claim 18.²⁰⁰ For the reasons explained in claim 17, Section IV.L, I disagree. Schrum discloses administering a mRNA vaccine with specific mRNA components (5’ and 3’ UTR, poly(A) tail) encapsulated in a lipid nanoparticle (which has lipid components within the claimed ranges), and incorporates Geall by reference, which teaches the S-protein as an immunogen for a betacoronavirus vaccine, to induce an immune response to the spike protein.

¹⁹⁸ Ex. 2199 ¶ 445.

¹⁹⁹ A POSA would understand that mRNA encoding the spike protein of SARS-CoV-2 would necessarily disclose an open reading frame, which is the portion of the mRNA that encodes the protein/polypeptide of interest. Ex. 1002 ¶ 73.

²⁰⁰ Ex. 2199 ¶¶ 446-448.

122. **Fourth**, Dr. Fuller asserts that a POSA would not have at once envisaged claim 18 for at least the reasons discussed regarding why Schrum does not disclose each element of claim 17 as arranged in the claim.²⁰¹ For the reasons explained in the paragraph above, and with respect to claim 17, I disagree.

N. Claim 20: “The method of claim 18, wherein at least 80% of the uracil in the open reading frame of the mRNA has a 1-methylpseudouridine modification.”

123. As I explained in my opening declaration²⁰² and for the reasons explained in claims 17 and 18, Sections IV.L and IV.M, Schrum discloses this limitation. I thus disagree with Dr. Fuller’s opinions to the contrary.

124. **First**, Dr. Fuller asserts that I do not address how claims 17 and 18, from which claim 20 depends, are met.²⁰³ For the reasons explained in my opening declaration,²⁰⁴ I disagree.

125. **Second**, Dr. Fuller asserts that I do not explain how Schrum discloses every element of claim 20 as arranged in the claim.²⁰⁵ As explained in my opening

²⁰¹ Ex. 2199 ¶¶ 449-450.

²⁰² Ex. 1002 § VIII.13.

²⁰³ Ex. 2199 ¶¶ 454-455.

²⁰⁴ Ex. 1002 §§ VIII.11-13.

²⁰⁵ Ex. 2199 ¶¶ 456-457.

declaration with respect to claims 17 and 18, Schrum discloses administering a mRNA vaccine (that may be modified) with specific mRNA components (5' and 3' UTR, poly(A) tail) encapsulated in a lipid nanoparticle (which has lipid components within the claimed ranges), and incorporates Geall by reference, which teaches the S-protein as an immunogen for a betacoronavirus vaccine, to induce an immune response to the spike protein.²⁰⁶ Moreover, as I explain with respect to claim 13 of my opening declaration, Schrum further explains that in the disclosed mRNA, “at least 80%, at least 90%, or 100% of the uracil in the nucleic acid may be replaced with a modified uracil successful production of protein *in vitro* and *in vivo*.”²⁰⁷ Indeed, Schrum notes that “exemplary nucleobases and nucleosides having a modified uracil include . . . N1-methyl-pseudouridine.”²⁰⁸ Thus, given Schrum’s disclosure of modified mRNA, including examples in which at least 80%, at least 90%, or 100% of the uracil in the nucleic acid such as mRNA may be replaced with a modified uracil, and its disclosure of several examples using 1-methylpseudouridine, a POSA would understand that Schrum discloses the

²⁰⁶ Ex. 1002 § VIII.11-12.

²⁰⁷ Ex. 1002 § VIII.13.

²⁰⁸ Ex. 1009 ¶ 283.

additional limitation of claim 20. Moreover, the examples of the '127 patent itself did not disclose whether or not the mRNA comprises a chemical modification, and the specification expressly states that “[b]oth chemically modified and unmodified RNA vaccines are useful according to the invention.”²⁰⁹

126. Dr. Fuller further states that Geall reported “ineffective results when using chemical modifications for self-amplifying mRNA.”²¹⁰ Irrespective of Geall’s disclosure, a POSA still would have understood that Schrum discloses that non-amplifying mRNA achieved high levels of protein expression with modified nucleotides, as explained in my opening declaration.²¹¹

127. **Third**, Dr. Fuller asserts that I do not explain how a POSA would have at once envisaged the claimed arrangement of claim 20.²¹² As explained in Section IV.L.3 and IV.M, a POSA would have at once envisaged the elements of claims 17 and 18. Moreover, for the reasons explained in the paragraph above, given that Schrum discloses modified mRNA, that the mRNA can be modified from at least 80%, and examples of modified mRNA (with 1-methylpseudouridine) successfully

²⁰⁹ Ex. 1001 at 21:8-9.

²¹⁰ Ex. 2199 ¶ 458.

²¹¹ Ex. 1002 § VIII.13.

²¹² Ex. 2199 ¶¶ 459-461.

expressing proteins, a POSA would have at once envisaged that the mRNA utilized in Schrum's disclosure of mRNA with 5' and 3' UTRs and poly(A) tail encoding a betacoronavirus S protein and encapsulated in an LNP would also contain modifications of at least 80% of its uracil residues with the 1-methylpseudouridine modification Schrum exemplifies, consistent with the additional limitation of claim 20.

V. GROUND 2: THE COMBINATION OF SCHRUM IN VIEW OF GEALL DISCLOSES ALL OF THE LIMITATIONS OF CLAIMS 1-3, 6-9, 11-13, 17-18, AND 20

128. In Section IX of my previous declaration, I explained that each of the limitations of claims 1-3, 6-9, 11-13, 17-18, and 20 had already been disclosed by Schrum in view of Geall by October 2015, which I understand is referred to as Ground 2 in this proceeding.²¹³ In Section IX of my previous declaration, I also explained why, as of October 2015, a POSA would have been motivated to combine the teachings of the prior art to arrive at the claimed combination of known elements, as well as why a POSA would have reasonably expected to do so successfully.

129. While Dr. Fuller purports to respond to my analysis in Section XI of her own declaration, she does not dispute the majority of my analysis. Instead, Dr. Fuller recycles many of the erroneous opinions discussed above with respect to

²¹³ Ex. 1002 § IX.

Ground 1, and makes a host of additional arguments as to why a POSA would allegedly disregard and not credit the teachings of the prior art, including in Schrum and Geall. In doing so, Dr. Fuller fails to apply accurately the relevant prior art disclosures or faithfully describe the true state of the art. I therefore disagree with Dr. Fuller, and my opinions remain unchanged.

- A. Claim 1: “A method comprising administering to a subject a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit formulated in a lipid nanoparticle in an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit, wherein the lipid nanoparticle comprises 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid.”**

130. Schrum in view of Geall discloses each limitation of claim 1, and a POSA would have had good reason to combine Schrum’s disclosure of a lipid nanoparticle encapsulating an mRNA encoding an immunogen that induces an immune response with Geall’s teaching that the immunogen of an RNA vaccine may be a betacoronavirus S protein, all with a reasonable expectation success. Dr. Fuller has not shown otherwise, and her opinions in response raise a host of inaccurate, and often irrelevant, points that I respond to further below.

1. Schrum and Geall Disclose Every Element of Claim 1

131. I have previously explained that Schrum in view of Geall teaches every limitation of claim 1.²¹⁴

132. **First**, in her declaration, Dr. Fuller asserts that the combination of Schrum and Geall does not disclose mRNA because Geall is focused on self-amplifying mRNA (which she asserts is not mRNA) rather than non-amplifying mRNA.²¹⁵ But there is no question that Schrum discloses non-amplifying mRNA vaccines encoding for an immunogen, as well as the encapsulation of such mRNA in lipid nanoparticles, as explained in Section IV.B.

133. **Second**, Dr. Fuller also repeats her argument from Ground 1 that Geall does not disclose a spike protein, including because it is not a full-length spike protein and there is no evidence that it forms a spike.²¹⁶ For the reasons explained in Section IV.B.1, a POSA reading Geall would understand it as teaching the use of a betacoronavirus S protein (a “full-length S protein”) as the immunogen for a

²¹⁴ Ex. 1002 § IX.1.

²¹⁵ Ex. 2199 ¶¶ 467-493.

²¹⁶ Ex. 2199 ¶¶ 494-495.

vaccine.²¹⁷

134. Moreover, as explained in Section IV.B.1, Schrum incorporates Geall for its disclosure of immunogens, including that the spike protein is the antigen for betacoronavirus, contrary to Dr. Fuller's argument. And as explained in Section IV.B.3, Schrum includes a discrete section on coronaviruses, and within that section, discloses only one immunogen: a spike protein. Geall further elaborates that delivery of the immunogen will "elicit[] an immune response in vivo against an immunogen of interest" and that the response "is preferably protective and preferably involves antibodies and/or cell-mediated immunity."²¹⁸ Specifically, it "may comprise an antibody response (usually including IgG) and/or a cell-mediated immune response."²¹⁹ Thus, a POSA looking to develop an mRNA vaccine for a coronavirus, and more specifically, a betacoronavirus, would have only one option, not five hundred, as Dr. Fuller contends.

²¹⁷ A POSA would understand that mRNA encoding the spike protein of a SARS-CoV would necessarily disclose an open reading frame, which is the portion of the mRNA that encodes the protein/polypeptide of interest. Ex. 1002 ¶ 73.

²¹⁸ Ex. 1002 § IX.3.

²¹⁹ Ex. 1002 § IX.3.

135. **Third**, Dr. Fuller asserts that concerns regarding antibody dependent enhancement (“ADE”) would have discouraged a POSA would have discouraged use of a spike protein. For the reasons explained in Section V.A.2.b.3, I disagree.

136. **Fourth**, Dr. Fuller repeats her arguments from ground 1 that Schrum in view of Geall does not disclose a S protein that can elicit a specific immune response, criticizing Schrum for “discussing an immune response generally” and not showing “working examples.”²²⁰ As an initial matter, as explained above this argument seems to flow from Dr. Fuller’s faulty premise that the prior art cannot disclose each limitation of a patent claim without such working examples.

137. Regardless, I disagree. As explained in my opening declaration, Schrum discloses that the administered mRNA may encode an “immunogen[]” that “elicit[s] or provoke an immune response in an organism.”²²¹ Schrum additionally teaches that such an immunogen may “be delivered to a vertebrate in a dose amount large enough to be immunogenic to the vertebrate.”²²² Moreover, in that same section, Schrum incorporates by reference Geall (Ex. 1010), which in turn, discloses

²²⁰ Ex. 2199 ¶¶ 500-504.

²²¹ Ex. 1002 § IX.1 (quoting Ex. 1009 ¶¶ 340, 342).

²²² Ex. 1002 § IX.1 (quoting Ex. 1009 ¶¶ 340, 342).

a spike polypeptide.²²³ As further explained in my opening declaration, Geall elaborates that delivery of the immunogen will “elicit[] an immune response *in vivo* against an immunogen of interest” and that the response “is preferably protective and preferably involves antibodies and/or cell-mediated immunity.”²²⁴ Specifically, it “may comprise an antibody response (usually including IgG) and/or a cell-mediated immune response.”²²⁵ Thus, a POSA would have understood Schrum in view of Geall as teaching the use of a betacoronavirus S protein to induce a specific immune response.

**2. A POSA Would Have Been Motivated
to Combine the Teachings of Schrum and
Geall With a Reasonable Expectation of Success**

138. In my previous declaration, I explained that a POSA would have been motivated to combine Schrum’s disclosure of the use of an mRNA vaccine encoding an immunogen and encapsulated in a lipid nanoparticle with Geall’s disclosure of an RNA vaccine encoding a betacoronavirus spike protein that induces an immune

²²³ Ex. 1002 § IX.1 (quoting Ex. 1009 ¶ 342; Ex. 1010 at 16:6-7; 19:26-30).

²²⁴ Ex. 1002 § IX.3 (quoting Ex. 1010 at 24:15-17).

²²⁵ Ex. 1002 § IX.3 (quoting Ex. 1010 at 16:1-3).

response, and would reasonably have expected to do so successfully in view of well-known methods of synthesizing mRNA, already known in the art.²²⁶

139. Dr. Fuller does not meaningfully dispute my analysis in her declaration.²²⁷ Nor could she, as she agreed at deposition that “a POSA, yeah, would be able to – once they had the genetic code be able to design an RNA or DNA molecule . . . encoding that” protein.²²⁸ Moreover, Dr. Fuller’s deposition testimony confirmed that it was “*basic fundamental nucleic acid vaccine biology* that when you have a DNA or an RNA vaccine and you can validate that it expresses a protein

²²⁶ Ex. 1002 § IX.1.

²²⁷ Ex. 2199 ¶ 511 (Dr. Fuller instead parrots that “neither Schrum nor Geall have any data or working example with **any** betacoronavirus immunogen—let alone an S protein or an S protein subunit.” This does not engage with or rebut my explanation that a POSA would reasonably expect to utilize well-known methods of making mRNA.)

²²⁸ Ex. 1104 at 78:11-16; *see also id.* at 78:5-10 (Dr. Fuller agreeing that “[f]or any given protein, once we know the genetic sequence or code, we can design an mRNA or DNA molecule that prompts a person’s cells to start making it.”).

in vitro, then the hypothesis is that if you inject that DNA or RNA vaccine into an animal . . . the hypothesis is that it will elicit an immune response.”²²⁹

140. In her declaration, Dr. Fuller was less forthright. She instead pivots to making a number of arguments as to why—in her view—a POSA would not credit the plain teachings of Schrum and Geall, which disclose an mRNA vaccine encoding a betacoronavirus S protein formulated in a lipid nanoparticle.²³⁰ Dr. Fuller identifies eight purported reasons as to why “a POSA would not have had a reasonable expectation of success of October 2015.”²³¹

141. As an initial matter, it is not clear that the additional arguments that Dr. Fuller makes are responsive to the analysis that I have previously provided. Many of Dr. Fuller’s opinions do not appear to relate, in fact, to the relevant question of whether a POSA would reasonably expect to successfully synthesize an mRNA molecule encoding a betacoronavirus spike protein formulated in a lipid nanoparticle, and use such a composition to induce an immune response. For example, Dr. Fuller alleges that “to the extent mRNA was being considered in the

²²⁹ Ex. 1104 at 51:22-52:9 (emphasis added).

²³⁰ *See, e.g.*, Ex. 2199 ¶ 512.

²³¹ Ex. 2199 ¶ 512.

clinical context, it was much more likely to be used for cancer applications than for infectious disease vaccines.”²³² She does not explain, however, how the use of mRNA for other therapeutic purposes would detract from a POSA’s reasonably expecting to combine the disclosures of Schrum and Geall to arrive at the method of claim 1. In my opinion it would not have done so.

142. Nevertheless, I respond to Dr. Fuller’s arguments below, none of which rebuts my explanation that a POSA would be motivated to combine the teachings of Schrum and Geall, and would reasonably expect to do so successfully. As I explain further, Dr. Fuller misreads, and misapplies, the prior art. A POSA would have been motivated to combine Schrum and Geall’s express disclosures with a reasonable expectation of success at arriving at the method of claim 1 because a POSA would: (a) be motivated to develop an mRNA vaccine and reasonably expect to induce an immune response with an mRNA vaccine; (b) be motivated to select a betacoronavirus spike protein as the immunogen to be encoded by an mRNA vaccine and reasonably expect to design an mRNA sequence encoding for that protein and use such a composition to induce an immune response; and (c) formulate an immunogen-encoding mRNA vaccine (like a betacoronavirus spike protein-

²³² Ex. 2199 ¶ 512.

encoding mRNA vaccine) in a lipid nanoparticle delivery system. Patent Owner's own scientific publications [REDACTED] further confirm my own opinions.²³³

a. Schrum's Teachings, Paired with the State of the Art, Would Motivate a POSA to Utilize an mRNA Vaccine with a Reasonable Expectation of Success

143. As I have discussed, Schrum teaches mRNA vaccines encoding an immunogen, like the betacoronavirus S protein. Under the heading, "Activation of the Immune Response: Vaccines," Schrum teaches, "[i]n one embodiment of the

²³³ Dr. Fuller also repeats a number of opinions from other portions from her Declaration. For example, Dr. Fuller asserts that Schrum incorporates Geall for dose amounts rather than immunogens. For the reasons explained in Section IV.B.1, I disagree. Dr. Fuller disputes that both Schrum and Geall relate to the same field of RNA vaccines. I disagree for the reasons explained in Section V.A.2.c.2. In addition, Dr. Fuller also mischaracterizes my testimony. Dr. Fuller contends that I testified that I "would need to see the data for a vaccine encoding a different protein choice to be able to evaluate it." My testimony, however, was specifically directed to whether a POSA would have reasonably expected enhanced disease and early death in patients who are administered vaccines containing the M and N proteins.

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.”²³⁴ A POSA would read, and credit that teaching, which would independently motivate a POSA to follow Schrum’s direction and develop an mRNA vaccine. That is particularly true where, as Dr. Fuller admitted during deposition, “[b]y 2013, it was pretty well known that you could do different nucleic acids [vaccines] and inject those into cells and those nucleic acids could express something and maybe provoke an immune response.”²³⁵

144. Dr. Fuller’s declaration, however, takes the surprising position that a POSA would entirely set aside, or ignore, the teachings of Schrum relating to vaccines encoding an immunogen due to such skepticism.

145. I disagree, including because, by October 2015:

- No alleged “skepticism” of mRNA vaccines in the field taught away from Schrum’s disclosure of mRNA vaccines encoding an immunogen. To the contrary, significant progress in the development of mRNA vaccines only confirmed Schrum’s teachings.

²³⁴ Ex. 1009 ¶ 340; *see also id.* ¶ 342 (“In one embodiment, the modified nucleic acid molecules and/or mmRNA of the invention may encode an immunogen.”).

²³⁵ Ex. 1104 at 212:18-213:4 (emphases added).

- mRNA vaccines encoding for infectious disease immunogens had demonstrated significant protective potential.
- mRNA vaccines had known benefits over other vaccine modalities, including over different nucleic acid vaccine modalities.

1) *No “Skepticism” of mRNA Vaccines*

146. Dr. Fuller contends that “[i]n 2015, the field was skeptical of mRNA vaccines and favored traditional or other nucleic acid vaccines instead due to a host of efficacy concerns in general and lack of any proven clinical success.”²³⁶ Dr. Krause offers a similar opinion.²³⁷ I disagree. Dr. Fuller’s deposition testimony and Dr. Fuller’s and Krause’s cited references undermine this contention.

147. As early as 1990, scientists demonstrated that mRNA administered to mice successfully induced protein production.²³⁸ Three years later, scientists extended their research to infectious diseases, showing that mice injected with mRNA encoding the nucleoprotein of the influenza virus encapsulated in liposomes elicited nucleoprotein-specific cytotoxic T cells in mice.²³⁹ Dr. Fuller recognized

²³⁶ Ex. 2199 ¶ 513.

²³⁷ *E.g.*, Ex. 2200 ¶ 179.

²³⁸ Ex. 1013 at 1.

²³⁹ Ex. 1014 at 1.

these early demonstrations of the potency of mRNA vaccines, testifying at deposition that “the idea that nucleic acid vaccines could enable rapid vaccine [development] came about at the earliest conception of the idea of nucleic acid vaccines,” which emerged in “[t]he 1990s.”²⁴⁰

148. In subsequent years, several other groups of researchers continued to research mRNA therapeutics and vaccines, making significant progress. For example, in 2000, researchers confirmed that injection of mRNA encoding a protein resulted in protein production and an immune response specific to the protein, and concluded that “RNA preparations are suitable tools for vaccination.”²⁴¹

149. As early as 2012, Novartis developed and tested a self-amplifying mRNA vaccine *in vivo*. In this study, by Geall et al., Novartis’s researchers demonstrated that “delivery of a 9-kb self-amplifying RNA encapsulated within an LNP” and encoding the RSV-F protein, elicited “broad, potent, and protective immune responses, that were comparable to a viral delivery technology, but without the inherent limitations of viral vectors.”²⁴² Notably, the lipid nanoparticles used in

²⁴⁰ Ex. 1104 at 74:15-75:2.

²⁴¹ Ex. 1117 at 5.

²⁴² Ex. 2021 at 14604.

Novartis's RSV vaccine study contained the same lipids, in the same ratios, as those claimed in the '127 patent.²⁴³ And while Novartis focused on self-amplifying mRNA vaccines, companies such as CureVac demonstrated in animal models that non-amplifying mRNA could also be used as effective vaccines, as discussed below with respect to Petsch.²⁴⁴

150. Based on these significant developments, Dr. Fuller agreed that “[b]y 2013, it was pretty well known that you could do different nucleic acids [vaccines] and inject those into cells and those nucleic acids could express something and maybe provoke an immune response.”²⁴⁵

151. Moreover, the conclusion that, “[i]n 2015, the field was skeptical of mRNA vaccines” is contradicted by the teachings of the prior art, including the very literature to which Drs. Fuller and Krause cite. Below, I address the literature that Dr. Fuller cites in turn.

²⁴³ Ex. 2021 at 14608.

²⁴⁴ Ex. 2025 at 1210.

²⁴⁵ Ex. 1104 at 212:18-213:4 (emphasis added).

152. **Petsch (Ex. 2025).** Drs. Fuller and Krause rely on Petsch as supporting skepticism of mRNA vaccines;²⁴⁶ it does not. Petsch teaches, as of its 2012 publication:

mRNA vaccines induce balanced, long-lived and protective immunity to influenza A virus infections in even very young and very old mice and that the vaccine remains protective upon thermal stress. This vaccine format ***elicits B and T cell-dependent protection*** and targets multiple antigens, including the highly conserved viral nucleoprotein, indicating its usefulness as a cross-protective vaccine. In ferrets and pigs, ***mRNA vaccines induce immunological correlates of protection and protective effects similar to those of a licensed influenza vaccine in pigs.***²⁴⁷

In her declaration, Dr. Fuller selectively quotes Petsch's statement that "whether mRNA vaccines induce protective antibody responses and are efficacious in infectious disease is not clear."²⁴⁸ Dr. Fuller, however, omits the next sentence of Petsch, in which the authors confirm that they answer the posed question in the

²⁴⁶ E.g., Ex. 2199 ¶ 533; Ex. 2200 ¶ 71.

²⁴⁷ Ex. 2025 at 1210 (emphases added).

²⁴⁸ Ex. 2199 ¶ 533 (citing Ex. 2025 at 1210-1211).

affirmative, writing that they have “validated the mRNA vaccine approach for a B cell-dependent mode of protection against an infectious disease, influenza.”²⁴⁹ [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

153. *Pardi 2018 (Ex. 2027)*. Drs. Fuller and Krause likewise rely on Pardi 2018 as showing skepticism of mRNA vaccines. As with Petsch, it does not. Dr. Fuller’s declaration again selectively quotes Pardi 2018’s statement that mRNA’s “early promising results did not lead to substantial investment in mRNA therapeutics.”²⁵¹ Dr. Fuller does not address the next sentence, which states that “[o]ver the past decade, major technological innovation and research investment have enabled mRNA to become a promising therapeutic tool in the fields of vaccine

²⁴⁹ Ex. 2025 at 1211.

²⁵⁰ [REDACTED]

[REDACTED]

[REDACTED]

²⁵¹ For example, Ex. 2199 ¶ 72 (quoting Ex. 2027), ¶ 514.

development and protein replacement therapy.”²⁵² That is, Pardi 2018 reports that due to work dating back to 2008, the “concerns” that Dr. Fuller cites (*i.e.*, instability, immunogenicity, and inefficient delivery) ***had already been solved.***²⁵³ Notably, Pardi 2018 cites pre-2015 studies from CureVac and Novartis (among others) for the proposition that “mRNA vaccines have elicited protective immunity against a variety of infectious agents in animal models and have therefore generated substantial optimism,”²⁵⁴ contradicting Dr. Fuller’s contention that the authors’ conclusions relied on “knowledge of the inventions described in the ’127 patent.”²⁵⁵

154. ***DeFrancesco 2017 (Ex. 2028).*** Dr. Fuller further relies on DeFrancesco 2017 as showing that the field was skeptical of mRNA vaccines (despite being published after 2015); it does the opposite. DeFrancesco 2017 quotes DARPA executives as reporting significant optimism, stating, “What you are seeing

²⁵² Ex. 2027 at 261 (emphases added).

²⁵³ As I discuss further below, Dr. Fuller’s own statements and publications echo that concerns with mRNA instability, immunogenicity, and inefficient delivery had been solved by October 2015. (*Infra* § V.A.2.b.1.b.)

²⁵⁴ Ex. 2027 at 267.

²⁵⁵ Ex. 2199 ¶ 516.

in the field now is that using a nucleic acid to get the body to do what you want it to do, whether it's a vaccine or other responses, is really exploding. We find that profoundly exciting.”²⁵⁶ And while Dr. Fuller tries to dismiss the optimism of DARPA executives on the theory that DARPA funds only “early-breakthrough, high-risk, things would not normally be funded,”²⁵⁷ she does not address the article’s description of other sources of mRNA funding, such as \$52 million-dollar contract from the Gates foundation.²⁵⁸

155. *Geall 2013 (Ex. 1016)*. Finally, Dr. Fuller also relies on Geall 2013 as showing skepticism, but again does not apply the teachings of the cited reference. Dr. Fuller points to Geall 2013’s statement that “development of RNA vaccines is still in its infancy.”²⁵⁹ However, she omits that Geall 2013 teaches that—even by its 2013 publication date—“RNA vaccines (*both mRNA and replicons*) are effective at eliciting antigen-specific humoral and cellular immune responses in animal models

²⁵⁶ Ex. 2028 at 193.

²⁵⁷ Ex. 2199 ¶ 518 (quoting Ex. 2028 at 193).

²⁵⁸ Ex. 2028 at 196.

²⁵⁹ For example, Ex. 2199 ¶ 547 (quoting Ex. 1016 at 156).

of infectious and non-infectious diseases.”²⁶⁰ The authors’ conclusion was further rooted in the fact that, by its 2013 publication date, “[h]aving achieved some important pre-clinical and clinical milestones already, RNA vaccines are now progressing into clinical testing for a number of prophylactic and therapeutic applications.”²⁶¹ Geall 2013 was published two years before the 2015 priority date of the ’127 patent. Even then, the authors emphasized that “RNA vaccines (*both mRNA and replicons*) are effective at eliciting antigen-specific humoral and cellular immune responses in animal models of infectious and non-infectious diseases” and that “[n]otably, improvements in the stability, durability and expression levels of mRNA-based vaccines have been achieved through the optimization of specific sequence elements.”²⁶²

156. ***Dr. Fuller’s Public Statements and Publications Referring to the State of the Art as of 2015 (Ex. 1100).*** Dr. Fuller’s own public statements and publications confirm that any alleged “skepticism” would not have led a POSA away from Schrum’s express teachings. In a January 2022 article—reviewed by Dr.

²⁶⁰ Ex. 1016 at 3 (emphases added).

²⁶¹ Ex. 1016 at 5.

²⁶² Ex. 1016 at 2-3 (emphases added).

Fuller—summarizing an interview in which she participated, Dr. Fuller explained that nucleic acid vaccines “ha[ve] been in the works for about 30 years. Nucleic acid vaccines are based on the idea that DNA makes RNA and then RNA makes proteins. For any given protein, once we know the genetic sequence or code, we can design an mRNA or DNA molecule that prompts a person’s cells to start making it.”²⁶³ She further explained that “about seven or eight years ago [*i.e.*, around 2014-2015], mRNA vaccines started to take the lead.”²⁶⁴

157. As to why “mRNA vaccines started to take the lead,” the article summarizing the conversation with Dr. Fuller continues, “Researchers solved a lot of the problems – notably the *instability* – and *discovered new technologies to*

²⁶³ Ex. 1100 at 1.

²⁶⁴ Ex. 1100 at 2. I understand that, at her deposition, Dr. Fuller contended that her previous statement that mRNA vaccines “started to take the lead” “seven or eight years ago” [*i.e.*, in 2014 or 2015] was “kind of hand waving,” and that “it was probably about 2016 that we began to take more notice of the capability of mRNA vaccines to potentially outperform DNA vaccines.” (Ex 1104 at 80:1-15.) She offered no support for recanting her previous statement, and instead arbitrarily recasting the date to one that is just after the priority date of the ’127 patent.

deliver mRNA into cells.”²⁶⁵ For the proposition that mRNA “instability” and “delivery,” had been solved, Dr. Fuller’s article cites Ex. 1022 (2008 article from Karikó et al.) and Ex. 2021 (2012 article from Geall et al.).²⁶⁶ Notably, the concerns of mRNA stability and delivery—identified by Ex. 1100 as being solved by 2012—are the same concerns that Dr. Fuller identifies as being the basis for skepticism towards mRNA vaccines. Since researchers had “solved” these concerns by 2012, based on the cited literature, they do not support skepticism.

158. ***Dr. Fuller’s Deposition Testimony.*** Finally, as I have previously noted, Dr. Fuller recognized at deposition that mRNA vaccines were “pretty well known” by 2013, which additionally undercuts her claim of skepticism.

Q. You don’t dispute that Schrum discloses an mRNA vaccine to elicit or provoke an immune response. Right?

A. By 2013, it was pretty well known that you could do different nucleic acids [vaccines] and inject those into cells and those nucleic acids could express something and maybe provoke an immune response.²⁶⁷

²⁶⁵ Ex. 1100 at 2 (emphases added).

²⁶⁶ Ex. 1100 at 2. *See* Ex. 1104 at 88:15-89:4, 101:16-103:2.

²⁶⁷ Ex. 1104 at 212:18-213:4.

159. No skepticism would teach away from Schrum's disclosure of an mRNA vaccine, and Drs. Fuller's and Krause's opinions to the contrary are incorrect.

2) *Clinical Trials of mRNA Vaccines Encoding for Infectious Disease Immunogens Do Not Demonstrate Skepticism*

160. Dr. Fuller next argues that, even if a POSA were motivated to pursue development of an mRNA vaccine, they would not do so for infectious diseases based on certain clinical trials that she identifies.²⁶⁸ In doing so, Dr. Fuller appears to impose an artificial requirement that a POSA need to have a reasonable expectation that the mRNA vaccine would meet efficacy endpoints in clinical trials and receive ultimate FDA approval as the measure of "success." The claims of the '127 patent require no such thing.

161. As a preliminary matter, the fact that there were no FDA authorized or approved mRNA vaccines for infectious diseases in 2015 does not mean the field was skeptical of mRNA vaccines. Under normal circumstances, the process of developing a vaccine can take 5-10 years. Phase II clinical trials alone often take 2-

²⁶⁸ See Ex. 2199 ¶¶ 515-28. Dr. Krause offers similar opinions citing the same studies in his declaration. See Ex. 2200 at ¶¶ 193-197. I disagree with Dr. Krause's opinions for the same reasons I disagree with Dr. Fuller's opinions.

3 years, and Phase III clinical trials can take another 2-4 years.²⁶⁹ Hence, even if companies like CureVac started clinical testing around 2012-2013 (after they had demonstrated the proof-of-concept for their respective mRNA vaccines, such as in the Petsch 2012 article discussed above), they would have been unlikely to secure FDA approval by 2015.

162. I also disagree with Dr. Fuller's opinion that the results of early clinical trials would have created skepticism towards mRNA vaccines. I address each of the studies that Dr. Fuller identifies below:

163. ***CureVac's Rabies Vaccine.*** Dr. Fuller cites a phase I clinical trial of a mRNA vaccine against rabies initiated in 2013, as reported by Alberer et al. In that study, participants received three doses of a mRNA vaccine against rabies through either a needle-syringe or a needle-free injection device.²⁷⁰ The study found that participants who received intradermal or intramuscular vaccines through a needle-free injection device developed virus neutralizing antibodies against the rabies virus, whereas participants who received the vaccine through a needle-syringe did not develop antibodies. The authors concluded that "a prophylactic mRNA-based

²⁶⁹ Ex. 1134 at 2-4.

²⁷⁰ Ex. 2046 at 1.

candidate vaccine can induce boostable functional antibodies against a viral antigen when administered with a needle-free device.”²⁷¹

164. Rather than addressing the full results of CureVac’s clinical study, Dr. Fuller focused on the fact that the vaccine “‘was ineffective’ when administered via ‘intramuscular[] . . . needle-syringe’ injection.”²⁷² The ’127 patent, however, does not require the vaccine to be delivered in a syringe as opposed to a needle free injector.²⁷³ The study authors emphasized how the “study provides the first proof-of-concept that an mRNA-based prophylactic vaccine is reasonably safe and capable of inducing rabies antibodies in humans.”²⁷⁴ The study further concluded that the results of this clinical study “could lay the foundation to expand this novel vaccine

²⁷¹ Ex. 2046 at 1.

²⁷² Ex. 2199 ¶ 525.

²⁷³ Claim 6 of the ’127 patent requires the mRNA vaccine to be delivered intramuscularly, but does not require a syringe. As noted in Alberer et al., intramuscular administration through a needle free injector successfully induced neutralizing antibodies against the rabies vaccine.

²⁷⁴ Ex. 2046 at 9.

platform to other infectious diseases where rapid supply is critical.”²⁷⁵ Thus, the CureVac rabies clinical trial demonstrates the field remained optimistic about mRNA vaccines.

165. *iHIVARNA Vaccine Against HIV*. Dr. Fuller also cites a Phase II clinical study of iHIVARNA, an investigational therapeutic vaccine for HIV. iHIVARNA is a therapeutic vaccine candidate that used naked mRNA encoding multiple HIV-1 target epitopes in combination with an adjuvant.

166. As a general matter, vaccinating against HIV poses unique challenges, including the lack of natural immunity to the virus, the genetic diversity of HIV, and its ability to rapidly evolve to avoid antibodies.²⁷⁶ Given the unique ability of HIV to avoid the immune system, there is still no approved HIV vaccine in the United States despite forty years of research. Unlike the complexity of immunizing against HIV, it had been well-known since as early as 2003 (in the context of the SARS epidemic) that targeting the S-protein of betacoronavirus would elicit neutralizing antibodies against the virus, as explained in Section V.A.2.b. Thus, the failure to develop an effective mRNA vaccine against HIV would not garner skepticism about a mRNA vaccine against a betacoronavirus.

²⁷⁵ Ex. 2046 at 9.

²⁷⁶ Ex. 1116 at 2-3.

167. The specific studies cited in Dr. Fuller’s declaration also do not demonstrate skepticism of mRNA vaccines. For example, Dr. Fuller cites a 2019 paper on iHIVARNA by Jong et al., and asserts that “the results of the Phase II clinical trials were not able to demonstrate immunogenic effects of the vaccine.”²⁷⁷ The results reported in Jong et al., however, do not demonstrate skepticism about mRNA vaccines against infectious disease, but reflect a mistake in one particular study. Jong et al. notes that the iHIVARNA vaccine “contained an error in the form of an unintended start codon upstream of the HTI immunogen coding sequence.”²⁷⁸ The error led Jong et al. to emphasize that it was “impossible to draw conclusions on the induction of cellular immune responses against the HTI immunogen.”²⁷⁹

168. Moreover, the results reported by Jong et al. do not reflect the state of the art in 2015. The Phase II clinical trials for iHIVARNA *started* in March 2017—well after Patent Owner’s purported invention in the ’127 patent.²⁸⁰ By contrast, the Phase I study for iHIVARNA started in June 2015, the results of which reflect

²⁷⁷ Ex. 2199 ¶ 526 (citing Ex. 2044).

²⁷⁸ Ex. 2044 at 2, 9.

²⁷⁹ Ex. 2044 at 2, 9.

²⁸⁰ Ex. 2044 at 2.

optimism about mRNA vaccines.²⁸¹ Reporting on the Phase I results, Lorna et al. observed that “iHIVARNA vaccination was feasible, harmless and well tolerated, was able to induce moderate HIV-specific immune responses and transiently increased caHIV-RNA expression and ultrasensitive plasma viremia.”²⁸² The study further noted that the Phase I study “support[s] further exploration of iHIVARNA in the currently ongoing phase II clinical trial.”²⁸³ Contrary to Dr. Fuller’s opinion, the development of iHIVARNA reflects the field’s belief in 2015 that mRNA was a promising platform for infectious disease vaccines, even for diseases (such as HIV) for which an effective vaccine had long been elusive.

169. *AGS-004 Autologous HIV-1 RNA.* Dr. Fuller also cites a different HIV therapeutic vaccine (“AGS-004”).²⁸⁴ For the second HIV trial, Dr. Fuller omits that the vaccine induced a T cell response against HIV. In particular, the authors reported that mRNA “induce[d] CD28+/CD45RA– effector memory CTL with expanded effector function when measured after 2 doses while participants were

²⁸¹ Ex. 1119 at 2534.

²⁸² Ex. 1119 at 2542.

²⁸³ Ex. 1119 at 2542.

²⁸⁴ Ex. 2199 ¶ 527.

receiving ART [antiretroviral therapy]” and “a robust expansion in the numbers of HIV-specific CTL in the CD28+/CD45RA – CTL compartment.”²⁸⁵ Although “no antiviral effect was seen,” the authors still concluded that “[i]t is conceivable that the boosted HIV-specific CD8+ T-cell responses observed could translate into an important clinical effect in another setting.”²⁸⁶ Further, the ability of the mRNA to induce an immune response indicates the mRNA successfully expressed the antigen, and would have encouraged a POSA to explore mRNA vaccines for other infectious diseases.

170. **Finally**, in addition to the infectious disease clinical trials, Dr. Fuller also identifies 52 clinical trials for mRNA cancer applications. Dr. Fuller asserts that the numerous clinical studies testing mRNA for cancer would have discouraged a POSA from pursuing mRNA for infectious diseases.

171. Contrary to Dr. Fuller’s assertion, the mRNA clinical trials for oncological indications in 2015 would have only strengthened a POSA’s understanding that mRNA could be successful for infectious diseases. mRNA treatments for both indications require translation of a protein and, in many cases,

²⁸⁵ Ex. 2043 at 8.

²⁸⁶ Ex. 2043 at 2, 9.

generation of specific antibodies. For example, mRNA cancer vaccines encode tumor-specific antigens, which the body recognizes as foreign. Once the cellular machinery translates the tumor-specific antigen, the body generates an immune response specific to the tumors, thus destroying the tumors.²⁸⁷ Similarly, as I explained in my opening declaration, mRNA vaccines for infectious diseases encode an antigen such as a viral spike protein. Following translation of the viral antigen, the body recognizes it as foreign, and stimulates an immune response specific to the protein.²⁸⁸ Thus, encouraging results for oncological indications would have only motivated a POSA to pursue mRNA for infectious diseases. Further, the high number of clinical trials for cancer indicates that the field was optimistic about the potential of mRNA in preventing or treating diseases that are difficult (if not impossible) to treat with more traditional vaccines or therapeutics.

3) *By October 2015, mRNA Vaccines Had Known Advantages Over Other Vaccine Modalities, Including Other Nucleic Acid Vaccines*

172. Dr. Fuller asserts that by 2015, the promise of DNA, viral vector, and self-amplifying mRNA vaccines would have outweighed mRNA vaccines.²⁸⁹

²⁸⁷ Ex. 1121 at 8-9.

²⁸⁸ Ex. 1002 ¶¶ 39-41.

²⁸⁹ Ex. 2199 ¶¶ 536-550, 826-829, 834-838.

173. I again note that Dr. Fuller's contention does not appear to be responsive to the analysis that I provided in my initial declaration. Whether a POSA might also be interested in using other nucleic acid vaccines does not change the fact that Schrum expressly discloses mRNA vaccines "encod[ing] an immunogenic peptide or polypeptide," and that the prior art provided good reason to credit, and follow, that teaching. Nor does the fact that there was interest in other nucleic acid vaccine modalities alter that a POSA would reasonably expect to combine successfully Schrum's teaching of an mRNA vaccine with Geall's identification of the SARS-CoV S protein as an RNA vaccine immunogen.

174. Regardless, I disagree with Dr. Fuller's contention that a POSA would have set aside Schrum's teachings of mRNA vaccines encoding an immunogen in favor of DNA, viral vector, or saRNA vaccines. The decades of research into mRNA, described in Section V.A.2.a, coupled with its unique advantages, rendered mRNA an especially attractive target for a POSA.

175. Before 2015, scientists recognized that mRNA was "perhaps . . . ideal in the sense that it brings together the immunological features of live attenuated vaccines such as endogenous antigen expression and T cell induction with those of killed or subunit vaccines like defined composition and safety."²⁹⁰ In particular,

²⁹⁰ Ex. 1019 at 1319.

scientists recognized several key benefits of mRNA vaccine platforms, including that mRNA vaccines (a) do not need to be transported across the nuclear membrane; (b) do not have the risk of genomic integration; (c) are not limited by pre-existing immunity; and (d) are highly scalable, allowing them to be deployed rapidly in a pandemic situation. In fact, Dr. Fuller confirmed many of these advantages of mRNA vaccines at her deposition.²⁹¹

- a) Unlike DNA vaccines, mRNA vaccines do not need to be transported across the nuclear membrane, but can be translated to protein in the cytosol of the cell

176. The field was particularly excited about mRNA vaccines because they did not require transporting the cargo nucleic acid across the nuclear membrane.²⁹² In the case of DNA vaccines, the immunogen-encoding DNA cargo must be transported across the nuclear membrane and into the nucleus of the cell, where it is transcribed into mRNA, transported out of the nucleus and into the cytosol, and subsequently expressed. This was a process that was known to be inefficient. By contrast, mRNA vaccines can be expressed in the cytosol and do not need to be

²⁹¹ Ex. 1104 at 187:11-190:3.

²⁹² Ex. 1019 at 1 (“In terms of efficacy, mRNA-based therapeutics profit from the fact that they do not need to cross the nuclear envelope as opposed to DNA”).

transported across the nuclear membrane.²⁹³ This was considered a more efficient process for expressing the antigen.²⁹⁴

- b) Unlike DNA vaccines, mRNA vaccines carry no risk of harmful genomic integration

177. Further, the field was particularly interested in mRNA vaccines because mRNA carries no risk of genomic integration, which occurs when exogenous DNA is inserted into the host cell's genome. This can, in turn, create a risk of insertional mutagenesis. As noted in a 2014 article, government health agencies such as the WHO, FDA, and EMA all identified genomic integration as a risk associated with DNA vaccines.²⁹⁵

178. By contrast, there is no risk of genomic integration with mRNA vaccines, as “mRNA does not interact with the genome. Thus, potentially detrimental genomic integration is excluded.”²⁹⁶ Indeed, in Brito et al., researchers pointed out, “safety concerns about pDNA integration into the host genome post-transfection, albeit low probability, are obviated by RNA as integration of RNA is

²⁹³ Ex. 2005 at 1.

²⁹⁴ Ex. 1019 at 1; Ex. 2005 at 1.

²⁹⁵ Ex. 1130 at 2.

²⁹⁶ Ex. 1019 at 1.

not possible.”²⁹⁷ Petsch et al. similarly recognized that “[u]nlike plasmid DNA, mRNA poses no danger of genomic integration and there remain no selective markers (e.g., antibiotic resistance genes) in the final vaccine product.”²⁹⁸ Hoerr et al. explained that “RNA vaccines can be produced in high amounts and have the same major advantages as DNA vaccines but lack the potentially harmful effect of DNA integration into the genome.”²⁹⁹

179. Dr. Fuller fails to acknowledge the concerns about DNA vaccines. For example, citing to Kutzler et al., Dr. Fuller posits that “[a]lthough there were no DNA vaccines approved for human use by 2016, such approval *was expected* in the near future”³⁰⁰ Kutzler et al., however, highlights several concerns about DNA vaccines. For example, the authors state DNA vaccines “modified or adjuvanted with the goal of increasing immunogenicity could increase the chances of integration. A further concern is that an integrated vaccine might cause insertional mutagenesis through the activation of oncogenes or the inactivation of tumour

²⁹⁷ Ex. 2005 at 2118.

²⁹⁸ Ex. 2025 at 1215.

²⁹⁹ Ex. 1117 at 1.

³⁰⁰ Ex. 2199 ¶ 59 (citing Ex. 2132) (emphases added).

suppressor genes.”³⁰¹ Dr. Fuller also points to Yang’s results in 2005 as supporting use of DNA vaccines over mRNA vaccines.³⁰² But for the reasons explained in Section V.A.2.a.3, a POSA would have been aware of specific safety concerns with DNA vaccines that are not present with mRNA vaccines. Further, by 2015, a POSA would have been aware of research that demonstrated how mRNA could be used as an effective vaccine platform, as described in Sections V.A.2.a.1-2.

180. Dr. Fuller further dismisses an article by Kallen et al., which states that “[r]ecent advances strongly suggest that mRNA rather than DNA will be the nucleotide basis for a new class of vaccines and drugs.”³⁰³ In particular, Dr. Fuller relies on Kallen’s statement that “contrary to former expectations, it is not DNA that emerges as the nucleotide basis for vaccines, but mRNA might be the ideal basis for the development of new vaccines against infectious pathogens.”³⁰⁴ But regardless of what the “*former* expectations” might have been, Kallen et al. makes clear that mRNA was recognized as a promising platform for new vaccines by 2013.

³⁰¹ Ex. 2132 at 781.

³⁰² Ex. 2199 ¶ 842.

³⁰³ Ex. 1020 at 1; Ex. 2199 ¶¶ 827-829 (citing Ex. 1020).

³⁰⁴ Ex. 2199 ¶¶ 827-829 (quoting Ex. 1020).

181. Finally, Dr. Fuller misleadingly alleges that “DNA vaccines were considered to have several advantages *over mRNA* including safety, stability, and immunogenicity.”³⁰⁵ For that statement, however, she cites a different portion of her declaration, which discusses an article comparing DNA vaccines with *traditional* vaccines, not mRNA vaccines.³⁰⁶

- c) Unlike viral vector vaccines, mRNA vaccines are not limited by preexisting immunity to viral vector serotypes

182. A POSA would have also been aware that other vaccine platforms such as viral vectors posed disadvantages. Specifically, portions of the population had been known to have preexisting immunity to certain vector serotypes, which can lower the efficacy of the vaccine or even trigger an adverse inflammatory reaction. For example, scientists recognized that, although “[r]ecombinant viral vector technologies efficiently deliver nucleic acids,” their “utility is often hampered by antivector immunity, production limitations, and safety concerns.”³⁰⁷ In contrast, mRNA vaccines obviate this problem, as mRNA vaccines do not use delivery

³⁰⁵ Ex. 2199 ¶ 834 (emphases added).

³⁰⁶ Ex. 2199 ¶ 834; *see also* ¶¶ 538-541 (citing Ex. 2132); Ex. 2132 at 781.

³⁰⁷ Ex. 2005 at 2118.

vehicles derived from natural viruses such as adenovirus, and thus the field expected that there would be no preexisting immunity to mRNA vaccines.

- d) mRNA vaccines are highly scalable and can be deployed rapidly in a pandemic situation

183. In addition, it was well recognized by 2015 that mRNA vaccines would be especially well-suited for responding to a pandemic, as they can be quickly developed and scaled up. As early as 2012, Schlake et al. emphasized how mRNA vaccines are highly flexible and can be scaled up quickly:

mRNA as the technological basis of therapeutics and vaccines is characterized by a great flexibility with respect to production and application. Any protein can be encoded and expressed by mRNA, in principle enabling the development of prophylactic and therapeutic vaccines fighting diseases as diverse as infections and cancer as well as protein replacement therapies. Since changes of the encoded protein just alter the sequence of the RNA molecule, leaving its physico-chemical characteristics largely unaffected, diverse products can be manufactured using the same established production process without any adjustment, saving time and reducing cost compared with other vaccine platforms.³⁰⁸

³⁰⁸ Ex. 1019 at 1.

184. Further, by 2015, the ability of mRNA to be quickly developed in response to an emerging pandemic had already been demonstrated. Indeed, researchers had demonstrated that they could make a self-amplifying mRNA vaccine against a new strain of influenza only *eight days* after the virus had been sequenced.³⁰⁹

b. A POSA Would Have Been Motivated to Encode a Betacoronavirus S Protein as the Immunogen in an mRNA Vaccine with a Reasonable Expectation of Success

185. In her declaration, Dr. Fuller opines that a POSA would have discounted Geall's disclosure, and selected an entirely different SARS-CoV protein as a vaccine immunogen.³¹⁰ I disagree.

186. I explained in my initial declaration that a POSA would have had good reason to combine Geall's disclosure of the SARS-CoV S protein as an RNA vaccine antigen with Schrum's disclosure of an mRNA vaccine formulated in a lipid nanoparticle.³¹¹ The S protein is, in fact, the only immunogen disclosed in Geall for SARS-CoV. Geall's disclosure of the S protein as an RNA vaccine immunogen in 2012 came with the benefit of the long-established knowledge that "among all

³⁰⁹ Ex. 1138 at 5.

³¹⁰ See Ex. 2199 ¶¶ 551-623.

³¹¹ Ex. 1002 § IX.1; ¶¶ 121-123.

structural proteins of SARS-CoV, [the] S protein is the main antigenic component that is responsible for inducing host immune response, neutralizing antibodies and/or protective immunity against virus infection . . . [and is thus] an important target for vaccine anti-viral development.”³¹²

187. As I further explained, a POSA would reasonably have expected to synthesize an mRNA encoding for a betacoronavirus S protein (like the SARS-CoV S protein) using methods well-known in the art by October 2015.³¹³ And again, a POSA would have reasonably expected to induce an immune response using an mRNA vaccine encoding for a betacoronavirus S protein.³¹⁴

188. Dr. Fuller largely does not engage with my analysis. She instead pivots to arguing that “a POSA was aware that there were safety and efficacy concerns with using a spike protein as an antigen” for a betacoronavirus vaccine.³¹⁵ Based on these alleged “concerns,” Dr. Fuller contends that a POSA would select a different antigen for a betacoronavirus vaccine despite the teachings of the Geall, Yang, and Altmeyer—each of which disclose the SARS-CoV S protein.

³¹² Ex. 1031 at 229.

³¹³ Ex. 1002 § IX.1; ¶¶ 124-126.

³¹⁴ *E.g.*, Ex. 1002 § IX.1; ¶¶ 124-126.

³¹⁵ Ex. 2199 ¶ 575.

189. I disagree with Dr. Fuller. By October 2015, a POSA would have been motivated to utilize the SARS-CoV S protein as a vaccine antigen, including for an mRNA vaccine, and would reasonably expect to be able to design such a vaccine and use it to induce an immune response because: (1) the SARS-CoV S protein was known to be the predominant protective immunogen, (2) S protein-based vaccines had already been shown to protect against SARS-CoV, (3) any concern with vaccine-associated enhanced disease would direct a POSA *towards* the S protein, and (4) vaccines based upon the “full-length” S protein were protective and had known advantages.

1) The SARS-CoV S Protein Was a Known, Protective Immunogen

190. Dr. Fuller writes in her declaration, “In 2015, the field was exploring antigens other than the spike protein for coronavirus vaccines.”³¹⁶ Even were Dr. Fuller correct, I disagree that the fact that other immunogens were also known would detract from a POSA being motivated to combine the teachings of Schrum and Geall to arrive at the method of claim 1, particularly where the S protein is the only RNA vaccine immunogen specifically called out by Geall for development of a coronavirus (specifically a SARS-CoV) vaccine.³¹⁷ Regardless, Dr. Fuller fails to

³¹⁶ Ex. 2199 ¶ 610.

³¹⁷ Ex. 1010 at 19:26-29.

accurately reflect the state of the art. By October 2015, the S protein had been entrenched as the known, predominant immunogen for betacoronavirus vaccine development for more than a decade.

- a) The Literature Taught that the SARS-CoV S Protein Was the “only significant SARS-CoV neutralization antigen and protective antigen”

191. As early as 2004, researchers associated with the NIH published “results [that] identify S [spike] among the structural proteins as *the only significant SARS-CoV neutralization antigen* and protective antigen and show that a single mucosal immunization is highly protective in an experimental animal [model].”³¹⁸ The researchers used vectors to express the various SARS-CoV structural proteins in mice prior to challenging the mice with the live virus in order to “evaluate immunogenicity and protective efficacy in hamsters” of those protein-expressing vectors.³¹⁹ The authors were unequivocal in reporting their findings: “Among the viral structural proteins, the S glycoprotein proved to be the only significant neutralization and protective antigen of SARS-CoV.”³²⁰

³¹⁸ Ex. 1132 at 9804 (emphases added).

³¹⁹ Ex. 1132 at 9808.

³²⁰ Ex. 1132 at 9808.

192. By contrast, and contradicting Dr. Fuller's argument that a POSA would discount Geall's teaching of the SARS-CoV S protein, the same authors demonstrated in 2004 that the other structural proteins were *not* protective immunogens. Bucholz et al., published that, while the SARS-CoV S protein vaccine "reduced challenge virus replication 500-fold,"³²¹ the "N, M, and E proteins, singly or in two combinations, did not make a significant contribution to a neutralization antibody response or protective immunity."³²² Based on those results, the authors concluded that the N, M, and E proteins "thus . . . were not significant protective antigens."³²³

193. Subsequent literature only confirmed those early findings. As I explained in my opening declaration, other groups had also concluded that the SARS-CoV spike protein was the obvious choice of immunogen for use in a vaccine

³²¹ Bucholz et al. further noted that "there was no evidence that immunization with any of the SARS-CoV antigens, involving the induction of either neutralizing or nonneutralizing antibodies, led to antibody-mediated enhancement of infection, as described for feline infectious peritonitis virus." Ex. 1132 at 9809.

³²² Ex. 1132 at 9808-9809.

³²³ Ex. 1132 at 9808.

and had shown its efficacy at producing an immunostimulatory response.³²⁴ For example, by 2009 researchers had concluded that “[b]ecause the S protein of SARS-CoV is involved in receptor recognition, as well as virus attachment and entry, it represents one of the most important targets for the development of SARS vaccines and therapeutics.”³²⁵ Indeed, the spike protein of SARS-CoV was known to be “the main antigenic component that is responsible for inducing host immune responses, neutralizing antibodies and/or protective immunity against virus infection.”³²⁶

b) Dr. Fuller’s Deposition Confirmed that the S Protein Was the Known Protective SARS-CoV Immunogen

194. Consistent with the scientific literature discussed above, Dr. Fuller testified at her deposition that the SARS-CoV S Protein was known to be the predominant protective immunogen and the basis of most betacoronavirus vaccines.

195. Explaining her decision to utilize the SARS-CoV-2 S protein (despite her testimony that a POSA would look to a different betacoronavirus vaccine antigen), Dr. Fuller testified:

³²⁴ See Ex. 1002 ¶¶ 47, 113, 122, 125, 152-157, 204-205.

³²⁵ Ex. 1031 at 227.

³²⁶ Ex. 1031 at 229.

We were familiar with the data from the SARS-CoV-2003 and the MERS outbreak that occurred and evidence that suggested that if you could raise decent neutralizing antibody responses against a spike protein that that should provide protection from infection.³²⁷

She then reiterated:

So basically what I meant was that those particular outbreaks [*i.e.*, SARS-CoV and MERS-CoV] provided evidence that the spike protein would be a target for neutralizing antibody. And if we could raise sufficient neutralizing antibodies against that target, we may have an effective vaccine.³²⁸

196. Dr. Fuller further confirmed that the functions of the BetaCoV S protein—known well before October 2015—rendered it the key target for betacoronavirus vaccine development. She testified:

Q. Around six lines down in the introduction, [Dr. Fuller’s article, Ex. 1099] reads, “The S protein mediates the binding of coronaviruses to angiotensin-converting enzyme 2 (ACE2) on the surface of various cell types

³²⁷ Ex. 1104 at 40:13-17.

³²⁸ Ex. 1104 at 41:20-42:3.

including epithelial cells at the pulmonary alveolus.”

Right?

A. That’s right.

Q. When was it discovered that the S protein of coronaviruses mediates viral binding at entry? . . . Would it have been before October 2015?

A. Yeah, likely that would have been before then.

Q. The function of the spike protein was understood as something relevant to highlight in the context of an article describing vaccine development. Fair?

A. Yes.

. . .

Q. What does it mean that “Protection is thought to be mediated by neutralizing antibodies against the S protein”?

A. What’s meant by that is that the antibody generated against the S protein is thought to interfere with the ability of the virus to attach to and infect the cells.³²⁹

³²⁹ Ex. 1104 at 58:3-60:16.

- 2) *By October 2015, S Protein-Based Vaccines Had Already Proven to Be Protective*
 - a) The Literature Reflected a Number of Protective SARS-CoV and MERS-CoV S Protein Vaccines

197. Moreover, the fact that the S-protein was the most obvious antigen for a betacoronavirus vaccine is further confirmed by the fact that multiple groups found it to be effective antigen choice across a wide variety of vaccine approaches. Indeed, one of the articles cited and relied upon by Dr. Fuller described the S protein as “the major target for vaccine and immune therapy.”³³⁰

198. For example, Yang discloses “that a DNA vaccine encoding the spike (S) glycoprotein of the SARS-CoV induces T cell and neutralizing antibody responses, as well as protective immunity, in a mouse model.”³³¹ Yang concluded that administration of the S protein-encoding nucleic acid vaccine showed that “[v]iral replication was reduced by more than six orders of magnitude in the lungs of mice vaccinated with these S plasmid DNA expression vectors.”³³² Yang’s demonstration of effective immunostimulatory results *in vivo* following

³³⁰ Ex. 2137 at 797.

³³¹ Ex. 1011 at 561.

³³² Ex. 1011 at 561.

administration of a nucleic acid vaccine encoding the SARS-CoV spike protein would have confirmed for a POSA that the S-protein was the leading antigen candidate for a betacoronavirus vaccine.³³³

199. Other groups had also found that S protein elicited a protective immune response. In one “open-label Phase I clinical trial, the VRC SARS DNA vaccine was evaluated as safe and well tolerated. The vaccine was immunogenic with SARS spike glycoprotein-specific T-cell responses induced in all subjects and neutralizing antibody responses detected in 8 of 10 subjects.”³³⁴ Further, as of October 2015, Altmeyer had disclosed data demonstrating the ability of nucleic acid vaccine encoding the betacoronavirus S protein to induce an immune response.³³⁵ Specifically, Altmeyer disclosed that a RNA vaccine encoding the SARS-CoV spike protein induces “[s]pike-specific antibodies” and “SARS CoV-specific antibodies.”³³⁶

³³³ Ex. 1002 ¶¶ 152-157.

³³⁴ Ex. 2138.

³³⁵ See Ex. 1002 ¶¶ 64-66, 204-205.

³³⁶ Ex. 1012 ¶ 116.

200. Likewise, traditional vaccines, such as “recombinant forms of the highly attenuated modified vaccinia virus Ankara (MVA) containing the gene encoding full-length SARS-CoV S . . . elicited protective immunity, as shown by reduced titers of SARS-CoV in the upper and lower respiratory tracts of mice after challenge.”³³⁷

201. Researchers had also found by 2015 that the S-protein of the MERS coronavirus—another betacoronavirus—was also the “primary target” for vaccine development.³³⁸ One group of researchers reported that, “immunogens based on full-length S DNA and S1 subunit protein elicit robust serum-neutralizing activity against several MERS-CoV strains in mice and non-human primates.”³³⁹ Similarly, a “recombinant MVA [vaccine] expressing the [MERS-CoV] S protein induced high levels of circulating antibodies that neutralize MERS-CoV in tissue culture infections.”³⁴⁰ The DNA vaccine encoding the full-length MERS-CoV spike protein further “induce[d] MERS-CoV neutralizing antibodies that target multiple epitopes,

³³⁷ Ex. 1115 at 6641.

³³⁸ Ex. 1101 at 1.

³³⁹ Ex. 1101 at 1.

³⁴⁰ Ex. 1109 at 11950.

both within and outside the RBD, which may potentially improve immunogenicity and reduce the likelihood of escape mutations.”³⁴¹

b) Previous Success with S-Protein Vaccines
Would Have Been Relevant to mRNA
Vaccine Development

202. In her declaration, Dr. Fuller attempts to dismiss the wealth of literature showing that S protein-based vaccines were protective as irrelevant to the choice of immunogen for an mRNA vaccine.³⁴² For example, Dr. Fuller states in her declaration, “vaccine technology (e.g., DNA, viral vectors, saRNA, mRNA) was not interchangeable—success with one vaccine technology (e.g., saRNA) did not mean that one could reasonably expect success with a different vaccine technology (e.g., mRNA).”³⁴³

203. At her deposition, Dr. Fuller contradicted that opinion. She testified that, not only was she aware of the significant literature teaching the use of a betacoronavirus S protein as a vaccine immunogen, she relied upon such previous data from other vaccine modalities in selecting the SARS-CoV-2 S protein in development of her own vaccine candidate.

³⁴¹ Ex. 1101 at 7.

³⁴² *E.g.*, Ex. 2199 ¶ 551.

³⁴³ Ex. 2199 ¶ 78.

204. **First**, Dr. Fuller confirmed that the prior art disclosed a significant number of different, protective SARS-CoV vaccines built upon an S protein immunogen. She testified:

Q. In the 2003 to 2005 time frame, there were experimental vaccines developed against related SARS-CoV. Correct?

A. There were, yes.

Q. And those studies from the 2003 to 2005 time frame suggested that protection was thought to be mediated by neutralizing antibodies against the S protein. Correct?

A. So the data from these studies demonstrated induction of neutralizing antibody. Many of those vaccines were designed for – for example, the common protein vaccines only include the S protein. And *the generation of the neutralizing antibody against an S protein corresponded with protection.*³⁴⁴

Dr. Fuller further confirmed that these different vaccine platforms using a betacoronavirus S protein immunogen all induced an immune response. In fact, she

³⁴⁴ Ex. 1104 at 61:12-62:4 (emphases added).

testified that “pretty much every type out there” of SARS-CoV vaccines using the spike proteins induced an immune response.³⁴⁵

205. **Second**, and contrary to the position in her declaration that a POSA simply would not look at data from other vaccine modalities in developing an mRNA vaccine, Dr. Fuller testified that she, herself, relied on this same data (from various different types of vaccines) in developing a self-amplifying mRNA vaccine. In fact, she testified that she did not look at a single self-amplifying mRNA vaccine reference during development of her own vaccine candidate:

Q. Why did you choose the SARS-CoV-2 spike protein as the antigen to be encoded in your vaccine candidate?

A. We were familiar with the data from the SARS-CoV-2003 and the MERS outbreak that occurred and evidence that suggested that if you could raise decent neutralizing antibody responses against a spike protein that that should provide protection from infection.

...

Q. In making your selection of the SARS-CoV-2 spike protein, you relied on scientific literature. Correct?

³⁴⁵ Ex. 1104 at 65:15-20.

A. So we reviewed the literature from – coronavirus literature, particularly from the SARS-CoV outbreak, SARS-CoV-1 specifically, and the MERS-CoV outbreaks. That was where the majority of the scientific literature related to coronavirus vaccines was in 2020.

...

Q. Fair enough. In selecting the spike protein as the antigen, did you look only at literature involving other self-amplifying [mRNA] vaccines?

A. No.

Q. Why Not?

A. We looked at all vaccine literature.³⁴⁶

206. Given her own reliance on other vaccine types in vaccine development, Dr. Fuller cannot credibly dispute that a POSA “would consider that an immunogen targeted by a self-replicating RNA vaccine [or indeed, other types of vaccines] could also be targeted by mRNA vaccine[s].”³⁴⁷

207. Dr. Fuller’s deposition testimony that she relied on various different types of vaccines in developing a self-amplifying mRNA vaccine is consistent with

³⁴⁶ Ex. 1104 at 40:10-43:14.

³⁴⁷ Ex. 2199 ¶ 551 (quoting Paper No. 20 (Institution Decision), 52).

what a POSA would have done in 2015 as well. For any type of nucleic acid vaccine, the nucleic acid encoding the immunogen ultimately must be translated by the cell's host cell machinery. Thus, the use of a DNA vaccine or a viral vector to deliver the spike protein and induce an immune response would have demonstrated that (1) a nucleic acid (including DNA and RNA) could be safely administered to patients, (2) the cellular machinery is capable of translating the protein, and that (3) the body can recognize the protein and generate an immune response. Those lessons would have been applicable across any nucleic acid vaccine. I discuss the applicability of studies on DNA vaccines and viral vectors vaccines to mRNA vaccines in greater detail in Sections VI.A.2 and VII.A.2, and I incorporate by reference those sections as if fully stated here.

3) *Concerns with Enhanced Disease Would Not Have Dissuaded a POSA from Using a Betacoronavirus S Protein as a Vaccine Immunogen*

208. As I have noted, the only betacoronavirus immunogen expressly called out by Geall (also identified by Yang and Altmeyer) is the S protein. Despite that, Dr. Fuller contends that a POSA would have set aside Geall's teaching and utilized a different betacoronavirus immunogen for vaccine development due to concerns with vaccine-associated enhanced disease.³⁴⁸ Dr. Krause similarly contends that a

³⁴⁸ Ex. 2199 ¶ 580.

POSA would have been skeptical of using an S protein immunogen because of concerns with vaccine-associated enhanced disease.³⁴⁹ I disagree.

209. **First**, disease enhancement is not a phenomenon unique to betacoronavirus vaccines using an S-protein antigen. Disease enhancement is a potential complication inherent to vaccines as a category of medical treatment. No potential antigen selection can guarantee that a vaccine will not cause disease enhancement in a patient, and disease enhancement would have remained a theoretical concern for a betacoronavirus vaccine using an immunogen of any other surface protein, surface protein fragment, or mixture of proteins and fragments.³⁵⁰ For example, by 2006, researchers studying viral vaccines expressing either a SAR-CoV N protein or S protein reported that the N protein vaccines led to ADE while the S protein vaccines did not.³⁵¹ If a POSA were dissuaded from designing vaccines

³⁴⁹ Ex. 2200 ¶¶ 187-191.

³⁵⁰ I note that I testified to this effect at my deposition. *See, e.g.*, Ex. 2114 129:21-130:5 (“The concept of disease enhancement is certainly always a consideration in vaccine development.”).

³⁵¹ *See* Ex. 1140 at 2369-70 (“[V]accination with VRP-N failed to inhibit viral replication within the lungs of either young or senescent animals, resulted in

because of the possibility of disease enhancement, then vaccine development would fully halt.³⁵²

210. Dr. Fuller misinterprets a POSA's general concern over disease enhancement as a concern for disease enhancement for S protein vaccines specifically. For example, Drs. Fuller and Krause rely on post-priority documents from the FDA that addressed, among other things, the potential for disease

enhanced immunopathology following viral challenge, and did not provide any measurable benefit when combined with VRP-S. . . . Therefore, caution is merited with respect to the inclusion of SARS-CoV N protein in any vaccine formulation.”); *Id.* at 2372 (“VRP-S–vaccinated animals challenged with homologous or heterologous icGD03-S recombinant viruses did not display vaccine mediated enhancement of virus replication or enhanced pathology.”); [REDACTED]

[REDACTED]

[REDACTED]

³⁵² *Cf* Ex. 2136 at 4789 (“[D]emonstration of some disease enhancement with any candidate vaccine after viral challenge in animal models should not necessarily represent a no-go signal for deciding whether to progress into early trials[.]”).

enhancement of COVID-19 vaccine candidates.³⁵³ In my opinion, this document supports that a POSA would not have harbored specific concerns about disease enhancement from an S protein vaccine because the guidance document only discusses the need for studies to address the potential for disease enhancement generally, without singling out a specific antigen choice or even a particular vaccine platform technology.³⁵⁴ Dr. Fuller also points to the fact that Pfizer and BioNTech conducted a preclinical study of their COVID vaccine candidate to demonstrate the lack of disease enhancement.³⁵⁵ Given that the FDA guidance reflected a general concern regarding (and requested studies investigating) disease enhancement in vaccine candidates, the fact that Pfizer, BioNTech, and Patent Owner investigated disease enhancement of their COVID-19 vaccines is not probative of whether a POSA in 2015 would have been so concerned about disease enhancement that they would set aside the clear teachings in the prior art regarding the protectiveness of S protein-based betacoronavirus vaccines.

211. ***Second***, to the extent a POSA was looking to minimize the risk of disease enhancement caused by a betacoronavirus vaccine, a POSA would be ***more***

³⁵³ See, e.g., Ex. 2199 ¶ 602 (citing Ex. 2104); Ex. 2200 ¶¶ 140-141.

³⁵⁴ Ex. 2104 at 8-9.

³⁵⁵ Ex. 2199 ¶ 607.

motivated to use an S protein immunogen. Enhanced disease tends to arise where vaccines are unable to induce a neutralizing antibody response. As Dr. Fuller acknowledges, [a]ntibody-dependent enhancement of disease (ADE) . . . refers to a phenomenon in which a vaccine induces the production of antibodies that, when exposed to a real virus, enhance the ability of the virus to infect cells and cause disease, instead of neutralize the virus.”³⁵⁶

212. Thus, a POSA looking to *minimize* the possibility of disease enhancement would want to maximize the likelihood that a given vaccine construct would induce neutralizing antibodies. As of 2015, the prior art demonstrated that S protein vaccines typically induced the highest level of neutralizing antibody titers. By 2004, scientists had shown that “[a]mong the viral structural proteins, the S glycoprotein proved to be the only significant neutralization and protective antigen

³⁵⁶ Ex. 2199 ¶ 126. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

of SARS-CoV.”³⁵⁷ Dr. Fuller agreed at deposition, testifying that the SARS-CoV and MERS-CoV “outbreaks provided evidence that the spike protein would be a target for neutralizing antibody. And if we could raise sufficient neutralizing antibodies against that target, we may have an effective vaccine.”³⁵⁸ Similarly, in a study using Venezuelan equine encephalitis virus replicon particles expressing the 2003 epidemic Urbani SARS-CoV strain S protein or N protein, the authors “demonstrate[d] that VRP-S, but not VRP-N vaccines provide complete short- and long-term protection against homologous strain challenge in young and senescent mice.”³⁵⁹ Thus, a POSA in 2015 would have concluded that an S-protein vaccine would likely maximize the production of neutralizing antibodies and thereby minimize the likelihood of disease enhancement.

³⁵⁷ Ex. 1132 at 9808; *See also id.* (concluding no disease enhancement); Ex. 1011 at 561 (“Here, we show that a DNA vaccine encoding the Spike (S) glycoprotein of the SARS-CoV induces T cell and neutralizing antibody responses, as well as protective immunity, in a mouse model.”).

³⁵⁸ Ex. 1104 at 41:20-42:3.

³⁵⁹ Ex. 1140 at 2359.

213. In her declaration, Dr. Fuller states that “one factor contributing to the likelihood that a vaccine will cause enhanced disease is the relationship between T helper type 1 (“Th1”) and T helper type 2 (“Th2”) cellular responses to vaccination.”³⁶⁰ During her deposition, Dr. Fuller asserted that “Th2 type immune responses had been associated with enhanced infection when used with the S protein. And we knew that Th1 type of responses were associated with lack of enhanced disease.”³⁶¹

214. I disagree with Dr. Fuller’s statement that “by 2020, but not in 2015, by 2020 we knew that RNA and DNA vaccines and nucleic vaccines in general drove more of a Th1 type of immune response.”³⁶² To the contrary, a POSA would have known by October 2015 that nucleic acid vaccines in general drove a Th1-type immune response. Notably, Petsch et al. reported that mRNA vaccines against influenza A elicited IFN- γ in a mouse model.³⁶³ A POSA would have understood that IFN- γ is a cytokine that is primarily produced by Th1 cells, and thus the results

³⁶⁰ Ex. 2199 ¶ 582.

³⁶¹ Ex. 1104 at 252:2-253:1.

³⁶² Ex. 1104 at 253:6-9

³⁶³ Ex. 1314 at 1211.

in Petsch demonstrate that mRNA vaccination drives a Th1 type immune response. As another example, Hattinger et al. reported that “mRNA vaccines induce a protective TH1-type response against a panel of different allergens, leading to inhibition of specific IgE production and prevention of lung inflammation and airway hyperresponsiveness (AHR) in mice.”³⁶⁴ Thus, Dr. Fuller’s statements are thus unsupported by the scientific literature.

215. **Third**, Dr. Fuller does not consider statements from the prior art associating disease enhancement with a betacoronavirus spike protein in the full context of the articles or the art as a whole. For example, although Du acknowledges that some groups have observed that S protein based SARS-CoV vaccines can lead to disease enhancement by antibody-dependent enhancement of disease (ADE),³⁶⁵ that statement is counterbalanced by the statement that the “full-length S protein of SARS-CoV Urbani strain resulted in the production of S protein-specific neutralizing antibodies, which protected vaccinated monkeys from subsequent homologous SARS-CoV challenge, suggesting that immunization with the S protein of SARS-CoV is highly effective in the prevention of SARS.”³⁶⁶

³⁶⁴ Ex. 1315 at 2.

³⁶⁵ Ex. 1031 at 229-30.

³⁶⁶ Ex. 1031 at 229.

216. In my opinion, a POSA considering Du for all that it teaches would ultimately remain motivated to use an S protein immunogen to achieve “highly effective . . . prevention of SARS”—the very goal of vaccines. Indeed, pre-priority date work confirms that a POSA would have understood Du as teaching that the S protein is “a key component of vaccines against coronavirus infection, including severe acute respiratory syndrome (SARS).”³⁶⁷

217. Drs. Fuller and Krause also cite the work of Jaume and colleagues to argue that a POSA would have been dissuaded from using an S protein-based vaccine.³⁶⁸ I disagree that Jaume would have dissuaded POSAs from pursuing an S protein based vaccine, an opinion further supported by the fact that a POSA’s awareness of Jaume, which was published in 2011, did not dissuade them from pursuing S protein based vaccines before the priority date.

218. As an initial matter, a POSA in 2015 would not have concluded that Jaume 2011 demonstrated that its vaccine candidates necessarily would have caused

³⁶⁷ Ex. 1109 at 11950 (citing Du for the proposition that “Importantly, the S protein is considered a key component of vaccines against coronavirus infection, including severe acute respiratory syndrome (SARS).”).

³⁶⁸ See Ex. 2199 ¶ 592, Ex. 2200 ¶ 188 (citing Ex. 2030).

enhanced disease in patients. In the study, five groups of mice were immunized with either a variation of SARS-CoV spike protein (“S”, “S1”, “Ssol”, or “S.ECD”) or a whole-killed SARS-CoV.³⁶⁹ The mice received two doses of the vaccine alongside an Alum adjuvant.³⁷⁰ The mice, however, were never challenged with a SARS-CoV infection after immunization with the vaccine candidate. There was never any observation in Jaume, then, of enhanced disease in the mice in response to the vaccine itself.³⁷¹

219. Instead, Jaume collected serum samples from each group of mice after the immunization, pooled the samples, and heat inactivated them to create antibody sera for use in further studies.³⁷² Jaume measured antibody-dependent enhancement of infection by infecting human immune cells *in vitro* with SARS-CoV virus in the presence of the antibody sera collected from the mice. Although Jaume found that some of the S-protein antibody sera allowed for infection of the cells compared to

³⁶⁹ Ex. 2030 at 10583-10584, 10589-10590.

³⁷⁰ Ex. 2030 at 10583.

³⁷¹ See Ex. 1105 at 68:19-21 (“Well, enhanced disease can *only* be evaluated after somebody’s been vaccinated *and then later infected* with the virus.” (emphases added)).

³⁷² Ex. 2030 at 10583.

the control, a POSA would not interpret these results as suggesting enhancement of disease in patients. As Dr. Krause explains in his declaration, administration of an antibody is “very different” from administration of an antigen, and a POSA cannot extrapolate results from one to the other related to enhanced disease:

Administration of an antibody is very different from administering an antigen (much less an mRNA encoding an antigen). The antigen could induce many types of antibodies and the path that induction takes in part is what determines whether there is a Th1- or Th2-biased response. A POSA in 2015 would have understood that the lack of enhanced disease following administration of an antibody does not mean that the POSA should reasonably expect administration of an mRNA encoding for an antigen to likewise show lack of enhanced disease.³⁷³

220. More importantly, however, is the fact that a POSA would not understand from the mere fact that SARS-CoV was able to infect the human immune cells in the presence of some S-protein based neutralizing antibodies during an *in vitro* assay that a patient would suffer from enhanced disease. Dr. Krause confirmed this understanding at his deposition: “Well, enhanced disease can *only* be evaluated

³⁷³ Ex. 2200 ¶ 161.

after somebody's been vaccinated and then later infected with the virus.”³⁷⁴ This is true, in part, because infection of cells does not necessarily lead to increased disease severity. A POSA reading Jaume would have been acutely aware of this fact because the virus that infected the human immune cells were unable to replicate and therefore could not produce infectious virus:

[A] significant percentage of SARS-CoV nucleocapsid protein-positive cells was visualized when infected in the presence of anti-Spike serum, although there was no evidence of productive virus replication and spread to infect other cells (Fig. 4B). . . . Altogether, these results indicate that despite the ability of SARS-CoV to exploit antiviral antibodies to invade Raji B cells, only abortive replication occurs upon infection, and no infectious virus is released from the ADE-infected Raji cells.³⁷⁵

221. Moreover, even if a POSA did interpret the results of Jaume's ADE assay as suggesting enhancement of infection in patients, that POSA ultimately would not have been dissuaded from pursuing an S-protein based vaccine because some of Jaume's S protein-based candidates did not result in enhancement of

³⁷⁴ Ex. 1105 at 68:19-21 (emphasis added).

³⁷⁵ Ex. 2030 at 10586-87.

disease. For example, although Jaume reported that “some vaccines targeting spike protein caused antibody-dependent enhancement of infection,” it also notes that “others did not.”³⁷⁶ Jaume further teaches that “ADE was dependent on the immunization strategy with two of five candidate vaccines [including one S-protein based candidate] displaying obvious neutralizing capabilities without triggering SARS CoV.”³⁷⁷

222. Finally, I note that researchers—aware of Jaume 2011—were in fact not dissuaded from pursuing S protein based vaccines before the priority date. For example, work by Song and colleagues on a MERS vaccine pursued an S-protein antigen in their vaccine design and “recommend[ed]” follow-up studies, notwithstanding the work of Jaume:

Future studies will be necessary to monitor for S antibody dependent enhancement of MERS-CoV infections, as previously discussed for ***SARS-CoV*** and feline coronavirus infections. [Citing, *inter alia*, ***Jaume 2011*** (Ex. 2030).] Furthermore, the safety and protective capacity of MVA-MERS-S immunization should be tested in animal models that reproduce MERS-CoV infections in

³⁷⁶ Ex. 2030 at 10595.

³⁷⁷ Ex. 2030 at 10595 (emphases added).

humans. However, the current absence of suitable preclinical models *recommends the development of an MVA vaccine delivering MERS-CoV S*.³⁷⁸

223. Drs. Fuller and Krause also cite the work of Vennema and colleagues in their opinions regarding ADE.³⁷⁹ Vennema describes the observation of enhanced disease after administration of a feline infectious peritonitis virus (“FIPV”) S protein viral vector vaccine.³⁸⁰ As an initial matter, I note that FIPV is not a betacoronavirus. Moreover, researchers in the field of betacoronavirus vaccines, however, *expressly* distinguished that the SARS-CoV S protein vaccines were protective and not associated with the same concerns raised in Vennema. The Bucholz 2004 publication from the NIH scientists that I have previously discussed taught, for example:

Thus, a single intranasal immunization with a recombinant vector expressing the S protein was highly immunogenic and protective against SARS-CoV challenge. In contrast, the N, M, and E proteins, singly or in two combinations, did not make a significant contribution to a neutralizing antibody response or protective immunity. Finally, there

³⁷⁸ Ex. 1109 at 11953 (emphases added).

³⁷⁹ Ex. 2199 ¶¶ 588-589; Ex. 2200 ¶ 190.

³⁸⁰ Ex. 2029 at 1407.

was *no evidence* that immunization with any of the SARS-CoV antigens, involving the induction of either neutralizing antibodies or nonneutralizing antibodies, led to antibody-mediated enhancement of infection, *as described for feline infectious peritonitis virus*. [Citing, inter alia, *Vennema 1990* (Ex. 2029).]³⁸¹

224. Other researcher groups, aware of the Vennema study, also continued to pursue S-protein based antigens. For example, the work by Song on a MERS vaccine described was also aware of the antibody dependent enhancement of “feline coronavirus infection,” and the Vennema study, yet nevertheless “recommend[ed] the development of an MVA vaccine delivering MERS-CoV S.”³⁸²

225. Yang echoes the conclusion of Bucholz et al. Yang first notes that “feline peritonitis virus is a coronavirus that causes significant morbidity and mortality in domestic animals for which vaccines have been investigated, but the development of these vaccines has been complicated by possible immune potentiation of the disease,” *i.e.*, enhanced disease. In contrast to the discussed FPIV vaccines, though, Yang teaches that “antibodies against SARS-CoV S glycoprotein suggest that antibodies against SARS-CoV S glycoprotein *protect against SARS-*

³⁸¹ Ex. 1132 at 9809 (emphases added).

³⁸² Ex. 1109 at 11953.

CoV challenge and do not enhance infection in this animal model.”³⁸³

226. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

227. In spite of the weight of the literature and the statements of Patent Owner’s own scientists, Dr. Fuller relies on certain literature as showing that a

³⁸³ Ex. 1011 at 563 (emphases added).

³⁸⁴ [REDACTED]

POSA would have set aside Geall's teaching of the S protein and selected a different immunogen not identified in Geall for betacoronavirus vaccine development. For instance, Dr. Fuller opines that 2005 paper by Yang and colleagues "discourages using full-length S protein as a vaccine antigen; it instead promotes the use of a certain truncated version of the S protein in a DNA vaccine."³⁸⁵ However, far from discouraging a POSA from pursuing S-protein vaccines, the paper's focus on S proteins would have reinforced to a POSA that the S protein is "*the major target for vaccine and immune therapy*."³⁸⁶ Further, the paper reports that "Ab-dependent enhancement has not been observed with any human SARS-CoV strain, which may allay concerns that such vaccines might enhance viral infection"; "it is unknown whether the Abs that enhance infection will exacerbate viral replication and/or disease *in vivo*;" and that "secreted cellular components . . . might potentiate [the disease enhancement] effect."³⁸⁷ Far from teaching away from the use of a full-length S protein, these statements reflect the authors' uncertainty that the unwelcome immunogenicity was caused by the use of the full-length S protein. Thus, a POSA

³⁸⁵ Ex. 2199 ¶ 596; *see also* ¶¶ 594-595.

³⁸⁶ Ex. 2137 at 797 (emphases added).

³⁸⁷ Ex 2137 at 800-801.

considering all that the article teaches would not be discouraged from using a full-length S protein or S-protein subunit in a betacoronavirus vaccine.

228. Dr. Fuller also assumes from the fact that Martin and colleagues used a truncated S protein vaccine that they were concerned with disease enhancement.³⁸⁸ However, the article does not explain the author's antigen choice and, as I explain below, the teachings of Martin and the art that it cites ultimately would have supported a POSA's use of a full-length spike protein.³⁸⁹

229. In short, disease enhancement is not a concern specific to S protein vaccines and, as Dr. Fuller acknowledges, only "some S-protein based choices result[ed] in enhancement of infections."³⁹⁰ Moreover, the S protein was the most widely studied protein antigen and was generally understood to produce the most neutralizing antibodies. Given the foregoing, it is my opinion that a POSA would have been motivated to apply Geall's teaching of an RNA vaccine encoding for a SARS-CoV S protein to Schrum's disclosure of an mRNA vaccine encoding an immunogen formulated in lipid nanoparticles.

³⁸⁸ Ex. 2199 ¶¶ 597, 648.

³⁸⁹ *See supra* § V.A.2.b.3.

³⁹⁰ Ex. 2199 ¶ 592.

4) *The “Full-Length” S Protein Had Known
Advantages as a Vaccine Immunogen*

230. Applying her interpretation that “S protein” in the claims of the ’127 patent refers only to a “full-length S” protein, Dr. Fuller alleges that a POSA would have avoided such a full-length S protein immunogen in favor of a truncated S protein.³⁹¹ As discussed earlier in this declaration, I disagree that the specification of the ’127 patent supports interpreting “S protein” as meaning only “full-length spike protein.”³⁹² But, even if Dr. Fuller’s interpretation is correct, a POSA would have been motivated to use a full-length S protein immunogen to maximize antibody response, and a POSA would reasonably expect to be able to express that protein to induce an immune response.

231. **First**, Geall teaches only the “spike” protein (*i.e.*, the “full-length” spike), and not any truncated S protein, as the immunogen for an RNA vaccine.³⁹³ A POSA would be motivated to follow Geall’s express teaching, without the need to select some different S protein-based immunogen like a truncated S protein, and

³⁹¹ See, *e.g.*, Ex. 2199 ¶ 598.

³⁹² *Supra* § III.2.

³⁹³ Ex. 1010 at 19:26-29 (“The coronavirus immunogen may be a spike polypeptide.”).

select the full S protein as the immunogen to be encoded by Schrum's mRNA vaccine.

232. **Second**, the prior art had already shown by October 2015 that full-length S protein-based vaccines were protective, providing further reason to follow Geall's teaching. Du 2009, for instance, catalogued a number of different full-length SARS-CoV S protein vaccines (using a variety of vaccine modalities) that proved protective and concluded that "[t]hese reports suggest that the full-length S protein is highly immunogenic and induces protection against SARS-CoV challenge and that neutralizing antibodies alone may be able to suppress virus proliferation, further justifying the rationale that vaccines can be developed based on the S protein."³⁹⁴ At deposition, Dr. Fuller agreed that this same publication from Du et al. demonstrated by March 2009 that the S protein of SARS-CoV was known to play key parts in the induction of neutralizing-antibody and T-cell responses as well as protective immunity.³⁹⁵

233. **Third**, it was known by October 2015 that full-length betacoronavirus S protein vaccines induced stronger antibody responses—a major goal of vaccine

³⁹⁴ Ex. 1031 at 229.

³⁹⁵ Ex. 1104 at 71:4-10.

administration—than truncated S protein-based vaccines. In July 2015, scientists demonstrated that a DNA vaccine encoding for the full-length MERS-CoV S protein “induced a significantly higher antibody response than the truncated S-ΔTM [truncated S protein-encoding DNA vaccine] or S1 [subunit] DNA regimens.”³⁹⁶ In that publication, Wang et al. further taught that the DNA vaccine encoding the full-length MERS-CoV spike protein further “induce[d] MERS-CoV neutralizing antibodies that target multiple epitopes, both within and outside the RBD, which may potentially improve immunogenicity and reduce the likelihood of escape mutations.”³⁹⁷

234. At deposition, Dr. Fuller testified that it was “not surprising[.]” that the full-length betacoronavirus S protein vaccine induced a more robust immune response. She stated in response to Wang et al.’s findings:

In this figure, [Wang et al.] ended up showing *the full-length spike protein not surprisingly actually induced higher antibody titers than the truncated version*. And that’s not surprising because it is going to – *the full-length*

³⁹⁶ Ex. 1101 at 2.

³⁹⁷ Ex. 1101 at 7.

***S protein will have more epitopes, neutralizing antibody
epitopes³⁹⁸ to target.³⁹⁹***

235. Dr. Fuller’s own declaration supports that Wang’s teaching of a more robust immune antibody response being achieved by a nucleic acid vaccine encoding the full-length MERS-CoV S protein could also be extrapolated to a nucleic acid vaccine encoding the SARS-CoV S protein (as Geall discloses). Dr. Fuller writes, “choosing the full-length S protein of MERS-CoV or choosing the full-length S protein of SARS-CoV would have been expected to yield similar results.”⁴⁰⁰ Applying Dr. Fuller’s own analysis, a POSA would therefore reasonably expect a SARS-CoV full-length S protein vaccine to “***not surprisingly actually induce***”

³⁹⁸ While Dr. Fuller contends that a POSA would avoid the full-length spike protein due to concerns with enhanced disease (e.g., Ex. 2199 ¶ 586), her own reasoning indicates the opposite. A POSA would recognize that presentation of more neutralizing antibody epitopes would likely increase the production of neutralizing antibodies, which Dr. Fuller has recognized as being a major factor in ***avoiding*** enhanced disease. (E.g., *id.* ¶¶ 581-582.)

³⁹⁹ Ex. 1104 at 260:9-15 (emphases added).

⁴⁰⁰ Ex. 2199 ¶ 566.

higher antibody titers than the truncated version.⁴⁰¹ Wang’s teachings, as well as Dr. Fuller’s own analysis, therefore provide further motivation to follow Geall’s teaching of developing an RNA vaccine encoding a full-length betacoronavirus S protein.

236. And while Wang described a DNA vaccine encoding for a full-length betacoronavirus S protein achieving a superior antibody response, a POSA would reasonably expect similar benefits when using an mRNA vaccine encoding for the same. Dr. Fuller agreed at deposition that “both DNA and mRNA lead to expression of the encoded proteins,” here the full-length betacoronavirus S protein.⁴⁰² Dr. Fuller further testified at deposition that it is “just basic fundamental nucleic acid vaccine biology” that “if you inject that DNA or RNA vaccine into an animal, the muscle cell . . . will express that antigen. You can give the antigen to express an animal, and the hypothesis is that it will elicit an immune response.”⁴⁰³ So, a POSA

⁴⁰¹ Ex. 1104 at 260:9-15 (emphases added).

⁴⁰² Ex. 1104 at 78:2-4. *See also id.* at 146:4-16 (Dr. Fuller testifying that “when a DNA vaccine gets injected into the body, it will transcribe into mRNA and then become a protein. When an mRNA gets injected in the body, the mRNA gets transcribed into protein.”).

⁴⁰³ Ex. 1104 at 51:22-53:9.

would recognize that where expression of the full-length betacoronavirus S protein achieved by a nucleic acid vaccine induced a stronger antibody response, then expression of that same protein by another nucleic acid vaccine modality would likewise reasonably be expected to provide similar benefits. I discuss this further below with respect to Ground III.

237. **Fourth**, Drs. Fuller and Krause contend that a POSA would be skeptical of being able to express a full-length betacoronavirus S protein using an mRNA molecule.⁴⁰⁴ This concern is unfounded, and a POSA would reasonably expect to express a full-length betacoronavirus S protein using mRNA encoding for the same. By October 2015, scientists had already demonstrated that full-length betacoronavirus spike proteins could be expressed using nucleic acid vaccines, including in the Wang publication discussed just above.⁴⁰⁵ Likewise, Dr. Fuller confirmed at deposition that, in her opinion, “For any given protein, once we know the genetic sequence or code, we can design an mRNA or DNA molecule that prompts a person’s cells to start making it.”⁴⁰⁶

⁴⁰⁴ Ex. 2199 ¶¶ 576-579; Ex. 2200 ¶ 192.

⁴⁰⁵ See generally Ex. 1101.

⁴⁰⁶ Ex. 1104 at 78:5-10.

c. A POSA Would Have Been Motivated to Formulate Immunogen-Encoding mRNA in Lipid Nanoparticles and Would Reasonably Expect to Do So Successfully

238. Dr. Fuller asserts that a POSA would have preferred delivery options other than lipid nanoparticles.⁴⁰⁷ I disagree. As I explain below, by October 2015: (1) lipid nanoparticles were well-established for the delivery of mRNA; and (2) lipid nanoparticles had already been shown to improve the potency of mRNA vaccines. I understand that Dr. Moon has provided additional opinions regarding the use of lipid nanoparticle technology.

1) By October 2015, Lipid Nanoparticles Were a Well-Known Delivery Approach for mRNA

239. Scientists have long known that naked (*i.e.*, unformulated) mRNA rapidly degrades in the body upon administration.⁴⁰⁸ To achieve a therapeutic effect, however, mRNA encoding for a protein (like the betacoronavirus S protein) must avoid degradation and sufficiently circulate in the body. Therefore, scientists have

⁴⁰⁷ Ex. 2199 ¶¶ 92-102, 621.

⁴⁰⁸ *E.g.*, Ex. 1133 at 760 (“Irrespective of whether the IVT mRNA is delivered to the cells *in vitro* or *in vivo*, two key factors determine its cytoplasmic bioavailability. One is rapid degradation by the highly active ubiquitous RNAses, which are abundant in the extracellular space.”).

long since turned to formulating mRNA in delivery vehicles (such as lipid nanoparticles, for instance). Dr. Fuller agreed at deposition; she testified:

So, it's that RNA, mRNA, does require a vehicle to get efficient delivery. It can be delivered naked. It can be injected and you can still get an immune response.

But to get – if you – to get levels of protein that you need to – for gene therapy or for an immune response, *it's well known now that you need a delivery vehicle.*⁴⁰⁹

240. Schrum's teachings alone provide motivation to use lipid nanoparticles, specifically, to deliver mRNA. Schrum instructs that "lipid 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 molecules or mmRNA; and/or increase the translation of the encoded protein."⁴¹⁰ As Dr. Fuller recognized in her declaration, a POSA would be motivated to use a delivery system that improves expression of the protein encoded by the mRNA, like lipid nanoparticles.⁴¹¹

⁴⁰⁹ Ex. 1104 at 192:4-11 (emphases added).

⁴¹⁰ Ex. 1009 ¶ 406.

⁴¹¹ Ex. 2199 ¶ 624 ("[D]elivery carriers may also be detrimental if the carrier impacts translation of the mRNA.").

241. In its examples, Schrum further demonstrates the use of lipid nanoparticles to improve protein expression. In Example 16, for instance, modified mRNA encoding Granulocyte colony stimulating factor (“G-CSF”) and Factor IX (involved in blood coagulation) was encapsulated in four-component lipid nanoparticles within the broad lipid nanoparticle ranges claimed by the ’127 patent (50:10:38.5:1.5 (DLin-KC2-DMA:DSPC:Cholesterol PEG-c-DOMG)).⁴¹² The mRNA was administered to mice at dose of 100, 10, or 1 ug. As shown in Schrum’s Table 28 and 29, respectively, “G-CSF protein expression determined by ELISA was approximately 17, 1200, and 4700 ng/ml for the 1, 10, and 100 ug dose groups, respectively” and “Factor IX protein expression determined by ELISA was approximately 36, 380, and 3000-11000 ng/ml for the 1, 10, and 100 ug dose groups.”

TABLE 28				TABLE 29			
G-CSF Protein Expression				Factor IX Protein Expression			
Dose (ug)	Conc (ng/ml)	Dilution Factor	Sample Volume	Dose (ug)	Conc (ng/ml)	Dilution Factor	Sample Volume
1	17.73	20x	5 ul	1	36.05	10x	5 ul
10	1204.82	2500x	0.04 ul	10	383.04	10x	5 ul
100	4722.20	2500x	0.04 ul	100*	3247.75	50x	1 ul
				100*	11177.20	250x	0.2 ul

242. And, based on the data reported, Example 16 concludes, “[T]he LNP formulations described above have about a 10,000-fold-100,000-fold increase in

⁴¹² Ex. 1009 ¶¶ 995-998 (Example 16).

protein production compared to” administration of mRNA using other lipid-based delivery vehicles.⁴¹³ A POSA would have readily recognized that achieving such a significant increase in protein production would be beneficial for nearly any purpose, including for vaccination.

243. I understand that Dr. Moon has further discussed the prior art’s use of lipid nanoparticle delivery technology.

2) *By October 2015, Lipid Nanoparticles Had
Already Been Shown to Improve mRNA Vaccine
Potency*

244. As I have previously explained, Schrum itself teaches a POSA to deliver immunogen-encoding mRNA in a lipid nanoparticle system.⁴¹⁴ Schrum’s instruction in 2013 came on the heels of literature that had already showed that encapsulating immunogen-encoding mRNA in lipid nanoparticles substantially improved performance of an mRNA vaccine against infectious diseases.

245. Specifically, in 2012, scientists had already demonstrated that formulation of a self-amplifying mRNA vaccine “within an LNP substantially increased immunogenicity [*i.e.*, vaccine potency].”⁴¹⁵ Comparing the performance

⁴¹³ Ex. 1009 ¶ 997.

⁴¹⁴ Ex. 1009 ¶ 397.

⁴¹⁵ Ex. 2021 at 14604.

of self-amplifying mRNA vaccines encoding for the respiratory syncytial virus (“RSV”)—also an infectious disease like SARS-CoV—fusion (“F”) protein⁴¹⁶ formulated in a four-component lipid nanoparticle system, Geall et al. determined that “the LNP/RNA formulation boosted F-specific IgG titers approximately 8-fold (GMTs 4,355) and neutralizations titers 10-fold (GMTs 1,493) relative to the same dose of naked RNA [(GMTs of 526 (F-specific IgG) and 154 (neutralization)].”⁴¹⁷ The next year, the authors reaffirmed their findings that lipid nanoparticles improved mRNA vaccine performance using a self-amplifying mRNA vaccine encoding for an influenza immunogen.⁴¹⁸

⁴¹⁶ Like the betacoronavirus S protein, the RSV F protein is a surface protein responsible for viral mediation and entry. *E.g.*, Ex. 1001 at 30:58-65.

⁴¹⁷ Ex. 2021 at 14606 (brackets in original).

⁴¹⁸ Ex. 1138 at 4-5 (“The [influenza immunogen-encoding] RNA was then encapsulated in a LNP delivery system, and the SAM (H7/LNP) vaccine was used to immunize mice Therefore, the immunogenicity of the SAM (H7/LNP) vaccine candidate was compared to the same dose of unformulated SAM (H7) RNA . . . [t]he HI titers were significantly higher than those elicited by the same dose of unformulated SAM [self-amplifying mRNA].”).

246. In their 2012 article, Geall et al. explained that the improved immunogenicity resulted from greater protection of the mRNA payload, as well as more efficient delivery of the immunogen-encoding mRNA into the cell. On the first, Ex. 2021 teaches that “LNPs protected the RNA from degradation by RNase A (Fig. 1C, lane 5). In contrast, the naked control RNA was degraded by RNase A.”⁴¹⁹ Further, “[e]ncapsulation [of RNA into lipid nanoparticles] was also required for efficient delivery of functional RNA into muscle.”⁴²⁰

247. A POSA would readily appreciate that Geall’s teachings were equally applicable to a non-replicating mRNA vaccine, as Dr. Fuller recognized at deposition. Regarding degradation prevention, Dr. Fuller testified that, “all RNA can be – [all] types of RNA forms can be degraded by RNase,” and protection from degradation by RNase would be important for all RNA types, including immunogen-encoding non-replicating mRNA.⁴²¹ And as to efficient delivery of mRNA into muscle, Dr. Fuller agreed that “to get levels of protein that you need to – for gene therapy or for an immune response, it’s well known now that you need a delivery

⁴¹⁹ Ex. 2021 at 14605.

⁴²⁰ Ex. 2021 at 14605.

⁴²¹ Ex. 1104 at 114:6-12.

vehicle.”⁴²² So, by October 2015, a POSA would have been motivated to follow Schrum’s teachings—confirmed by Geall et al.’s 2012 publications—to utilize a lipid nanoparticle system for immunogen-encoding, non-replicating mRNA vaccines (as in Ex. 2021) to achieve similar benefits.

248. Patent Owner’s own scientists have echoed that sentiment, and acknowledged in their published literature that Geall et al.’s 2012 work demonstrated “[t]he ability of LNPs, which have been optimized for siRNA delivery, to be repurposed for mRNA delivery.”⁴²³

249. In her declaration, though, Dr. Fuller attempts to dismiss Geall et al.’s 2012 publication as not relevant to an mRNA vaccine.⁴²⁴ To the extent that Dr. Fuller contends that self-amplifying mRNA is not a type of mRNA as a scientific matter, I disagree with her opinion. In the context of an mRNA vaccine, self-amplifying mRNA is a type of mRNA that encodes for both the antigen as well as the proteins that form the replicon, whereas the non-amplifying mRNA encodes for

⁴²² Ex. 1104 at 192:4-11.

⁴²³ Ex. 2049 at 2.

⁴²⁴ *E.g.*, Ex. 2199 ¶ 636.

only the antigen.⁴²⁵ The terminology of non-amplifying mRNA (NRM), also known as conventional mRNA vaccines, and self-amplifying mRNA (SAM) vaccines, also known as replicons, is commonly used in the scientific literature.

250. In both cases, however, the RNA acts as an intermediary between DNA and protein, and is involved in translating the DNA's genetic code into amino acids that form proteins. The scientific literature accordingly refers to self-amplifying mRNA as a type of mRNA consistently. For example, Patent Owner's scientists (including an inventor of the '127 patent), explained that "[i]mmunization in mice . . . with a self-amplifying mRNA, induced HAI and IgG titers that were comparable to those achieved in our study at similar doses."⁴²⁶ The same paper described self-amplifying mRNA as "very large-sized mRNAs."⁴²⁷

251. Even were Dr. Fuller's interpretation of mRNA correct, a POSA would nevertheless understand Geall's teachings as equally applicable to a non-replicating mRNA vaccine as I have explained above, and as Patent Owner itself has recognized.

⁴²⁵ Dr. Fuller also refers to saRNA as mRNA. Ex. 1104 at 25:4-7 ("We insert them into *self-amplifying mRNA* and insert them into mRNA . . .") (emphases added).

⁴²⁶ Ex. 1118 at 1321.

⁴²⁷ Ex. 1118 at 1321.

Self-amplifying mRNA and non-amplifying mRNA are made up of negatively charged nucleotides (i.e., the four canonical nucleotides such as adenosine, guanosine, uridine, and cytosine; or modified nucleotides such as pseudouridine or 1-methyl-pseudouridine). These negatively charged nucleotides would interact in the same way with the ionizable cationic lipids in the LNPs, regardless of whether the nucleotides encode for only the antigen, or both the antigen and the replicase.⁴²⁸ Hence, the ability of LNPs to encapsulate self-amplifying mRNA would have also indicated that the same LNPs could be used to encapsulate non-amplifying mRNA.

252. Likewise, the studies on self-amplifying mRNA also demonstrate that molecules larger than small-interfering RNA and mRNA could be successfully delivered using LNPs. Initially, LNPs were developed for small-interfering RNAs, which (as their name suggests) are significantly smaller than mRNA. Novartis's studies on self-amplifying mRNA proved that the same LNPs developed for small interfering RNA could also be used for much larger molecules such as self-amplifying mRNA. Size-wise, non-amplifying mRNA usually sits between small-interfering RNA and self-amplifying mRNA. Because LNPs could be used for both small-interfering RNA and self-amplifying mRNA, a POSA would have understood that LNPs would also be suitable for non-amplifying mRNA.

⁴²⁸ Ex. 1004 ¶ 35.

253. My opinion regarding the applicability of self-amplifying mRNA research to mRNA research is further confirmed by Patent Owner's own scientists

[REDACTED] For example, an article authored by several Patent Owner scientists describes how "mRNA vaccines are rapidly emerging as a powerful platform for infectious diseases because they are well tolerated, immunogenic, and scalable and are built on precise but adaptable antigen design."⁴²⁹ Notably, the authors explain that mRNA's potential was built on the foundation of self-amplifying mRNA research, stating "[t]he potential of rapid mRNA vaccine development and production was demonstrated by the ability to produce a self-amplifying mRNA (SAM) vaccine platform for pre-pandemic influenza just eight days after release of the viral gene sequence."⁴³⁰

254. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

⁴²⁹ Ex. 1108 at 2635.

⁴³⁰ Ex. 1108 at 2635.

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

255. In her declaration, Dr. Fuller identifies purported structural and functional differences between self-amplifying mRNA and non-amplifying mRNA.⁴³³ Dr. Fuller does not, however, explain why these differences would have led a POSA to believe that non-amplifying mRNA would not have succeeded as a vaccine. Like non-amplifying mRNA, self-amplifying mRNA must be delivered intact into the cell and be capable of translating the encoded protein after delivery. The success of self-amplifying mRNA encapsulated in LNP demonstrates that LNPs can successfully deliver mRNA into the cell, and the mRNA can in turn express the encoded proteins. A POSA would have understood that these results indicate that non-amplifying mRNA could also be successfully delivered into a cell using LNPs.

[REDACTED]

[REDACTED]

⁴³³ Ex. 2199 ¶¶ 470-483.

256. Dr. Fuller also points to a study by Brito 2014 et al., which purportedly shows that self-amplifying mRNA was immunogenic in mice, but not non-amplifying mRNA.⁴³⁴ Brito, however, recognizes that the non-amplifying mRNA was not administered at sufficiently high doses, stating that “mRNA was unable to induce responses ... perhaps due to the low dose being tested here.”⁴³⁵ Brito further explains that “[p]revious reports with mRNA have shown that much higher doses (80 µg) of mRNA have been used to generate immune responses in mice.”⁴³⁶ A POSA would have understood that mRNA would need to be administered at higher doses as compared to saRNA, not that it would fail to work all together. [REDACTED]

[REDACTED]

[REDACTED]

⁴³⁴ Ex. 2199 ¶¶ 553-565.

⁴³⁵ Ex. 2005 at 2124.

⁴³⁶ Ex. 2005 at 2124.

⁴³⁷ [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

257.

258.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

259. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

260. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

261. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

262. [REDACTED]

[REDACTED]

[REDACTED]

263. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

264. [REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

265. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

266. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

b) Scientific Literature Published by Patent
Owner's Scientists

267. [REDACTED] Patent Owner's scientists likewise relied on prior art publications demonstrating the promise of mRNA vaccines—contrary to Dr. Fuller's reliance on purported "skepticism." In various peer-reviewed publications, Patent Owner's scientists repeatedly emphasized that scientists at Novartis and CureVac had demonstrated the efficacy of mRNA vaccines. For example, in a paper co-authored by Patent Owner's scientist (including Dr. Giuseppe Ciaramella, one of the inventors on the '127 patent), Liang et al. stated that "*mRNA platforms have also shown strong potential as vaccines against infectious diseases*" based in part on the results of Hekele et al. and Petsch et al.⁴⁵³ In the same paper, Patent Owner's scientists also highlighted the results in Hekele et al., stating that "[t]he potential of rapid mRNA vaccine development and production was demonstrated by the ability to produce a self-amplifying mRNA

⁴⁵³ Ex. 1108 at 2635 (emphases added).

(SAM) vaccine platform for pre-pandemic influenza just eight days after release of the viral gene sequence.”⁴⁵⁴

268. Patent Owner’s scientists also highlighted the efficacy of CureVac’s non-amplifying mRNA vaccine. For example, Bahl et al. (another paper co-authored by Dr. Ciaramella) published:

Using mRNA complexed with protamine (RNAActive, CureVac), Petsch et al. demonstrated that intradermal (ID) vaccination of mice with RNAActive encoding full-length HA from influenza virus H1N1 (A/Puerto Rico/8/1934) induced effective seroconversion and virus-neutralizing antibodies in all vaccinated animals. Immunity was long lasting and protected both young and old animals from lethal challenge with the H1N1, H3N2, and H5N1 strains of the influenza A virus. Efficacy of these RNAActive vaccines was also shown in ferrets and pigs.⁴⁵⁵

269. Additionally, and consistent with my previous explanation, Patent Owner’s scientists also represented that mRNA vaccines had demonstrable advantage over other vaccine technologies. For example, Bahl et al. also stated “this

⁴⁵⁴ Ex. 1108 at 2635.

⁴⁵⁵ Ex. 1118 at 1316-17.

mRNA-based vaccine technology overcomes the challenges other nucleotide approaches pose, such as pre-existing antivector immunity for viral vectors, and concern for genome integration, or the high doses and devices needed (e.g., electroporation), for DNA-based vaccines”⁴⁵⁶ Bahl et al. further notes that “one of the major limitations with other nucleic acid-based technologies, such as plasmid DNA, has been translation to higher-order species, such as nonhuman primates.”⁴⁵⁷

270.

271.

⁴⁵⁶ Ex. 1118 at 1321.

⁴⁵⁷ Ex. 1118 at 1320.

⁴⁵⁸ *See, e.g.*, Ex. 1132 at 9808; *supra* § V.A.2.b.

[REDACTED]

[REDACTED]

[REDACTED]

272.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

273. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

274. [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

275. [REDACTED]

[REDACTED]

⁴⁶² Ex. 2138 at 6341-42 (emphases added).

⁴⁶³ Ex. 2199 ¶¶ 597-598, 648.

[REDACTED]

[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

⁴⁶⁴ Ex. 2200 ¶ 129 (emphasis added).

3) *Publications of Patent Owner's Scientists Confirm that Lipid Nanoparticles Were Well-Established for the Delivery of mRNA*

276. Finally, Patent Owner's scientists likewise confirmed that Novartis's research in self-amplifying mRNA vaccines demonstrated that lipid nanoparticles can be used to deliver mRNA. In a book chapter citing to the Geall 2012 (Ex. 2021) publication that I have previously discussed, Stanton & Benenato (both Patent Owner scientists) explained that:

The ability of LNPs, which have been optimized for siRNA delivery, to be repurposed for mRNA delivery has been verified by three different groups. In 2012 researchers at *Novartis demonstrated intramuscular delivery of a self-amplifying RNA vaccine* in a rodent model of RSV using D-Lin-DMA (5, Fig. 5) based LNPs, a vehicle that has been employed by Alnylam in a Phase I study for the delivery of siRNA. *This was 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.*⁴⁶⁵

Geall 2012's teachings reinforce the disclosures of Schrum pertaining to lipid nanoparticle delivery systems, and confirm that a POSA would have been motivated

⁴⁶⁵ Ex. 2049 at 2 (emphases added).

to use lipid nanoparticles to deliver immunogen-encoding mRNA as of the priority date, and would further have reasonably expected to encapsulate immunogen-encoding mRNA lipid nanoparticles and induce an immune response using such a composition.

277.

[illegible]

278.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

279. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

* * *

280. Schrum and Geall disclose each element of claim 1. Those references, the remainder of the prior art, and Patent Owner's own statements demonstrate that a POSA would have been motivated to combine their teachings, and would have reasonably expected success in arriving at the method of claim 1.

B. Claim 2: "The method of claim 1, wherein the open reading frame encodes a BetaCoV S protein."

⁴⁷¹ *Supra* ¶¶ 218-221; *see also* Krause Depo, 68:19-21 ("Well, enhanced disease can only be evaluated after somebody's been vaccinated and then later infected with the virus.").

⁴⁷² *Supra* § V.A.2.b.

281. As I explained in my opening declaration⁴⁷³ and for the reasons explained in claim 1, Section V.A, Schrum in view of Geall discloses this limitation. I disagree with Dr. Fuller's opinions to the contrary.

282. **First**, Dr. Fuller incorporates the arguments made with respect to claim 1.⁴⁷⁴ For the reasons explained in claim 1, Section V.A, I disagree.

283. **Second**, Dr. Fuller asserts that Schrum in view of Geall does not disclose that an "open reading frame encodes a BetaCoV S protein."⁴⁷⁵ For the reasons explained in claim 1, Section V.A, I disagree.⁴⁷⁶

284. **Third**, Dr. Fuller asserts that I have not opined that a POSA would have been motivated to combine Schrum with Geall with a reasonable expectation of

⁴⁷³ Ex. 1002 § IX.2.

⁴⁷⁴ Ex. 2199 ¶ 674.

⁴⁷⁵ Ex. 2199 ¶¶ 675-676.

⁴⁷⁶ A POSA would understand that mRNA encoding the spike protein of a SARS-CoV would necessarily disclose an open reading frame, which is the portion of the mRNA that encodes the protein/polypeptide of interest. Ex. 1002 ¶ 73.

success to arrive at claim 2.⁴⁷⁷ As I explained in my opening declaration⁴⁷⁸ and for the reasons explained with respect to claim 1, Section V.A, a POSA would have been motivated to combine Schrum with Geall, with a reasonable expectation of success to arrive at claim 2. Dr. Fuller further alleges that “[b]ecause of the significant challenges posed by delivering a nucleic acid for expression of a large protein (such as the full-length betacoronavirus S protein), a POSA would not have been motivated to combine . . . Schrum with Geall.”⁴⁷⁹ I disagree, as by 2015, Geall et al. had successfully expressed a 9-kb self-amplifying RNA encapsulated within an LNP, on par with the size of the spike protein.⁴⁸⁰

C. Claim 3: “The method of claim 2, wherein the immune response is a neutralizing antibody response specific to the BetaCoV S protein.”

285. As I explained in my opening declaration⁴⁸¹ and for the reasons explained in claims 1 and 2, Sections V.A and V.B, Schrum in view of Geall discloses this limitation.

⁴⁷⁷ Ex. 2199 ¶¶ 677-682.

⁴⁷⁸ Ex. 1002 § IX.2

⁴⁷⁹ Ex. 2199 ¶ 682.

⁴⁸⁰ Ex. 2021 at 14604.

⁴⁸¹ Ex. 1002 § IX.3.

286. **First**, Dr. Fuller asserts that I do not address how claims 1 and 2, from which claim 3 depends, are met.⁴⁸² For the reasons explained in my opening declaration,⁴⁸³ I disagree.

287. **Second**, Dr. Fuller asserts that Schrum in combination with Geall does not teach a “neutralizing antibody response specific to the BetaCoV S protein.”⁴⁸⁴ I disagree. As explained in my opening declaration, Schrum discloses that the administered mRNA may encode an “immunogen[]” that “elicit[s] or provoke an immune response in an organism.”⁴⁸⁵ Schrum additionally teaches that such an immunogen may “be delivered to a vertebrate in a dose amount large enough to be immunogenic to the vertebrate.”⁴⁸⁶ Geall further discloses that delivery of the immunogen will “elicit[] an immune response *in vivo* against an immunogen of interest” and that the response “is preferably protective and preferably involves

⁴⁸² Ex. 2199 ¶¶ 686-687.

⁴⁸³ Ex. 1002 §§ IX.1-3.

⁴⁸⁴ Ex. 2199 ¶¶ 688-690.

⁴⁸⁵ Ex. 1002 § IX.1. (quoting Ex. 1009 ¶¶ 340, 342).

⁴⁸⁶ Ex. 1002 § IX. 1 (quoting Ex. 1009 ¶¶ 340, 342).

antibodies and/or cell-mediated immunity.”⁴⁸⁷ Specifically, it “may comprise an antibody response (usually including IgG) and/or a cell-mediated immune response.”⁴⁸⁸

288. **Third**, Dr. Fuller asserts that I do not explain how a POSA would have been motivated to combine Schrum with Geall with a reasonable expectation of success to arrive at claim 3.⁴⁸⁹ As explained in my opening declaration with respect to claims 1-2, Schrum in combination with Geall discloses administering a lipid nanoparticle encapsulating a mRNA vaccine encoding a spike protein that induces specific immune response to the spike protein.⁴⁹⁰ Moreover, as explained in my opening declaration with respect to claim 3, Geall discusses that delivery of the

⁴⁸⁷ Ex. 1002 § IX.3 (quoting Ex. 1010 24:15-17); By 2015, the POSA would have recognized that Geall’s teaching that the immune response is “preferably protective” and may comprise “an antibody response (usually including IgG)” would encompass a neutralizing antibody response specific to the Beta-Cov S protein. Ex. 1002 ¶ 87.

⁴⁸⁸ Ex. 1002 § IX.3 (quoting Ex.1010 at 16:1-16:3).

⁴⁸⁹ Ex. 2199 ¶¶ 691-693.

⁴⁹⁰ Ex. 1002 §§ IX.1-2.

immunogen will “elicit[] an immune response *in vivo* against an immunogen of interest” and that the response “is preferably protective and preferably involves antibodies and/or cell-mediated immunity.”⁴⁹¹ Specifically, it “may comprise an antibody response (usually including IgG) and/or a cell-mediated immune response.”⁴⁹²

289. Thus, given Schrum’s disclosure of mRNA encoding an immunogen and encapsulated in the claimed composition and ranges, and Geall’s disclosure that an immunogen (including the S protein) can elicit a neutralizing antibody response, a POSA would have been motivated to use the mRNA encoding a S protein to elicit a neutralizing antibody response specific to the S protein, with a reasonable expectation of success.

D. Claim 6: “The method of claim 1, wherein the mRNA formulated in a lipid nanoparticle is administered intramuscularly.”

⁴⁹¹ Ex. 1002 § IX.3 (quoting Ex. 1010 24:15-17); By 2015, the POSA would have recognized that Geall’s teaching that the immune response is “preferably protective” and may comprise “an antibody response (usually including IgG)” would encompass a neutralizing antibody response specific to the Beta-Cov S protein. Ex. 1002 ¶ 87.

⁴⁹² Ex. 1002 § IX.3 (quoting Ex.1010 at 16:1-16:3).

290. As I explained in my opening declaration⁴⁹³ and for the reasons explained in claim 1, Section V.A, Schrum discloses this limitation.

291. **First**, Dr. Fuller asserts that I do not address how claim 1, from which claim 6 depends, is met.⁴⁹⁴ For the reasons explained in my opening declaration,⁴⁹⁵ I disagree.

292. **Second**, Dr. Fuller asserts that I do not explain how a POSA would have been motivated to combine Schrum with Geall with a reasonable expectation of success to arrive at claim 6.⁴⁹⁶ As explained in my opening declaration with respect to claim 1, Schrum in combination with Geall discloses administering mRNA encoding a spike protein and encapsulated in a lipid nanoparticle to induce an immune response.⁴⁹⁷ And, as explained in my opening declaration with respect to claim 6, Schrum discusses specific examples where the mRNA of the invention can be administered intramuscularly.⁴⁹⁸

⁴⁹³ Ex. 1002 § IX.4.

⁴⁹⁴ Ex. 2199 ¶¶ 696-697.

⁴⁹⁵ Ex. 1002 §§ IX.1, 4.

⁴⁹⁶ Ex. 2199 ¶¶ 698-699.

⁴⁹⁷ Ex. 1002 § IX.1.

⁴⁹⁸ Ex. 1002 § IX.4.

293. Thus, given that Schrum discloses mRNA, that the LNP-mRNA of the invention can be administered intramuscularly, and specific examples of such intramuscular delivery, a POSA would have been motivated to administer the LNP-mRNA intramuscularly with a reasonable expectation of success.

E. Claim 7: “The method of claim 1, wherein the mRNA further comprises a 5' untranslated region and a 3' untranslated region.”

294. As I explained in my opening declaration⁴⁹⁹ and for the reasons explained in claim 1, Section V.A, Schrum discloses this limitation.

295. *First*, Dr. Fuller asserts that I do not address how claim 1, from which claim 7 depends, is met.⁵⁰⁰ For the reasons explained in my opening declaration,⁵⁰¹ I disagree.

296. *Second*, Dr. Fuller asserts that I do not explain how a POSA would have been motivated to combine Schrum with Geall with a reasonable expectation of success to arrive at claim 7.⁵⁰² I disagree. As explained in my opening declaration with respect to claim 1, Schrum in combination with Geall discloses administering

⁴⁹⁹ Ex. 1002 § IX.5.

⁵⁰⁰ Ex. 2199 ¶¶ 703-704.

⁵⁰¹ Ex. 1002 §§ IX.1, 5.

⁵⁰² Ex. 2199 ¶¶ 705-706.

mRNA encoding a spike protein and encapsulated in a lipid nanoparticle to induce an immune response.⁵⁰³ And as further explained in my opening declaration, a POSA would have understood that mature eukaryotic mRNA transcripts contain a 5' UTR and a 3' UTR, which regulate translation of the mRNA into polypeptide and direct the mRNA to certain locations within a cell.⁵⁰⁴ Schrum further confirms that “[t]here is providing a growing body of evidence about the regulatory roles played by the UTRs in terms of stability of the nucleic acid molecule and translation.”⁵⁰⁵ The ’127 patent itself confirms that “[t]he *basic components of an mRNA molecule typically include* at least one coding region, *a 5’ untranslated region (UTR), a 3’ UTR*, a 5’ cap and a poly(A) tail.”⁵⁰⁶ Indeed, as explained in my opening declaration with respect to claim 7, Schrum discusses such examples of mRNA comprising UTRs.⁵⁰⁷ A POSA would thus have been aware that the mRNA

⁵⁰³ Ex. 1002 § IX.1.

⁵⁰⁴ Ex. 1002 ¶¶ 26-27.

⁵⁰⁵ Ex. 1009 ¶ 61. *See also* Ex. 1009 ¶ 904 (method for making modified mRNA including 5’ and 3’ UTRs).

⁵⁰⁶ Ex. 1001 at 41:65-67 (emphases added).

⁵⁰⁷ Ex. 1002 § IX.5.

disclosed in Schrum incorporates such “basic [mRNA] components,” and would have been motivated to use mRNA with these basic components to express the S-protein with a reasonable expectation of success.

F. Claim 8: “The method of claim 1, wherein the mRNA further comprises a poly(A) tail.”

297. As I explained in my opening declaration⁵⁰⁸ and for the reasons explained in claim 1, Section V.A, Schrum discloses this limitation.

298. *First*, Dr. Fuller asserts that I do not address how claim 1, from which claim 8 depends, are met.⁵⁰⁹ For the reasons explained in my opening declaration,⁵¹⁰ I disagree.

299. *Second*, Dr. Fuller asserts that I do not explain how a POSA would have been motivated to combine Schrum with Geall with a reasonable expectation of success to arrive at claim 8.⁵¹¹ As explained in my opening declaration with respect to claim 1, Schrum in combination with Geall discloses administering mRNA encoding a spike protein and encapsulated in a lipid nanoparticle to induce an

⁵⁰⁸ Ex. 1002 § IX.6.

⁵⁰⁹ Ex. 2199 ¶¶ 710-711.

⁵¹⁰ Ex. 1002 §§ IX.1, 6.

⁵¹¹ Ex. 2199 ¶¶ 712-713.

immune response, and that the mRNA can be modified.⁵¹² And as further explained in my opening declaration, a POSA would have understood that mature eukaryotic mRNA transcripts contain a poly(A) tail that plays a role in mRNA stability and the regulation of protein translation.⁵¹³ In fact, the '127 patent itself confirms that “[t]he *basic components of an mRNA molecule typically include* at least one coding region, a 5’ untranslated region (UTR), a 3’ UTR, a 5’ cap and *a poly(A) tail.*”⁵¹⁴ Moreover, as explained in my opening declaration with respect to claim 8, Schrum discusses such examples of mRNA comprising a poly(A) tail.⁵¹⁵ A POSA would have thus been aware that the mRNA disclosed in Schrum incorporates such “basic [mRNA] components,” and would have been motivated to use mRNA with these basic components to express the S-protein with a reasonable expectation of success.

G. Claim 9: “The method of claim 1, wherein the mRNA further comprises a 5' cap analog.”

⁵¹² Ex. 1002 § IX.1.

⁵¹³ Ex. 1002 ¶¶ 26-27.

⁵¹⁴ Ex. 1001 at 41:65-67 (emphases added).

⁵¹⁵ Ex. 1002 § IX.6.

300. As I explained in my opening declaration⁵¹⁶ and for the reasons explained in claim 1, Section V.A, Schrum discloses this limitation.

301. **First**, Dr. Fuller asserts that I do not address how claim 1, from which claim 9 depends, is met.⁵¹⁷ For the reasons explained in my opening declaration,⁵¹⁸ I disagree.

302. **Second**, Dr. Fuller asserts that I do not explain how a POSA would have been motivated to combine Schrum with Geall with a reasonable expectation of success to arrive at claim 9.⁵¹⁹ As explained in my opening declaration with respect to claim 1, Schrum in combination with Geall discloses administering mRNA encoding a spike protein and encapsulated in a lipid nanoparticle to induce an immune response.⁵²⁰ And as further explained in my opening declaration, a POSA would have understood that mature eukaryotic mRNA transcripts contain a 5' cap,

⁵¹⁶ Ex. 1002 § IX.5.

⁵¹⁷ Ex. 2199 ¶¶ 717-718.

⁵¹⁸ Ex. 1002 § IX.1, 7.

⁵¹⁹ Ex. 2199 ¶¶ 719-720.

⁵²⁰ Ex. 1002 § IX.1.

which stabilize mRNA and align it on the ribosome appropriately for translation.⁵²¹ In fact, the '127 patent itself confirms that “[t]he *basic components of an mRNA molecule typically include* at least one coding region, a 5’ untranslated region (UTR), a 3’ UTR, a *5’ cap* and a poly(A) tail.”⁵²² Moreover, as explained in my opening declaration with respect to claim 9, Schrum discusses such examples of mRNA comprising a 5' cap.⁵²³ A POSA would have thus been aware that the mRNA disclosed in Schrum incorporates such basic mRNA components, and would have been motivated to use mRNA with these basic components to express the S-protein with a reasonable expectation of success.

H. Claim 11: “The method of claim 1, wherein the mRNA comprises a chemical modification.”

303. As I explained in my opening declaration⁵²⁴ and for the reasons explained in claim 1, Section V.A, Schrum discloses this limitation.

304. *First*, Dr. Fuller asserts that I do not address how claim 1, from which

⁵²¹ Ex. 1002 ¶¶ 26-27.

⁵²² Ex. 1001 at 41:65-67 (emphases added).

⁵²³ Ex. 1002 § IX.7.

⁵²⁴ Ex. 1002 § IX.8.

claim 11 depends, is met.⁵²⁵ For the reasons explained in my opening declaration,⁵²⁶ I disagree.

305. *Second*, Dr. Fuller asserts that I do not explain how a POSA would have been motivated to combine Schrum with Geall with a reasonable expectation of success to arrive at claim 1.⁵²⁷ As explained in my opening declaration with respect to claim 1, Schrum in combination with Geall discloses administering mRNA encoding a spike protein and encapsulated in a lipid nanoparticle to induce an immune response.⁵²⁸ In fact, Schrum summarizes that its disclosure provides “formulation compositions comprising *modified nucleic acid molecules* which may encode a protein,” such as an immunogen.⁵²⁹ Moreover, as explained in my opening declaration with respect to claim 11, Schrum discusses examples of modified mRNA resulting in successful protein expression.⁵³⁰ Thus, given that Schrum discloses

⁵²⁵ Ex. 2199 ¶¶ 724-725.

⁵²⁶ Ex. 1002 §§ IX.1, 8.

⁵²⁷ Ex. 2199 ¶¶ 726-727.

⁵²⁸ Ex. 1002 § IX.1.

⁵²⁹ Ex. 1009 ¶ 4 (emphases added).

⁵³⁰ Ex. 1002 § IX.8.

modified mRNA, and examples of modified mRNA resulting in successful protein expression, a POSA would have been motivated to use mRNA with such chemical modifications to express the S-protein and elicit an immune response, with a reasonable expectation of success.

306. **Third**, Dr. Fuller makes a number of misstatements regarding the prior art teachings of nucleotide (*i.e.*, “chemical”) modifications, including that “[b]efore October 2015, Dr. Karikó and Dr. Weissman were researching the use of modified nucleosides for therapeutic applications of mRNA—not for mRNA vaccines.”⁵³¹ Dr. Fuller further points to a statement by Dr. Kariko that “amazingly,” non-immunogenic mRNA containing modified uridines also turned out to be a more suitable molecule for vaccine development.”⁵³² I disagree with Dr. Fuller’s opinions. Dr. Fuller’s restrictive reading of Dr. Karikó and Dr. Weissman’s teachings is incorrect. As early as 2008, Drs. Karikó and Weissman described

⁵³¹ Ex. 2199 ¶ 730.

⁵³² Ex. 2199 ¶ 733 (quoting Ex. 2118 at 619).

modified mRNA as a “promising tool for both gene replacement and *vaccination*.”⁵³³

307. Dr. Fuller also cites several articles to argue that there was skepticism regarding modified mRNA for vaccines.⁵³⁴ For example, Dr. Fuller points to Petsch et al.’s statement that “mRNA is naturally recognized by innate pattern recognition receptors, thereby inducing an effective, adaptive, immune response and potentially reducing the need for adjuvants.”⁵³⁵ Dr. Fuller further cites Schlake et al.’s statement that “[w]hile such modifications can enhance translation of the mRNA . . . they interfere with the design of mRNA-vaccines with self-adjuvantivity.”⁵³⁶

308. Dr. Fuller also does not address the disclosure in Schrum, which would have motivated a POSA to use modified nucleotides in an mRNA vaccine with a

⁵³³ Ex. 1022 at 1 (emphasis added). In their 2008 article, Drs. Karikó and Weissman contemplate the coadministration of adjuvant, but the claims of the ’127 patent do not exclude the use of such an adjuvant.

⁵³⁴ Ex. 2199 ¶¶ 731-732.

⁵³⁵ Ex. 2199 ¶ 731 (quoting Ex. 2025 at 1215); [REDACTED]

[REDACTED]

[REDACTED]

⁵³⁶ Ex. 2199 ¶ 732 (quoting Ex. 1019 at 1323).

reasonable expectation of success. Under the section “Activation of the Immune Response: Vaccines,” Schrum explains that “certain modified nucleosides, or combinations thereof, when introduced into the modified nucleic acid molecules or mmRNA of the invention *will activate the innate immune response*.”⁵³⁷ Schrum further states that “the activating molecules contain a translatable region which encodes for a polypeptide sequence useful as a vaccine, thus providing the ability to be a self-adjuvant,” and “the modified nucleic acid molecules and/or mmRNA encoding an immunogen may be delivered to cells to trigger multiple innate response pathways.”⁵³⁸ This is consistent with Drs. Karikó and Weissman’s earlier teaching that for purposes of vaccination, a POSA could simply co-administer an adjuvant, which the claims of the ’127 patent do not in any way preclude. Based on Schrum’s teachings, a POSA would be motivated to incorporate a chemical modification into an immunogen-encoding mRNA sequence, and reasonably expect to do so successfully.

309. **Fourth**, Dr. Fuller asserts that (1) with saRNA, the sub-genomic RNA from which the protein of interest is eventually generated cannot contain a chemical

⁵³⁷ Ex. 1009 ¶ 341 (emphasis added).

⁵³⁸ Ex. 1009 ¶¶ 341-42.

modification, and that (2) Geall's reported ineffective results when using saRNA with chemical modifications.⁵³⁹ Irrespective of Geall's disclosure, a POSA would have understood that Schrum discloses that non-amplifying mRNA achieved high levels of protein expression with modified nucleotides, as explained in my opening declaration.⁵⁴⁰ Moreover, the examples of the '127 patent itself did not disclose whether or not the mRNA comprises a chemical modification, and the specification expressly states that "[b]oth chemically modified and unmodified RNA vaccines are useful according to the invention."⁵⁴¹ Dr. Fuller's discussion of chemical modifications to self-amplifying mRNA is also in tension with her own opinions. Dr. Fuller asserts throughout that "Geall relates to self-amplifying RNA, **not mRNA**."⁵⁴² If Dr. Fuller's argument on that point were credited (and it should not be), then Geall's disclosure would not detract from Schrum's express teaching of chemically-modified mRNA, including chemically-modified mRNA encoding for an immunogen used for vaccination.

I. Claim 12: "The method of claim 11, wherein the chemical

⁵³⁹ Ex. 2199 ¶¶ 734-738.

⁵⁴⁰ Ex. 1002 § IX.8.

⁵⁴¹ Ex. 1001 at 21:8-9.

⁵⁴² Ex. 2199 ¶ 199.

modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification.”

310. As I explained in my opening declaration⁵⁴³ and for the reasons explained in claims 1 and 11, Sections V.A. and V.H, Schrum discloses this limitation.

311. *First*, Dr. Fuller asserts that I do not address how claims 1 and 11, from which claim 12 depends, are met.⁵⁴⁴ For the reasons explained in my opening declaration,⁵⁴⁵ I disagree.

312. *Second*, Dr. Fuller asserts that I do not explain how a POSA would have been motivated to combine Schrum with Geall with a reasonable expectation of success to arrive at claim 12.⁵⁴⁶ As explained in my opening declaration with respect to claim 1, Schrum in combination with Geall discloses administering mRNA encoding a spike protein and encapsulated in a lipid nanoparticle to induce an immune response, and that the mRNA can be modified.⁵⁴⁷ Moreover, as explained

⁵⁴³ Ex. 1002 § IX.9.

⁵⁴⁴ Ex. 2199 ¶¶ 742-743.

⁵⁴⁵ Ex. 1002 §§ IX.1, 8-9.

⁵⁴⁶ Ex. 2199 ¶¶ 744-745.

⁵⁴⁷ Ex. 1002 § IX.1.

in my opening declaration with respect to claim 11, Schrum discusses examples of modified mRNA resulting in successful protein expression.⁵⁴⁸ And as I explain with respect to claim 12 of my opening declaration, Schrum provides examples of successful production of protein *in vitro* and *in vivo* after administration of N1-methylpseudouridine-modified mRNA.⁵⁴⁹ Indeed, Schrum notes that “exemplary nucleobases and nucleosides having a modified uracil include . . . 1-methylpseudouridine.”⁵⁵⁰ Thus, given Schrum’s disclosure of modified mRNA, its instruction that modified mRNA can include 1-methylpseudouridine or 1-ethylpseudouridine, and its disclosure of several examples, a POSA would have been motivated to use the mRNA with a 1-methylpseudouridine modification to express the S-protein with a reasonable expectation of success.

313. Dr. Fuller makes a number of misstatements regarding the prior art teachings of nucleotide (*i.e.*, “chemical”) modifications, including that before October 2015, Dr. Karikó and Dr. Weissman were researching the use of modified nucleosides for therapeutic applications of mRNA—not for mRNA vaccines and that

⁵⁴⁸ Ex. 1002 § IX.8.

⁵⁴⁹ Ex. 1002 § IX.9.

⁵⁵⁰ Ex. 1009 ¶ 283.

there was skepticism regarding modified mRNA for vaccines.⁵⁵¹ For the reasons explained in Section V.H, I disagree.

J. Claim 13: “The method of claim 11, wherein at least 80% of the uracil in the open reading frame of the mRNA has a chemical modification.”

314. As I explained in my opening declaration⁵⁵² and for the reasons explained in claims 1 and 11, Schrum discloses this limitation.

315. *First*, Dr. Fuller asserts that I do not address how claims 1 and 11, Sections V.A. and V.H, from which claim 13 depends, are met.⁵⁵³ For the reasons explained in my opening declaration,⁵⁵⁴ I disagree.

316. *Second*, Dr. Fuller asserts that I do not explain how a POSA would have been motivated to combine Schrum with Geall with a reasonable expectation of success to arrive at claim 13.⁵⁵⁵ As explained in my opening declaration with respect to claim 1, Schrum in combination with Geall discloses administering mRNA encoding a spike protein and encapsulated in a lipid nanoparticle to induce an

⁵⁵¹ Ex. 2199 ¶¶ 746-747.

⁵⁵² Ex. 1002 § IX.10.

⁵⁵³ Ex. 2199 ¶¶ 751-752.

⁵⁵⁴ Ex. 1002 §§ IX.1, 8, 10.

⁵⁵⁵ Ex. 2199 ¶¶ 753-754.

immune response, and that the mRNA can be modified.⁵⁵⁶ Moreover, as explained in my opening declaration with respect to claim 11, Schrum discusses examples of modified mRNA resulting in successful protein expression.⁵⁵⁷ And as I explain with respect to claim 13 of my opening declaration, Schrum explains that in the disclosed mRNA, “at least 80%, at least 90%, or 100% of the uracil in the nucleic acid may be replaced with a modified uracil.”⁵⁵⁸ Thus, given that Schrum discloses the successful use of modified mRNA, including examples in which at least 80%, at least 90%, or 100% of the uracil in the nucleic acid such as mRNA may be replaced with a modified uracil, a POSA would have been motivated to use the mRNA with at least 80% modification of a uracil to express the S-protein with a reasonable expectation of success.

317. Dr. Fuller makes a number of misstatements regarding the prior art teachings of nucleotide (*i.e.*, “chemical”) modifications, including that before October 2015, Dr. Karikó and Dr. Weissman were researching the use of modified nucleosides for therapeutic applications of mRNA—not for mRNA vaccines and that

⁵⁵⁶ Ex. 1002 § IX.1.

⁵⁵⁷ Ex. 1002 § IX.8.

⁵⁵⁸ Ex. 1002 § IX.10.

there was skepticism regarding modified mRNA for vaccines.⁵⁵⁹ For the reasons explained in Sections V.H, I disagree.

K. Claim 17: “A method comprising administering to a subject an mRNA comprising a 5' cap analog, a 5' untranslated region, an open reading frame encoding a BetaCoV S protein or S protein subunit, a 3' untranslated region, and a poly(A) tail formulated in a lipid nanoparticle in an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit, wherein the lipid nanoparticle comprises 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid.”

318. Schrum in view of Geall discloses each limitation of claim 17, and a POSA would have had good reason to combine (1) Schrum’s disclosure of an mRNA with a 5’ and 3’ UTR and a poly(A) tail encoding an immunogen that induces an immune response and encapsulated in an LNP of the claimed composition and ranges with (2) Geall’s teaching that the immunogen of an RNA vaccine may be a betacoronavirus S protein, all with a reasonable expectation of success. Dr. Fuller has not shown otherwise, and her opinions in response raise a host of inaccurate, and often irrelevant, points that I respond to further below.

1. Schrum and Geall Disclose Every Element of Claim 17

⁵⁵⁹ Ex. 2199 ¶¶ 755-757.

319. I have previously explained that Schrum in view of Geall teaches every limitation of claim 17.⁵⁶⁰

320. For claim 17, Dr. Fuller recycles many of her arguments with respect to claim 1, including that Geall focuses on self-amplifying mRNA, that Geall does not disclose a spike protein that induces an immune response, that there was skepticism regarding mRNA vaccines, and that concerns regarding ADE would have discouraged use of a spike protein.⁵⁶¹ For the reasons explained in Section V.A, I disagree.⁵⁶²

**2. A POSA Would Have Been Motivated
to Combine the Teachings of Schrum and
Geall With a Reasonable Expectation of Success**

321. In my previous declaration, I explained that a POSA would have been motivated to combine Schrum's disclosure of the use of an mRNA vaccine (with a 3' UTR and a poly(A)) tail encoding an immunogen encapsulated in a lipid nanoparticle with Geall's disclosure of an RNA vaccine encoding a betacoronavirus

⁵⁶⁰ Ex. 1002 § IX.11.

⁵⁶¹ Ex. 2199 ¶¶ 775-776.

⁵⁶² A POSA would understand that mRNA encoding the spike protein of SARS-CoV-2 would necessarily disclose an open reading frame, which is the portion of the mRNA that encodes the protein/polypeptide of interest. Ex. 1002 ¶ 73.

spike protein, to induce an immune response specific to the spike protein and would reasonably have expected to do so successfully in view of well-known methods of synthesizing mRNA, already known in the art.⁵⁶³

322. In particular, with respect to the lipid nanoparticles, as explained building on its disclosures of mRNA vaccines encapsulated by lipid nanoparticles, Schrum further provides concrete examples of lipid nanoparticles comprising 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid.”⁵⁶⁴ A POSA would have understood that the mRNA vaccines disclosed in Schrum could be delivered using the lipid nanoparticles disclosed in the examples.

323. And with respect to the 5' and 3' UTR and poly(A) tail, a POSA would have been aware that the mRNA disclosed in Schrum incorporates such basic mRNA components and would have been motivated to use the mRNA with these basic components to express the S-protein with a reasonable expectation of success.⁵⁶⁵

⁵⁶³ Ex. 1002 § IX.11.

⁵⁶⁴ Ex. 1002 § IX.11.

⁵⁶⁵ Ex. 1002 § IX.11.

324. Dr. Fuller does not meaningfully dispute my analysis in her declaration.⁵⁶⁶ Instead, she refers back to her eight purported reasons as to why “a POSA would not have had a reasonable expectation of success of October 2015.”⁵⁶⁷ As explained in Section V.A.2, many of Dr. Fuller’s arguments are irrelevant. Nevertheless, for the reasons explained in Section V.A.2, I disagree with Dr. Fuller’s arguments, none of which rebuts my explanation that a POSA would be motivated to combine the teachings of Schrum and Geall, and would reasonably expect to do so successfully.

* * *

325. Schrum and Geall disclose each element of claim 17. Those references, the remainder of the prior art, and Patent Owner’s own statements demonstrate that a POSA would have been motivated to combine their teachings, and reasonably expect to arrive at the claimed method successfully.

L. Claim 18: “The method of claim 17, wherein the open reading frame encodes a BetaCoV S protein.”

326. As I explained in my opening declaration⁵⁶⁸ and for the reasons

⁵⁶⁶ Ex. 2199 ¶ 766-768.

⁵⁶⁷ Ex. 2199 ¶¶ 509, 759.

⁵⁶⁸ Ex. 1002 § IX.12.

explained in claim 17, Section V.K, Schrum in view of Geall discloses this limitation. I disagree with Dr. Fuller's opinions to the contrary.

327. **First**, Dr. Fuller incorporates the arguments made with respect to claim 17.⁵⁶⁹ For the reasons explained in claim 17, Section V.K, I disagree.

328. **Second**, Dr. Fuller asserts that Schrum in view of Geall does not disclose an "open reading frame encodes a BetaCoV S protein."⁵⁷⁰ For the reasons explained in claim 17, Section V.K, I disagree.⁵⁷¹

329. **Third**, Dr. Fuller asserts that I have not opined that a POSA would have been motivated to combine Schrum with Geall with a reasonable expectation of success to arrive at claim 18.⁵⁷² As I explained in my opening declaration⁵⁷³ and for the reasons explained with respect to claim 17, Section V.K, a POSA would have

⁵⁶⁹ Ex. 2199 ¶¶ 772-773.

⁵⁷⁰ Ex. 2199 ¶ 774.

⁵⁷¹ A POSA would understand that mRNA encoding the spike protein of SARS-CoV-2 would necessarily disclose an open reading frame, which is the portion of the mRNA that encodes the protein/polypeptide of interest. Ex. 1002 ¶ 73.

⁵⁷² Ex. 2199 ¶¶ 775-776.

⁵⁷³ Ex. 1002 § IX.12.

been motivated to combine Schrum with Geall, with a reasonable expectation of success to arrive at claim 18.

M. Claim 20: “The method of claim 18, wherein at least 80% of the uracil in the open reading frame of the mRNA has a 1-methylpseudouridine modification.”

330. As I explained in my opening declaration⁵⁷⁴ and for the reasons explained in claims 17 and 18, Sections V.K and V.L, Schrum discloses this limitation.

331. *First*, Dr. Fuller asserts that I do not address how claims 17 and 18, from which claim 20 depends, are met.⁵⁷⁵ For the reasons explained in my opening declaration,⁵⁷⁶ I disagree.

332. *Second*, Dr. Fuller asserts that I do not explain how a POSA would have been motivated to combine Schrum with Geall with a reasonable expectation of success to arrive at claim 20.⁵⁷⁷ As explained in my opening declaration with respect to claims 17-18, Schrum in combination with Geall discloses administering mRNA (with a 5' and 3' UTR, poly(A) tail) encoding a spike protein and encapsulated in a

⁵⁷⁴ Ex. 1002 § IX.13.

⁵⁷⁵ Ex. 2199 ¶¶ 780-781.

⁵⁷⁶ Ex. 1002 §§ IX.11-13.

⁵⁷⁷ Ex. 2199 ¶¶ 782-783.

lipid nanoparticle to induce an immune response.⁵⁷⁸ Moreover, as I explain with respect to claim 20 of my opening declaration, Schrum further explains that in the disclosed mRNA, “at least 80%, at least 90%, or 100% of the uracil in the nucleic acid may be replaced with a modified uracil, and provides examples of successful production of protein *in vitro* and *in vivo* after administration of N1-methylpseudouridine-modified mRNA.”⁵⁷⁹ Indeed, Schrum notes that “exemplary nucleobases and nucleosides having a modified uracil include . . . 1-methylpseudouridine.”⁵⁸⁰ Thus, given that Schrum discloses successful use of modified mRNA, including examples in which at least 80%, at least 90%, or 100% of the uracil in the nucleic acid such as mRNA may be replaced with a modified uracil, and examples of mRNA modified with 1-methylpseudouridine resulting in successful protein expression, a POSA would have been motivated to use the mRNA with at least 80% 1-methylpseudouridine modification to express the S-protein with a reasonable expectation of success.

⁵⁷⁸ Ex. 1002 §§ IX.11-12.

⁵⁷⁹ Ex. 1002 § IX.13.

⁵⁸⁰ Ex. 1009 ¶ 283.

333. Dr. Fuller makes a number of misstatements regarding the prior art teachings of nucleotide (*i.e.*, “chemical”) modifications, including that before October 2015, Dr. Karikó and Dr. Weissman were researching the use of modified nucleosides for therapeutic applications of mRNA—not for mRNA vaccines and that there was skepticism regarding modified mRNA for vaccines.⁵⁸¹ For the reasons explained in Section V.H, I disagree.

VI. GROUND 3: THE COMBINATION OF SCHRUM IN VIEW OF YANG DISCLOSES ALL OF THE LIMITATIONS OF CLAIMS 1-3, 6-9, 11-13, 17-18, AND 20

334. In Section X of my previous declaration, I explained that each of the limitations of claims 1-3, 6-9, 11-13, 17-18, and 20 had already been disclosed by Schrum in view of Yang by October 2015, which I understand is referred to as Ground 3 in this proceeding.⁵⁸² In Section X of my previous declaration, I also explained why, as of October 2015, a POSA would have been motivated to combine the teachings of the prior art to arrive at the claimed combination of known elements, as well as why a POSA would have reasonably expected to do so successfully. Section XII of Dr. Fuller’s declaration, in which she discusses Ground 3, recycles

⁵⁸¹ Ex. 2199 ¶ 786.

⁵⁸² Ex. 1002 § X.

many of the opinions discussed above with respect to Grounds 1 and 2. I therefore disagree with Dr. Fuller, and my opinions remain unchanged.

- A. Claim 1: “A method comprising administering to a subject a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit formulated in a lipid nanoparticle in an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit, wherein the lipid nanoparticle comprises 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid.”**

335. Schrum in view of Yang discloses each limitation of claim 1, and a POSA would have had good reason to combine Schrum’s disclosure of a lipid nanoparticle encapsulating an mRNA encoding an immunogen that induces an immune response with Yang’s teaching that the immunogen of a nucleic acid vaccine may be a betacoronavirus S protein, all with a reasonable expectation of doing success. Dr. Fuller has not shown otherwise, and her opinions in response raise a host of inaccurate, and often irrelevant, points that I respond to further below.

1. Schrum and Yang Disclose Every Element of Claim 1

336. I have previously explained that Schrum in view of Yang teach every limitation of claim 1.⁵⁸³

⁵⁸³ Ex. 1002 § X.1.

337. **First**, Dr. Fuller asserts that the combination of Schrum and Yang does not disclose mRNA because Yang is focused on DNA rather than non-amplifying mRNA.⁵⁸⁴ This is of no import to the ultimate analysis, as there is no question that Schrum discloses non-amplifying mRNA vaccines encoding for an immunogen, as well as the encapsulation of such mRNA in lipid nanoparticles, as explained in Section IV.B. Dr. Fuller further asserts that Yang does not teach delivering a full-length S protein or S protein subunit.⁵⁸⁵ Contrary to Dr. Fuller’s assertion, Yang in fact discloses a full-length spike protein. In its abstract, Yang states that “we show that a DNA vaccine encoding the spike (S) glycoprotein of the SARS-CoV induces T cell and neutralizing antibody responses, as well as protective immunity.”⁵⁸⁶ Yang further discloses that “[i]njection of S, SΔTM and SΔCD expression vectors induced a substantial immune response.”⁵⁸⁷ Yang further provides a diagram of a full length spike protein, which would have confirmed to a POSA that the “S” protein that “induced a substantial immune response” was the full length S protein.⁵⁸⁸

⁵⁸⁴ Ex. 2199 ¶ 789.

⁵⁸⁵ Ex. 2199 ¶¶ 790-809.

⁵⁸⁶ Ex. 1011 at 561.

⁵⁸⁷ Ex. 1011 at 561.

⁵⁸⁸ Ex. 1011 at Fig. 1.



338. Yang additionally discloses: (1) DNA encoding an S protein with transmembrane and cytoplasmic domains removed (SΔTM) and (2) DNA encoding an S protein with the cytoplasmic domain removed (SΔCD).

339. **Second**, Dr. Fuller further asserts that a POSA would not understand Yang's disclosure of a spike protein to form a structural protein forming a spike.⁵⁸⁹ For the reasons explained in claim 1, Section IV.B.1, a POSA would have understood a scientific publication's reference to a spike protein to mean a structural protein forming a spike.

340. **Third**, Dr. Fuller asserts that concerns about disease enhancement undermine Yang's disclosure of a spike protein.⁵⁹⁰ For the reasons explained in

⁵⁸⁹ Ex. 2199 ¶ 810.

⁵⁹⁰ Ex. 2199 ¶¶ 811-815.

Section V.A.2.b.3, I disagree that any concerns about ADE would have discouraged a POSA from using a spike protein.

341. *Fourth*, Dr. Fuller argues that Schrum in view of Yang does not disclose a S protein that can elicit a specific immune response, criticizing Schrum for “discussing an immune response generally” and Yang for not showing “working examples” or having examples for only truncated proteins.⁵⁹¹ As an initial matter, as explained above, this argument seems to flow from Dr. Fuller’s faulty premise that the prior art cannot disclose each limitation of a patent claim without such working examples.

342. Regardless, I disagree. As explained in my opening declaration, Schrum discloses that the administered mRNA may encode an “immunogen[]” that “elicit[s] or provoke an immune response in an organism.”⁵⁹² Schrum additionally teaches that such an immunogen may “be delivered to a vertebrate in a dose amount large enough to be immunogenic to the vertebrate.”⁵⁹³

343. And as I further explained in my opening declaration, Yang, in turn,

⁵⁹¹ Ex. 2199 ¶¶ 817-822.

⁵⁹² Ex. 1002 § X.1 (quoting Ex. 1009 ¶¶ 340, 342).

⁵⁹³ Ex. 1002 § X.1 (quoting Ex. 1009 ¶¶ 340, 342).

states that “a DNA vaccine encoding the **spike (S) glycoprotein** of the SARS-CoV induces T cell and neutralizing antibody responses, as well as protective immunity.”⁵⁹⁴ Yang further provides a diagram of a full length spike protein, which would have confirmed to the POSA that the “S” protein that “induced a substantial immune response” was the full length S protein.⁵⁹⁵ Yang also discloses that “[i]njection of S, SATM and S Δ CD expression vectors induced a substantial immune response.”⁵⁹⁶ Thus, a POSA would have understood Schrum in view of Yang as teaching the use of a betacoronavirus S protein to elicit a specific immune response.

2. A POSA would have been motivated to combine the teachings of Schrum and Yang with a reasonable expectation of success

344. In my opening declaration, I explained that a POSA would have been motivated to combine Schrum’s disclosure of the use of an mRNA vaccine encoding an immunogen that induces an immune response, and encapsulated in lipid nanoparticle, with Yang’s disclosure of a DNA vaccine encoding a betacoronavirus spike protein, and would reasonably have expected to do so successfully in view of

⁵⁹⁴ Ex. 1002 § X.1 (quoting Ex. 1011 at 561) (emphases added).

⁵⁹⁵ Ex. 1011 at Fig. 1.

⁵⁹⁶ Ex. 1011 at 561.

well-known methods of synthesizing mRNA, already known in the art.⁵⁹⁷ I disagree with Dr. Fuller's opinions to the contrary.

345. **First**, as explained in Section V.A.2, Dr. Fuller does not meaningfully dispute my analysis in her declaration.⁵⁹⁸ Instead, she refers back to her eight purported reasons as to why “a POSA would not have had a reasonable expectation of success of October 2015.”⁵⁹⁹ As explained in Section V.A.2, many of Dr. Fuller's arguments are irrelevant. Nevertheless, for the reasons explained in Section V.A.2, I disagree with Dr. Fuller's arguments, none of which rebuts my explanation that a POSA would be motivated to combine the teachings of Schrum and Yang, and would reasonably expect to do so successfully.

346. **Second**, Dr. Fuller further suggests that a POSA would not have looked to publications regarding DNA vaccines in order to develop a mRNA vaccine against a betacoronavirus, and that success with a DNA vaccine would not have informed a POSA regarding success with an mRNA vaccine.⁶⁰⁰ I disagree.

⁵⁹⁷ Ex. 1002 ¶¶ X.1.

⁵⁹⁸ Ex. 2199 ¶¶ 829-854.

⁵⁹⁹ Ex. 2199 ¶¶ 825.

⁶⁰⁰ Ex. 2199 ¶¶ 830-833.

347. Contrary to Dr. Fuller's assertion, the successful generation of antibodies following a DNA vaccine encoding a spike protein would have encouraged a POSA to also use the spike protein for an mRNA vaccine. In both DNA vaccines and mRNA vaccines, a nucleic acid encoding an immunogen is administered to patients. In both cases, the immunogen is ultimately translated by the cell's host cell machinery. The use of a DNA vaccine to deliver the spike protein and induce an immune response would have demonstrated that (1) a nucleic acid (including DNA and RNA) could be safely administered to patients, (2) the cellular machinery is capable of translating the protein, and (3) the body can recognize the protein and generate an immune response. Those lessons would have been applicable across DNA and mRNA vaccines.

348. And to the extent there are differences between DNA and mRNA vaccines, those differences would have only supported a POSA's expectation of success. For example, as Dr. Fuller explains "[w]hen a DNA vaccine is administered, it must enter the host cell's nucleus and be transcribed into mRNA using the host cell's transcriptional machinery."⁶⁰¹ In other words, the DNA vaccine introduces more complexity. To that end, a POSA would be encouraged by the

⁶⁰¹ Ex. 2199 ¶ 831.

results of a DNA vaccine, and understood that mRNA, which has fewer intervening steps, could similarly succeed.⁶⁰²

349. Still, Dr. Fuller alleges that because of differences in the results of immune responses across DNA and mRNA vaccines, a POSA would not have looked to Yang's teaching regarding the use of the spike protein.⁶⁰³ Dr. Fuller points to a study by Brito and Geall et al. demonstrating that DNA vaccines and mRNA vaccines resulted in different in immune responses.⁶⁰⁴

350. The results in Brito, however, would have only confirmed that a POSA would have looked to studies on DNA vaccines to find a suitable antigen for a mRNA vaccine. Brito et al. sought to establish a proof of concept for a cationic nanoemulsion delivery (CNE) system for self-amplifying mRNA by expressing the

⁶⁰² I also disagree with Dr. Fuller's statement that I "contradict[ed]" myself by also pointing out that DNA vaccines cannot integrate into the host cell. Ex. 2199 ¶ 832. That I pointed out a difference between a DNA vaccine and mRNA vaccine does not negate my additional statement that the technologies share several similarities.

⁶⁰³ Ex. 2199 ¶ 830.

⁶⁰⁴ Ex. 2199 ¶ 833 (citing Ex. 2005).

RSV-F protein.⁶⁰⁵ In doing so, Brito et al. relied on CNE-formulated plasmid DNA encoding the same RSV-F protein as a benchmark.⁶⁰⁶ The use of plasmid DNA as a benchmark reflects the field's understanding that DNA expressing the RSV-F protein would be expected to generate an immune response, and could be used as a comparator against the self-amplifying mRNA vaccine.⁶⁰⁷

351. The results in Brito further confirm that a POSA would have looked to the literature on DNA vaccines to identify an antigen for a mRNA vaccine against a betacoronavirus. For example, Brito explains how “[t]he lowest dose tested (0.015 µg of SAM RNA) elicited a geometric mean titer (GMT) of 4.9×10^3 , comparable to a 1,000-fold higher dose (15 µg) of unformulated SAM RNA (GMT 7.4×10^3) or pDNA (GMT 3.5×10^3).”⁶⁰⁸ Although the non-amplifying mRNA did not elicit a measurable IgG titer, Brito explained that it was “perhaps due to the low dose being tested here” and “[p]revious reports with mRNA have shown that much higher doses (80 µg) of mRNA have been used to generate immune responses in mice.”⁶⁰⁹ The

⁶⁰⁵ Ex. 2005 at 2118.

⁶⁰⁶ Ex. 2005 at 2119.

⁶⁰⁷ Ex. 2005 at 2118-19.

⁶⁰⁸ Ex. 2005 at 2119.

⁶⁰⁹ Ex. 2005 at 2123-24.

results in Brito would have suggested to a POSA that, if an antigen elicited an immune response through a DNA vaccine, that same antigen would likely induce an immune response when expressed through a mRNA vaccine as well, albeit with different dosing. Thus, the results in Yang would have motivated a POSA to use the S-protein as an immunogen in the mRNA vaccines disclosed in Schrum. As noted in Section V.A.2.d.2, Patent Owner relied on data from DNA vaccines in its document discussing protocols for SARS-CoV-2 mRNA clinical studies.⁶¹⁰

352. **Third**, Dr. Fuller disputes that as of October 2015, mRNA vaccines were known to have significant advantages over DNA vaccines.⁶¹¹ For the reasons explained in Section V.A.2.a.3, I disagree. In particular, Dr. Fuller points to Martin 2008's results, which she describes as "promising."⁶¹² However, Martin 2008's results do not detract from the advantages of mRNA vaccines, described in Section V.A.2.a.3.

353. **Fourth**, Dr. Fuller further repeats her argument that a POSA would not have turned to Yang because it focuses on DNA vaccines rather than mRNA

⁶¹⁰ [REDACTED]

⁶¹¹ Ex. 2199 ¶¶ 834-838.

⁶¹² Ex. 2199 ¶ 835.

vaccines, and that Yang provides data on spike proteins with certain domains removed rather than “full length” spike proteins.⁶¹³ For the reasons explained in claim 1, Sections VI.A, I disagree with Dr. Fuller’s assertions.

354. *Fifth*, Dr. Fuller asserts that there is no reason a “POSA would have taken Yang’s truncated S protein . . . and altered its design to turn it into a full-length S protein or S protein subunit to arrive at the claimed invention.”⁶¹⁴ For the reasons explained in Section VI.A.1, Yang discloses a full-length spike protein. Moreover, as explained in Section V.A.2.b, a POSA would have been aware of numerous studies prior to October 2015 demonstrating that the spike protein, including full-length one, would have been an effective immunogen. In view of these studies, a POSA would have been motivated to use the S-protein disclosed in Yang as the immunogen encoded in Schrum’s mRNA vaccine encoding for an immunogen.

* * *

355. Schrum and Yang disclose each element of claim 1. Those references, the remainder of the prior art, and Patent Owner’s own statements demonstrate that a POSA would have been motivated to combine their teachings, and reasonably expected to arrive at the method of claim 1 successfully.

⁶¹³ Ex. 2199 ¶¶ 839-845.

⁶¹⁴ Ex. 2199 ¶¶ 846-848.

B. Claim 2: “The method of claim 1, wherein the open reading frame encodes a BetaCoV S protein.”

356. As I explain in my opening declaration,⁶¹⁵ and for the reasons explained in claim 1, Section VI.A, Schrum in view of Yang discloses this limitation. I disagree with Dr. Fuller’s opinions to the contrary.

357. *First*, Dr. Fuller incorporates the arguments made with respect to claim 1.⁶¹⁶ For the reasons explained in claim 1, Section VI.A, I disagree.

358. *Second*, Dr. Fuller asserts that Schrum in view of Yang does not disclose an “open reading frame encodes a BetaCoV S protein.”⁶¹⁷ For the reasons explained in claim 1, Section VI.A, I disagree.

359. *Third*, Dr. Fuller asserts that I have not opined that a POSA would have been motivated to combine Schrum with Yang with a reasonable expectation of success to arrive at claim 2.⁶¹⁸ I disagree. As I explained in my opening declaration⁶¹⁹ and for the reasons explained with respect to claim 1, Section VI.A, a

⁶¹⁵ Ex. 1002 § X.2.

⁶¹⁶ Ex. 2199 ¶ 851.

⁶¹⁷ Ex. 2199 ¶¶ 852-853.

⁶¹⁸ Ex. 2199 ¶¶ 854-855.

⁶¹⁹ Ex. 1002 § X.2.

POSA would have been motivated to combine Schrum with Yang, with a reasonable expectation of success to arrive at claim 2.

C. Claim 3: “The method of claim 2, wherein the immune response is a neutralizing antibody response specific to the BetaCoV S protein.”

360. As I explained in my opening declaration⁶²⁰ and for the reasons explained in claims 1 and 2, Sections VI.A and VI.B, Schrum in view of Yang discloses this limitation.

361. *First*, Dr. Fuller asserts that I do not address how claims 1 and 2, from which claim 3 depends, are met.⁶²¹ For the reasons explained in my opening declaration,⁶²² and Sections VI.A and VI.B, I disagree.

362. *Second*, Dr. Fuller asserts that Schrum in combination with Yang does not teach a “neutralizing antibody response specific to the BetaCoV S protein.”⁶²³ I disagree. As explained in my opening declaration, Yang elaborates that “a DNA vaccine encoding the **spike (S) glycoprotein** of the SARS-CoV induces T cell and

⁶²⁰ Ex. 1002 § X.3.

⁶²¹ Ex. 2199 ¶¶ 859-860.

⁶²² Ex. 1002 §§ X.1-3.

⁶²³ Ex. 2199 ¶¶ 861-863.

neutralizing antibody responses, as well as protective immunity.”⁶²⁴ Yang further provides a diagram of a full length spike protein, which would have confirmed to the POSA that the “S” protein that “induced a substantial immune response” was the full length S protein.⁶²⁵ Yang also discloses that “[i]njection of S, SΔTM and S ΔCD expression vectors induced a substantial immune response.”⁶²⁶ Moreover, Yang reports that DNA encoding the truncated spike proteins “induce[d] T cell and *neutralizing antibody* responses, as well as protective immunity,” further providing evidence and data that an immunogen such as a spike protein could elicit a neutralizing antibody response.⁶²⁷

363. **Third**, Dr. Fuller asserts that I do not explain how a POSA would have been motivated to combine Schrum with Yang with a reasonable expectation of success to arrive at claim 3.⁶²⁸ As explained in my opening declaration with respect to claims 1-2, Schrum in combination with Yang discloses administering mRNA

⁶²⁴ Ex. 1002 § X.1 (quoting Ex. 1011 at 561-562).

⁶²⁵ Ex. 1011 at Fig. 1.

⁶²⁶ Ex. 1011 at 561.

⁶²⁷ Ex. 1002 § X.3 (Ex. 1011 at 561) (emphases added).

⁶²⁸ Ex. 2199 ¶¶ 864-865.

encoding a spike protein and encapsulated in a lipid nanoparticle to induce an immune response.⁶²⁹ Moreover, as explained in my opening declaration with respect to claim 3, Yang in turn, discloses that the spike protein can elicit an immune response and more specifically, that the truncated spike proteins could elicit neutralizing antibody response, stating that a vaccine encoding the “spike (S) glycoprotein of the SARS-CoV induce[d] T cell and *neutralizing antibody* responses, as well as protective immunity.”⁶³⁰ Thus, given that Schrum’s disclosure of mRNA encoding an immunogen, and Yang’s disclosure that an immunogen (including the S protein) can elicit a neutralizing antibody response, a POSA would have been motivated to use the mRNA encoding a S protein to elicit a neutralizing antibody response specific to the S protein, with a reasonable expectation of success.

D. Claim 6: “The method of claim 1, wherein the mRNA formulated in a lipid nanoparticle is administered intramuscularly.”

364. For the reasons explained in Ground 2, claim 6, Section V.D, Schrum discloses this limitation.

E. Claim 7: “The method of claim 1, wherein the mRNA further comprises a 5' untranslated region and a 3' untranslated region.”

⁶²⁹ Ex. 1002 §§ X.1-2.

⁶³⁰ Ex. 1002 §§ X.3. (citing Ex. 1011 at 561-562) (emphases added).

365. For the reasons explained in Ground 2, claim 7, Section V.E, Schrum discloses this limitation.

F. Claim 8: “The method of claim 1, wherein the mRNA further comprises a poly(A) tail.”

366. For the reasons explained in Ground 2, claim 8, Section V.F, Schrum discloses this limitation.

G. Claim 9: “The method of claim 1, wherein the mRNA further comprises a 5' cap analog.”

367. For the reasons explained in Ground 2, claim 9, Section V.G, Schrum discloses this limitation.

H. Claim 11: “The method of claim 1, wherein the mRNA comprises a chemical modification.”

368. For the reasons explained in Ground 2, claim 11, Section V.H, Schrum discloses this limitation.

369. Dr. Fuller also asserts that Yang’s DNA vaccine cannot result in chemically modified mRNA.⁶³¹ Irrespective of Yang’s disclosure, however, a POSA would have understood that Schrum discloses that non-amplifying mRNA achieved high levels of protein expression with modified nucleotides, as explained in my opening declaration.⁶³²

⁶³¹ Ex. 2199 ¶¶ 907-912.

⁶³² Ex. 1002 § X.8.

I. Claim 12: “The method of claim 11, wherein the chemical modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification.”

370. For the reasons explained in Ground 2, claim 12, Section V.I, Schrum discloses this limitation.

J. Claim 13: “The method of claim 11, wherein at least 80% of the uracil in the open reading frame of the mRNA has a chemical modification.”

371. For the reasons explained in Ground 2, claim 13, Section V.J, Schrum discloses this limitation.

K. Claim 17: “A method comprising administering to a subject an mRNA comprising a 5' cap analog, a 5' untranslated region, an open reading frame encoding a BetaCoV S protein or S protein subunit, a 3' untranslated region, and a poly(A) tail formulated in a lipid nanoparticle in an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit, wherein the lipid nanoparticle comprises 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid.”

372. Schrum in view of Yang discloses each limitation of claim 17, and a POSA would have had good reason to combine (1) Schrum’s disclosure of an mRNA with a 5’ and 3’ UTR and a poly(A) tail encoding an immunogen that induces an immune response and encapsulated in a LNP (which has lipid components within the claimed ranges) with (2) Yang’s teaching that the immunogen of a DNA vaccine may be a betacoronavirus S protein that induces an immune response, all with a reasonable expectation of success. Dr. Fuller has not shown otherwise, and her

opinions in response raise a host of inaccurate, and often irrelevant, points that I respond to further below.

1. Schrum and Yang Disclose Every Element of Claim 17

373. I have previously explained that Schrum in view of Yang teaches every limitation of claim 17.⁶³³

374. For claim 17, Dr. Fuller recycles many of her arguments with respect to claim 1, including that Yang focuses on DNA, that Yang does not disclose a spike protein, that there was skepticism regarding mRNA vaccines, and that concerns regarding ADE would have discouraged use of a spike protein.⁶³⁴ For the reasons explained in claim 1, Section VI.A, I disagree.

2. A POSA Would Have Been Motivated to Combine the Teachings of Schrum and Yang With a Reasonable Expectation of Success

375. In my opening declaration, I explained that a POSA would have been motivated to combine (1) Schrum's disclosure of the use of an mRNA vaccine (with a 3' UTR and a poly(A)) tail encoding an immunogen that induces an immune response, encapsulated in a lipid nanoparticle of the claimed composition and ranges with (2) Yang's disclosure of a DNA vaccine encoding a betacoronavirus spike

⁶³³ Ex. 1002 § X.11.

⁶³⁴ Ex. 2199 ¶¶ 930-932.

protein that induces an immune response, and would reasonably have expected to do so successfully in view of well-known methods of synthesizing mRNA, already known in the art.⁶³⁵

376. In particular, with respect to the lipid nanoparticles of the claimed composition and ranges, as explained building on its disclosures of mRNA vaccines encapsulated by lipid nanoparticles, Schrum further provides concrete examples of lipid nanoparticles comprising 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid.”⁶³⁶ A POSA would have understood that the mRNA vaccines disclosed in Schrum could be delivered using the lipid nanoparticles disclosed in the examples.

377. And with respect to the 5' and 3' UTR and poly(A) tail, a POSA would have been aware that the mRNA disclosed in Schrum incorporates such basic mRNA components and would have been motivated to use the mRNA with these basic components to express the S-protein with a reasonable expectation of success.⁶³⁷

⁶³⁵ Ex. 1002 § X.11.

⁶³⁶ Ex. 1002 § X.11.

⁶³⁷ Ex. 1002 § X.11.

378. Dr. Fuller does not meaningfully dispute my analysis in her declaration.⁶³⁸ Instead, she refers back to her eight purported reasons as to why “a POSA would not have had a reasonable expectation of success of October 2015.”⁶³⁹ As explained in Section V.A.2 many of Dr. Fuller’s arguments are irrelevant. Nevertheless, for the reasons explained in Section V.A.2, I disagree with Dr. Fuller’s arguments, none of which rebuts my explanation that a POSA would have been motivated to combine the teachings of Schrum and Yang, and would reasonably have expected to do so successfully.

* * *

379. Schrum and Yang disclose each element of claim 17. Those references, the remainder of the prior art, and Patent Owner’s own statements demonstrate that a POSA would have been motivated to combine their teachings, and reasonably expected to do so successfully.

L. Claim 18: “The method of claim 17, wherein the open reading frame encodes a BetaCoV S protein.”

⁶³⁸ Ex. 2199 ¶¶ 936-939.

⁶³⁹ Ex. 2199 ¶¶ 936-939.

380. As I explain in my opening declaration,⁶⁴⁰ and for the reasons explained in claim 17, Section VI.K, Schrum in view of Yang discloses this limitation. I disagree with Dr. Fuller's opinions to the contrary.

381. **First**, Dr. Fuller incorporates the arguments made with respect to claim 17.⁶⁴¹ For the reasons explained in claim 17, Section VI.K, I disagree.

382. **Second**, Dr. Fuller asserts that Schrum in view of Yang does not disclose an "open reading frame encodes a BetaCoV S protein."⁶⁴² For the reasons explained in claim 17, Section VI.K, I disagree.

383. **Third**, Dr. Fuller asserts that I have not opined that a POSA would have been motivated to combine Schrum with Yang with a reasonable expectation of success to arrive at claim 18.⁶⁴³ As I explained in my opening declaration⁶⁴⁴ and for the reasons explained with respect to claim 17, a POSA would have been motivated to combine Schrum with Yang, with a reasonable expectation of success to arrive at claim 18.

⁶⁴⁰ Ex. 1002 § X.12.

⁶⁴¹ Ex. 2199 ¶¶ 942-943.

⁶⁴² Ex. 2199 ¶ 944.

⁶⁴³ Ex. 2199 ¶¶ 945-947.

⁶⁴⁴ Ex. 1002 § X.12.

M. Claim 20: “The method of claim 18, wherein at least 80% of the uracil in the open reading frame of the mRNA has a 1-methylpseudouridine modification.”

384. For the reasons explained in Ground 2, claim 20, Section V.M, Schrum discloses this limitation.

VII. GROUND 4: THE COMBINATION OF SCHRUM IN VIEW OF ALTMAYER DISCLOSES ALL OF THE LIMITATIONS OF CLAIMS 1-3, 6-9, 11-13, 17-18, AND 20

385. In Section XI of my opening declaration, I explained that each of the limitations of claims 1-3, 6-9, 11-13, 17-18, and 20 had already been disclosed by Schrum in view of Altmeyer by October 2015, which I understand is referred to as Ground 4 in this proceeding. In Section XI of my previous declaration, I also explained why, as of October 2015, a POSA would have been motivated to combine the teachings of the prior art to arrive at the claimed combination of known elements, as well as why a POSA would have reasonably expected to do so successfully. Section XIII of Dr. Fuller’s declaration, in which she discusses Ground 4, recycles many of the opinions discussed above with respect to Grounds 1, 2, and 3. I therefore disagree with Dr. Fuller, and my opinions remain unchanged.

- A. Claim 1: “A method comprising administering to a subject a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit formulated in a lipid nanoparticle in an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit, wherein the lipid nanoparticle comprises 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid.”**

386. Schrum in view of Altmeyer discloses each limitation of claim 1, and a POSA would have had good reason to combine Schrum’s disclosure of a lipid nanoparticle of the claimed composition and ranges encapsulating an mRNA encoding an immunogen that induces an immune response with Altmeyer’s teaching that the immunogen of a vaccine may be a betacoronavirus S protein, all with a reasonable expectation of success. Dr. Fuller has not shown otherwise, and her opinions in response raise a host of inaccurate, and often irrelevant, points that I respond to further below.

1. Schrum and Altmeyer Disclose Every Element of Claim 1

387. I have previously explained that Schrum in view of Altmeyer teach every limitation of claim 1.⁶⁴⁵

⁶⁴⁵ Ex. 1002 § XI.1.

388. **First**, in her declaration, Dr. Fuller asserts that Altmeyer does not disclose mRNA.⁶⁴⁶ This is of no import to the ultimate analysis, as there is no question that Schrum discloses non-amplifying mRNA vaccines encoding for an immunogen that induces an immune response, as well as the encapsulation of such mRNA in lipid nanoparticles of the claimed composition and ranges, as explained in Section IV.B, and would have been motivated to use the modified mRNA disclosed in Schrum to express the S-protein, which Altmeyer identifies as the antigen for betacoronavirus

389. **Second**, Dr. Fuller also asserts that Altmeyer does not disclose a spike protein.⁶⁴⁷ In particular, Dr. Fuller states that Altmeyer fails to specify whether the spike protein is a “full-length spike protein.”⁶⁴⁸ I disagree with Dr. Fuller’s assertion. Altmeyer “provides a method of RNA and/or DNA vaccination” against SARS-CoV that “includes administering any combination of the nucleic acids encoding *[s]pike polypeptides*.”⁶⁴⁹ Example 5 reports that “[m]ice were immunized

⁶⁴⁶ Ex. 2199 ¶¶ 958-974; Dr. Fuller does not dispute that Altmeyer discloses RNA.

⁶⁴⁷ Ex. 2199 ¶¶ 975-977.

⁶⁴⁸ Ex. 2199 ¶ 976.

⁶⁴⁹ Ex. 1012 ¶ 97 (emphasis added).

intramuscularly with *SFV Spike RNA*, followed by intraperitoneal (IP) injection of *Spike protein* at day 14 and at day 35.”⁶⁵⁰ For the reasons explained in Section IV.B.1, a POSA would have understood a reference to a spike protein to mean a full-length spike protein. And notably, Example 4 explains that “[t]he Spike protein was expressed as a *full-length protein*, including the C-terminal and transmembrane domains as well as a C-terminal Flag tag, in the SFV vector system . . . The Spike protein is correctly folded, *i.e.* in its native conformation.”⁶⁵¹

390. **Third**, Dr. Fuller asserts that Altmeyer does not disclose a structural protein forming a spike.⁶⁵² Notably, Example 4 explains that “[t]he Spike protein was expressed as a full-length protein, including the C-terminal and transmembrane domains as well as a C-terminal Flag tag, in the SFV vector system . . . The Spike protein is correctly folded, *i.e.* in its native conformation.”⁶⁵³ Moreover, for the reasons explained in Section IV.B.1, a POSA would have understood a scientific

⁶⁵⁰ Ex. 1012 ¶ 116 (emphases added).

⁶⁵¹ Ex. 1012 ¶ 111.

⁶⁵² Ex. 2199 ¶¶ 978-981.

⁶⁵³ Ex. 1012 ¶ 111.

publication's reference to a spike protein to mean a structural protein forming a spike.

391. Dr. Fuller's statements regarding the purported lack of working examples in Altmeyer are simply incorrect.⁶⁵⁴ As explained in my opening declaration, Altmeyer reports in Example 5 explains that "[m]ice were immunized intramuscularly with SFV Spike RNA, followed by intraperitoneal (IP) injection of Spike protein at day 14 and at day 35" and that "[s]erum taken at day 34, day 42, and day 55 from immunized mice showed the presence of recombinant Spike-specific antibodies by Western Blot (Figure 6), FACS (Figure 7), and SARS CoV-specific antibodies by immunofluorescence on SARS CoV infected FRHK4 cells (Figure 8.)."⁶⁵⁵ Still, Dr. Fuller asserts that it is "not possible to tease apart the individual immune results" that are attributable to the "SFV Spike RNA."⁶⁵⁶ But regardless of whether the immune response was caused by the SFV spike RNA or by the protein booster, a POSA would have understood that the spike protein induced

⁶⁵⁴ Ex. 2199 ¶¶ 979-980.

⁶⁵⁵ Ex. 1002 § XI.1 (quoting Ex. 1012 ¶ 116).

⁶⁵⁶ Ex. 2199 ¶ 980.

“high titer anti-SARS antibodies in mice,” and would have been motivated to use the spike protein as the immunogen in the mRNA vaccine disclosed by Schrum.

392. **Fourth**, Dr. Fuller asserts that concerns about disease enhancement undermine Altmeyer’s disclosure of a spike protein.⁶⁵⁷ For the reasons explained in Section V.A.2.b.3, I disagree that any concerns about ADE would have discouraged a POSA from using a spike protein.

393. **Fifth**, Dr. Fuller argues that Schrum in view of Altmeyer does not disclose a S protein that can elicit a specific immune response, criticizing Schrum for “discussing an immune response generally” and both Schrum and Altmeyer for not showing “working examples.”⁶⁵⁸ As an initial matter, as explained above, this argument seems to flow from Dr. Fuller’s faulty premise that the prior art cannot disclose each limitation of a patent claim without such working examples. Regardless, I disagree, given Altmeyer’s numerous working examples.⁶⁵⁹ And explained above, regardless of whether the immune response was caused by the SFV spike RNA or by the protein booster, a POSA would have understood that the spike protein resulted in a high titer anti-SARS antibodies in mice, and would have been

⁶⁵⁷ Ex. 2199 ¶¶ 982-986.

⁶⁵⁸ Ex. 2199 ¶¶ 987-1006.

⁶⁵⁹ Ex. 1002 § XI.1.

motivated to use the spike protein as an immunogen in the mRNA vaccine disclosed by Schrum.

2. A POSA would have been motivated to combine Schrum and Altmeyer with a reasonable expectation of success

394. In my opening declaration, I explained that a POSA would have been motivated to combine Schrum's disclosure of the use of an mRNA vaccine encoding an immunogen that induces an immune response and encapsulated in lipid nanoparticle of the claimed composition and ranges, with Altmeyer's disclosure of spike protein, and would reasonably have expected to do so successfully in view of well-known methods of synthesizing mRNA, already known in the art.⁶⁶⁰ I disagree with Dr. Fuller's opinions to the contrary.

395. *First*, as explained in Section V.A.2, Dr. Fuller does not meaningfully dispute my analysis in her declaration.⁶⁶¹ Instead, she refers back to her eight purported reasons as to why "a POSA would not have had a reasonable expectation of success of October 2015."⁶⁶² As explained in Section V.A.2, many of Dr. Fuller's arguments are irrelevant. Nevertheless, for the reasons explained in Section V.A.2, I disagree with Dr. Fuller's arguments, none of which rebuts my explanation that a

⁶⁶⁰ Ex. 1002 § XI.1.

⁶⁶¹ Ex. 2199 ¶¶ 1007-1019.

⁶⁶² Ex. 2199 ¶¶ 1009.

POSA would be motivated to combine the teachings of Schrum and Altmeyer, and would reasonably expect to do so successfully.

396. *Second*, Dr. Fuller further suggests that a POSA would not have looked to publications regarding viral vector vaccines in order to develop a mRNA vaccine against a betacoronavirus.⁶⁶³ I disagree.

397. In my opinion, the successful generation of antibodies following a viral vector vaccine encoding a spike protein would have encouraged a POSA regarding the possibility of using a spike protein for an mRNA vaccine. Even Dr. Fuller agrees, in both viral vectors (such as SFV) and mRNA vaccines, RNA encoding an immunogen is administered to patients.⁶⁶⁴ The RNA is either packaged in a carrier such as a lipid nanoparticle (for a mRNA vaccine) or a viral particle (for a viral vector vaccine). In both cases, the immunogen is ultimately translated by the cell's host cell machinery. Thus, success with a viral vaccine would prove that (1) mRNA could be safely administered to patients, (2) cellular machinery is capable of translating the protein, and that (3) the body can recognize the protein and generate

⁶⁶³ Ex. 2199 ¶¶ 1010-1012; to the extent that Dr. Fuller contends Altmeyer relates to saRNA, I disagree that a POSA would not have looked at literature regard saRNA to inform regarding mRNA, as explained in Section V.A.2.c.2.

⁶⁶⁴ Ex. 2199 ¶¶ 60-64.

an immune response. Those lessons would have been applicable across viral vector and mRNA vaccines.

398. To the extent there are differences between viral vector and mRNA vaccines, they would have only supported a POSA's reasonable expectation of success. For example, Dr. Fuller notes how the RNA in viral vectors is larger than non-amplifying mRNA delivered through an LNP as the viral vectors encode genes for replicase proteins, the sub-genomic promoter, and genes for the antigen; whereas, non-amplifying mRNA vaccines encode only the antigen.⁶⁶⁵ However, in my opinion, given this difference in size, a viral vector vaccine that successfully translated the proteins would have encouraged a POSA regarding the successful use for mRNA. As Dr. Fuller states repeatedly, "it was known that large proteins are difficult to express due to protein synthesis errors."⁶⁶⁶ Thus, a POSA would be encouraged by data showing that a (larger) viral vector protein, as in Altmeyer, could be translated successfully and be immunogenic, and to pursue a mRNA vaccine, that encodes only for the (smaller) antigen, with a reasonable expectation of success.

⁶⁶⁵ Ex. 2199 ¶ 1093.

⁶⁶⁶ Ex. 2199 ¶ 252.

399. Dr. Fuller also notes that, for viral vectors, “the protein of interest can **only** be generated after additional, intermediate steps take place in the host cell—not simply upon entry into the host cell like with mRNA.”⁶⁶⁷ In other words, Dr. Fuller explains the translation process for viral vector vaccine includes more steps, potentially introducing additional complexity. To that end, a POSA would be encouraged by the results of viral vector expression, and would have understood that mRNA, which has fewer intervening steps, could similarly express the S-protein. Moreover, regardless of the number of intermediate steps, the viral vector ultimately expresses the S-protein, and the results in Altmeyer would have encouraged a POSA to use the S-protein as an antigen for betacoronavirus.

400. I further disagree with Dr. Fuller’s assertion that a POSA would not have been motivated to use the S-protein because Altmeyer purportedly describes data only for the protein vaccine booster. As explained in Section VII.A.1, regardless of whether the immune response was caused by the SFV spike RNA or the protein booster, a POSA would have understood that it was ultimately the spike protein that caused the immune response.

⁶⁶⁷ Ex. 2199 ¶ 973.

401. *Third*, Dr. Fuller asserts that other data on the successful use of the spike protein like that disclosed in Yang is effectively irrelevant, because it focuses on DNA vaccines rather than mRNA vaccines.⁶⁶⁸ For the reasons explained in Section VI.A.2, I disagree with Dr. Fuller’s argument that a POSA could not have relied on studies from a DNA vaccine.

B. Claim 2: “The method of claim 1, wherein the open reading frame encodes a BetaCoV S protein.”

402. As I explain in my opening declaration,⁶⁶⁹ and for the reasons explained in claim 1, Section VII.A, Schrum in view of Altmeyer discloses this limitation. I disagree with Dr. Fuller’s opinions to the contrary.

403. *First*, Dr. Fuller incorporates the arguments made with respect to claim 1.⁶⁷⁰ For the reasons explained in claim 1, Section VII.A, I disagree.

404. *Second*, Dr. Fuller asserts that Schrum in view of Altmeyer does not disclose an “open reading frame encodes a BetaCoV S protein,” incorporating her opinions for claim 1.”⁶⁷¹ For the reasons explained in claim 1, Section VII.A, I

⁶⁶⁸ Ex. 2199 ¶¶ 1013-1018.

⁶⁶⁹ Ex. 1002 § XI.2.

⁶⁷⁰ Ex. 2199 ¶ 1022.

⁶⁷¹ Ex. 2199 ¶¶ 1023-1024.

disagree.

405. *Third*, Dr. Fuller asserts that I have not opined that a POSA would have been motivated to combine Schrum with Altmeyer with a reasonable expectation of success to arrive at claim 2.⁶⁷² I disagree. As I explained in my opening declaration⁶⁷³ and for the reasons explained with respect to claim 1, a POSA would have been motivated to combine Schrum with Altmeyer to arrive at the method of claim 2 with a reasonable expectation of success.

C. Claim 3: “The method of claim 2, wherein the immune response is a neutralizing antibody response specific to the BetaCoV S protein.”

406. As I explained in my opening declaration⁶⁷⁴ and for the reasons explained in claims 1 and 2, Sections VII.A and VII.B, Schrum in view of Altmeyer discloses this limitation.

407. *First*, Dr. Fuller asserts that I do not address how claims 1 and 2, from which claim 3 depends, are met.⁶⁷⁵ For the reasons explained in my opening

⁶⁷² Ex. 2199 ¶¶ 1025-1026.

⁶⁷³ Ex. 1002 § XI.2.

⁶⁷⁴ Ex. 1002 § XI.3.

⁶⁷⁵ Ex. 2199 ¶¶ 1030-1031.

declaration,⁶⁷⁶ and Sections VII.A and VII.B, I disagree.

408. **Second**, Dr. Fuller asserts that Schrum in combination with Altmeyer does not teach a “neutralizing antibody response specific to the BetaCoV S protein.”⁶⁷⁷ I disagree. Dr. Fuller concedes that Example 8 of Altmeyer measures “neutralization titer,” but alleges that such data is irrelevant given that it resulted from a protein vaccine.⁶⁷⁸ But, regardless of whether in Altmeyer, the immune response was caused by a protein vaccine or a nucleic acid vaccine, a POSA would have understood that the spike protein resulted in neutralizing antibodies, and would have been motivated to use the spike protein as an immunogen in the mRNA vaccine disclosed by Schrum.

409. **Third**, Dr. Fuller asserts that I do not explain how a POSA would have been motivated to combine Schrum with Altmeyer with a reasonable expectation of success to arrive at claim 3.⁶⁷⁹ As explained in my opening declaration,⁶⁸⁰ a POSA

⁶⁷⁶ Ex. 1002 §§ XI.1-3.

⁶⁷⁷ Ex. 2199 ¶¶ 1032-1045.

⁶⁷⁸ Ex. 2199 ¶ 1044 (citing Ex. 1012 ¶ 128, Fig. 17).

⁶⁷⁹ Ex. 2199 ¶¶ 1046-1047.

⁶⁸⁰ Ex. 1002 § XI.3.

would have been motivated to combine Schrum with Altmeyer with a reasonable expectation of success to arrive at claim 3. Specifically, as explained in my opening declaration with respect to claims 1-2, Schrum in combination with Altmeyer discloses administering mRNA encoding a spike protein and encapsulated in a lipid nanoparticle to induce an immune response.⁶⁸¹ And as explained for claim 3, Altmeyer in turn, discloses that analyzed sera from mice immunized with a Spike protein raised both reactive antibody responses and neutralizing activity against SARS CoV infection.⁶⁸²

410. Thus, given that Schrum discloses of mRNA encoding an immunogen, and Altmeyer disclosure that an immunogen (including the S protein) can elicit a neutralizing antibody response, a POSA would have been motivated to use the mRNA encoding a S protein to elicit a neutralizing antibody response specific to the S protein, with a reasonable expectation of success.

D. Claim 6: “The method of claim 1, wherein the mRNA formulated in a lipid nanoparticle is administered intramuscularly.”

411. For the reasons explained in Ground 2, claim 6, Section V.D, Schrum discloses this limitation.

⁶⁸¹ Ex. 1002 § XI.1-2.

⁶⁸² Ex. 1002 §§ XI.3 (quoting Ex. 1012 ¶ 56; Figure 17).

E. Claim 7: “The method of claim 1, wherein the mRNA further comprises a 5' untranslated region and a 3' untranslated region.”

412. For the reasons explained in Ground 2, claim 7, Section V.E, Schrum discloses this limitation.

F. Claim 8: “The method of claim 1, wherein the mRNA further comprises a poly(A) tail.”

413. For the reasons explained in Ground 2, claim 8, Section V.F, Schrum discloses this limitation.

G. Claim 9: “The method of claim 1, wherein the mRNA further comprises a 5' cap analog.”

414. For the reasons explained in Ground 2, claim 9, Section V.G, Schrum discloses this limitation.

H. Claim 11: “The method of claim 1, wherein the mRNA comprises a chemical modification.”

415. For the reasons explained in Ground 2, claim 11, Section V.H, Schrum discloses this limitation.

416. Dr. Fuller also asserts that Altmeyer does not disclose chemically modified mRNA.⁶⁸³ Irrespective of Altmeyer’s disclosure, however, a POSA would have understood that Schrum discloses this limitation, and in particular that non-

⁶⁸³ Ex. 2199 ¶¶ 1089-1097.

amplifying mRNA achieved high levels of protein expression with modified nucleotides, as explained in my opening declaration.⁶⁸⁴

I. Claim 12: “The method of claim 11, wherein the chemical modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification.”

417. For the reasons explained in Ground 2, claim 12, Section V.I, Schrum discloses this limitation.

J. Claim 13: “The method of claim 11, wherein at least 80% of the uracil in the open reading frame of the mRNA has a chemical modification.”

418. For the reasons explained in Ground 2, claim 13, Section V.J, Schrum discloses this limitation.

K. Claim 17: “A method comprising administering to a subject an mRNA comprising a 5' cap analog, a 5' untranslated region, an open reading frame encoding a BetaCoV S protein or S protein subunit, a 3' untranslated region, and a poly(A) tail formulated in a lipid nanoparticle in an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit, wherein the lipid nanoparticle comprises 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid.”

419. Schrum in view of Altmeyer discloses each limitation of claim 17, and a POSA would have had good reason to combine (1) Schrum’s disclosure of an mRNA with a 5’ and 3’ UTR and a poly(A) tail encoding an immunogen that induces

⁶⁸⁴ Ex. 1002 § XI.8.

an immune response and encapsulated in an LNP of the claimed composition and ranges with (2) Altmeyer's teaching that the immunogen may be a betacoronavirus S protein that induces an immune response, all with a reasonable expectation of success. Dr. Fuller has not shown otherwise, and her opinions in response raise a host of inaccurate, and often irrelevant, points that I respond to further below.

1. Schrum and Altmeyer Disclose Every Element of Claim 17

420. I have previously explained that Schrum in view of Altmeyer teaches every limitation of claim 17.⁶⁸⁵

421. For claim 17, Dr. Fuller recycles many of her arguments with respect to claim 1, including that Altmeyer does not disclose mRNA, that Altmeyer does not disclose a spike protein, that there was skepticism regarding mRNA vaccines, and that concerns regarding ADE would have discouraged use of a spike protein.⁶⁸⁶ For the reasons explained in Section VII.A, I disagree.

2. A POSA would have been motivated to combine Schrum and Altmeyer with a reasonable expectation of success

422. In my opening declaration, I explained that a POSA would have been motivated to combine (1) Schrum's disclosure of the use of an mRNA vaccine (with a 3' UTR and a poly(A)) tail encoding an immunogen that induces an immune

⁶⁸⁵ Ex. 1002 § XI.11.

⁶⁸⁶ Ex. 2199 ¶¶ 1115-1120.

response, and encapsulated in a lipid nanoparticle of the claimed composition and ranges with (2) Altmeyer's disclosure of a betacoronavirus spike protein that induces an immune response, to arrive at the method of claim 17, and would reasonably have expected to success in view of well-known methods of synthesizing mRNA, already known in the art.⁶⁸⁷

423. In particular, with respect to the lipid nanoparticles of the claimed composition and ranges, as explained building on its disclosures of mRNA vaccines encapsulated by lipid nanoparticles, Schrum further provides concrete examples of lipid nanoparticles comprising 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid.”⁶⁸⁸ A POSA would have understood that the mRNA vaccines disclosed in Schrum could be delivered using the lipid nanoparticles disclosed in the examples.

424. And with respect to the 5' and 3' UTR and poly(A) tail, a POSA would have been aware that the mRNA disclosed in Schrum incorporates such basic mRNA

⁶⁸⁷ Ex. 1002 § XI.11.

⁶⁸⁸ Ex. 1002 § XI.11.

components and would have been motivated to use the mRNA with these basic components to express the S-protein with a reasonable expectation of success.⁶⁸⁹

425. Dr. Fuller does not meaningfully dispute my analysis in her declaration.⁶⁹⁰ Instead, she refers back to her eight purported reasons as to why “a POSA would not have had a reasonable expectation of success of October 2015.”⁶⁹¹ As explained in Section V.A.2, many of Dr. Fuller’s arguments are irrelevant. Nevertheless, for the reasons explained in Section V.A.2, I disagree with Dr. Fuller’s arguments, none of which rebuts my explanation that a POSA would be motivated to combine the teachings of Schrum and Altmeyer, and would reasonably expect to do so successfully.

* * *

426. Schrum and Altmeyer disclose each element of claim 17. Those references, the remainder of the prior art, and Patent Owner’s own statements demonstrate that a POSA would have been motivated to combine their teachings, to arrive at the method of the claim, with a reasonable expectation of success.

⁶⁸⁹ Ex. 1002 § XI.11.

⁶⁹⁰ Ex. 2199 ¶¶ 1121-1124.

⁶⁹¹ Ex. 2199 ¶¶ 1121-1124.

L. Claim 18: “The method of claim 17, wherein the open reading frame encodes a BetaCoV S protein.”

427. As I explain in my opening declaration,⁶⁹² and for the reasons explained in claim 17, Section VII.K, Schrum in view of Altmeyer discloses this limitation. I disagree with Dr. Fuller’s opinions to the contrary.

428. *First*, Dr. Fuller incorporates the arguments made with respect to claim 17.⁶⁹³ For the reasons explained with respect to claim 17, I disagree.

429. *Second*, Dr. Fuller asserts that Schrum in view of Altmeyer does not disclose an “open reading frame encodes a BetaCoV S protein.”⁶⁹⁴ For the reasons explained in claim 17, Section VII.K, I disagree.

430. *Third*, Dr. Fuller asserts that I have not opined that a POSA would have been motivated to combine Schrum with Altmeyer with a reasonable expectation of success to arrive at claim 18.⁶⁹⁵ As I explained in my opening declaration⁶⁹⁶ and for the reasons explained with respect to claim 17, a POSA would have been motivated

⁶⁹² Ex. 1002 § XI.12.

⁶⁹³ Ex. 2199 ¶¶ 1127-1128.

⁶⁹⁴ Ex. 2199 ¶ 1129.

⁶⁹⁵ Ex. 2199 ¶¶ 1130-1132.

⁶⁹⁶ Ex. 1002 § XI.12.

to combine Schrum with Altmeyer to arrive at the method of claim 18, with a reasonable expectation of success.

M. Claim 20: “The method of claim 18, wherein at least 80% of the uracil in the open reading frame of the mRNA has a 1-methylpseudouridine modification.”

431. For the reasons explained in Ground 2, claim 20, Section V.M, Schrum discloses this limitation.

VIII. THERE ARE NO OBJECTIVE INDICIA THAT SUPPORT THE NON-OBVIOUSNESS OF THE '127 PATENT

432. I understand from counsel that objective indicia or secondary considerations, can provide evidence regarding the non-obviousness of a claimed invention. But in order for secondary considerations to be afforded weight in the obviousness analysis, those considerations must result from the allegedly novel features of the claimed invention. In other words, there must be a causal correlation, or “nexus,” between what is claimed in the patent and the secondary factors. I understand that to establish nexus, a Patent Owner must show that the claims are co-extensive with a relevant product, or that the evidence of secondary considerations is commensurate in scope with the claims of the patent.

433. Dr. Fuller relies on the opinion of Dr. Krause regarding objective indicia of non-obviousness for the '127 patent. Accordingly, I address Dr. Krause's arguments below.

A. Nexus

434. In my opinion, there is no nexus between Spikevax® and Comirnaty® and the claims of the '127 patent. As I explain below, Dr. Krause fails to recognize that the claims of the '127 patent are broad and unbounded. She further ignores that the challenged claims neither recite nor are limited to many features of mRNA that are otherwise important to the overall performance of an mRNA vaccine.

1. Spikevax® and Comirnaty® Do Not Embody the Challenged Claims

435. I disagree with Dr. Krause's assertion that Spikevax® and Comirnaty® embody the challenged claims. Dr. Krause alleges that "[t]he high efficacy and strong safety profile of . . . Petitioners' COVID-19 vaccines is the direct result" of Patent Owner's "vaccine design: specifically, mRNA encoding a betacoronavirus S protein or S protein subunit formulated in lipid nanoparticles."⁶⁹⁷ However, Dr. Krause ignores the numerous unclaimed aspects of the vaccines' mRNA technology, including (1) the 2-proline modification, (2) specific mRNA structural features, and (3) the lipid nanoparticle composition.

a. Two-Proline Mutation

⁶⁹⁷ Ex. 2200 ¶¶ 227-228.

436. The COVID-19 vaccine uses a modified version of the spike protein that introduces two proline residues, which is not described or claimed in the '127 patent. Notably, Dr. Krause agrees that the two-proline ("2P") mutation helps improve the immunogenicity of the mRNA vaccines.⁶⁹⁸ Still, Dr. Krause insists that the mutation "is not required."⁶⁹⁹ In doing so, he fails to account for its presence and function.⁷⁰⁰

437. The 2P mutation, or more properly, 2-proline amino acid substitution, has been used in every COVID-19 vaccine that has been approved for use in the United States, regardless of vaccine platform. The 2P mutation's impact stems from its effect on the spike protein's function. In nature, the spike protein is unstable, and has both a pre-fusion and post-fusion conformation. The 2P mutation stabilizes the spike protein in the pre-fusion conformation, maximizing the availability of antibody epitopes and improving vaccine performance.⁷⁰¹

⁶⁹⁸ Ex. 2200 ¶ 232.

⁶⁹⁹ Ex. 2200 ¶ 232.

⁷⁰⁰ Ex. 2200 ¶¶ 232-240.

⁷⁰¹ Ex. 1114 at 1-13.

438. In a 2020 paper co-authored by Patent Owner’s scientists and the Vaccine Research Center, the authors explained that “[s]tructural studies have led to the development of mutations that stabilize *Betacoronavirus* spike proteins in the prefusion state, improving their expression and increasing immunogenicity.”⁷⁰² Based on their experiments, the authors concluded that “MERS-CoV S(2P) protein was more immunogenic at lower doses than wild-type S protein. The 2P mutation has similar effects on the stability of S proteins from other betacoronaviruses, suggesting a generalizable approach for designing stabilized-prefusion *Betacoronavirus* S protein antigens for vaccination.”⁷⁰³

439. Despite the results, Dr. Krause asserts that the same study indicates the 2P mutation had no clinically relevant effect on the amount of neutralizing antibodies.⁷⁰⁴ In particular, he states that the increase in neutralizing antibodies occurred only for the 0.016 µg dose in mice, which is “quite low, and not comparable to the doses used for [Patent Owner]’s and Petitioners’ COVID-19 vaccines.”⁷⁰⁵ Dr. Krause provides no support for his observation, either from his own research

⁷⁰² Ex. 2142 at 567.

⁷⁰³ Ex. 2142 at 567.

⁷⁰⁴ Ex. 2200 ¶¶ 237-240.

⁷⁰⁵ Ex. 2200 ¶ 238.

experience or from other scientific publications. And more notably, he ignores that researchers would have undoubtedly been interested in a feature that would allow them to achieve the same degree of neutralizing antibodies at a lower dose.

440. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

706 [REDACTED].

441. In another 2023 review article, Pedenko et al. observed that “[i]t has long been recognized that the conformation of the immunogen used for vaccination is important for the induction of neutralizing antibody responses.”⁷⁰⁷ In summarizing the studies on the double-proline substitution, Pedenko noted that:

[A] number of preclinical studies showed the benefit of the S '2P' mutations over the unmodified wild-type sequence, with regard to immunogenicity and protection from infection via neutralizing antibody titers. This was first confirmed for the MERS-CoV S glycoprotein, SARS-CoV-2 S glycoprotein vaccines, AD26-based vectors expressing S variants, and the Sanofi mRNA vaccine MRT5500.

Notably, a comparison of the overall antibody reactivity against prefusion versus post-fusion conformations, and the induced neutralizing antibody activity of clinically approved vaccines carrying the S '2P' stabilization versus S vaccines without stabilization . . . confirmed the positive effect of S '2P' stabilization.⁷⁰⁸

⁷⁰⁷ Ex. 1139 at 6.

⁷⁰⁸ Ex. 1139 at 7.

442. Thus, the scientific literature widely recognizes the impact of the 2P mutation. Dr. Krause does not address any of the studies that demonstrate the 2P modified spike protein plays a role in the efficacy of the COVID-19 vaccines.

b. mRNA Structural Features

443. Other elements of the vaccines' mRNA technology that affect protein translation and immunogenicity are not claimed in the '127 patent. These include the identity of the proprietary 5' cap, the sequence of the 5' untranslated region ("UTR") or 3' UTR, the length of the poly(A) tail, and codon optimization, for both Comirnaty® and Spikevax®. Dr. Krause asserts that "these features may have a small effect on the mRNA's expression or the immunogenicity of the vaccine," but they amount to, at most, "tweaks."⁷⁰⁹ I disagree.

444. For example, as of October 2015, the literature reported that poly(A) tail length impacts translation efficiency, and further has a synergistic effect with the 5' cap.⁷¹⁰ Holtkamp et al., for example, assessed the impact of the poly(A) tail length on protein yield, using a series of IVT RNAs that differed in their poly(A) tail lengths. They found that "intracellular IVT RNA levels of d2eGFP [a green fluorescent protein] variants at different time points after transfection were highest

⁷⁰⁹ Ex. 2200 ¶ 231.

⁷¹⁰ Ex. 1129.

for poly(A)₁₂₀-tailed RNA, suggesting that RNAs with shorter poly(A) tails undergo faster degradation.”⁷¹¹ The poly(A) tail and the 3' UTR region also act synergistically on mRNA stability and translational efficiency. For example, Holtkamp et al. reported that “[t]he combination of the optimal poly(A) length, a free-ending poly(A) tail, and an optimized 3' UTR act synergistically on RNA stability and translational efficiency.”⁷¹² Specifically, they found that combining these specific modifications “significantly improved RNA stability by approximately 2 orders of magnitude” compared with “a standard IVT RNA containing a masked poly(A) tail of 67 bp and lacking regulatory UTR . . .”⁷¹³ And well before October 2015, scientists realized that codon optimization techniques could result in dramatic improvements in protein expression. For example, in 2003, researchers demonstrated that codon optimization resulted in a 6-9 fold increase in expression of the *C. elegans* GluCl ion channel genes.⁷¹⁴ Thus, to the extent that Dr. Krause suggests that codon optimization has only a minimal effect on protein expression, I disagree. Codon optimization is an important part of mRNA design

⁷¹¹ Ex. 1129 at 4013.

⁷¹² Ex. 1129 at 4014.

⁷¹³ Ex. 1129 at 4014.

⁷¹⁴ Ex. 1106 at 75.

precisely because codon optimized mRNA sequences can encode for the same sequence of amino acids, but can vary dramatically in the amount of protein expressed.

c. Lipid Nanoparticle Composition

445. I understand that Comirnaty® and Spikevax® both use specific lipid nanoparticle formulations, which are different from each other and not described in the '127 patent. The choice of particular cationic lipid nanoparticle can have a significant effect on the protein translation and immunogenicity of a mRNA vaccine.⁷¹⁵

446. Thus, as explained above, unclaimed aspects of the vaccines' mRNA technology are crucial to their success. Nevertheless, Dr. Krause alleges that these aspects cannot be attributed to the COVID-19 vaccines' success, "[d]espite any differences in their codon optimization, 5' cap, 5' UTR, 3' UTR, poly(A) tail and ionizable cationic lipid, [as] Petitioners' COVID-19 vaccines have nearly identical efficacy."⁷¹⁶ However, Dr. Krause's argument is illogical because it is based on the success of both vaccines—created years after filing the 2015 priority applications to the '127 patent to combat a virus that did not exist in 2015. That Pfizer and

⁷¹⁵ Ex. 1004 ¶ 37.

⁷¹⁶ Ex. 2200 ¶ 231.

BioNTech, as well as Patent Owner, *independently* researched and implemented specific proprietary mRNA and lipid nanoparticle compositions for their COVID-19 vaccines, that proved to be effective, does not detract from the importance of those specific, unclaimed elements.

2. Many features of SpikeVax®, and Comirnaty® were known in the prior art

447. In his report, Dr. Krause contends that there is a nexus to the challenged claims of the '127 patent for (1) the 1-methylpseudouridine modification, (2) the full-length spike protein, (3) and lipid nanoparticles.⁷¹⁷ I disagree. I understand that if any secondary considerations are attributable to features of the product or method that were already known in the prior art, that will undermine the case for nexus. As I explain below, Comirnaty® and Spikevax® are mRNA vaccines that were built on technology that was not developed by Patent Owner and certainly was not first taught by the '127 patent.

a. 1-methylpseudouridine Modification

448. As explained in my opening declaration,⁷¹⁸ Drs. Karikó and Weissman made the fundamental discovery that modifying mRNA reduces the innate immune

⁷¹⁷ Ex. 2200 ¶¶ 227, 241-244.

⁷¹⁸ Ex. 1002 ¶ 43.

response produced by such mRNA and can thereby enhance protein expression and patented their discovery. Thus, to the extent that the success of Comirnaty® and Spikevax® was based on 1-methylpseudouridine, as Dr. Krause alleges,⁷¹⁹ this feature was already known in the prior art, as explained in my opening declaration.⁷²⁰

449. Dr. Krause also ignores that Dr. Karikó and Dr. Weissman's work formed the foundation for an infectious disease vaccine. The use of modified nucleotides dates back almost 20 years, when Drs. Karikó and Weissman at the University of Pennsylvania discovered that modifying the nucleotides in exogenous mRNA reduced immunogenicity and enhanced the translational capacity of the RNA.⁷²¹ Drs. Karikó and Weissman immediately recognized the potential of modified mRNA for use in vaccines and described their invention, which identified 1-methyl-pseudouridine as a modification, and that later issued as U.S. Patent No. 8,691,966.⁷²² They further understood that their work would be useful for both therapeutic and infectious diseases indications. For example, in 2008, Drs. Karikó

⁷¹⁹ Ex. 2200 ¶¶ 215-217, 241-242.

⁷²⁰ Ex. 1002 ¶¶ 43, 93.

⁷²¹ Ex. 1021 (published in 2005); Ex. 1022 (published in 2008).

⁷²² Ex. 1023.

and Weissman described modified mRNA was a “promising tool for both gene replacement and *vaccination*.”⁷²³

450. Others, including Patent Owner, recognized the significance of Dr. Karikó and Dr. Weissman’s work. For example, I understand that Patent Owner licensed Dr. Karikó and Dr. Weissman’s patents on 1-methyl-pseudouridine.⁷²⁴ Moreover, in awarding the Nobel Prize to Drs. Karikó and Weissman, the Nobel Committee explained that it was for their “[d]iscoveries concerning nucleoside base modifications that enabled the development of *effective mRNA vaccines against COVID-19*.”⁷²⁵ Likewise, the Nobel Committee stated that “[w]hen the pandemic broke in early 2020, mRNA companies acted quickly to develop COVID-19 vaccines. BioNTech and [Patent Owner] chose to use mRNA with modified bases building on the discoveries by Karikó and Weissmann.”⁷²⁶

b. Full-length Spike Protein

451. As explained above in Section V.A.2.b, use of a full-length spike protein was well-known in the prior art. Thus, to the extent that the success of

⁷²³ Ex. 1022 at 1833.

⁷²⁴ Ex. 1026.

⁷²⁵ Ex. 1124 at 1 (emphases added).

⁷²⁶ Ex. 1124 at 8.

Comirnaty® and Spikevax® is based on the use of a full-length spike protein, as Dr. Krause alleges,⁷²⁷ I disagree that this provides any evidence of nexus.

c. Lipid Nanoparticle Composition

452. I disagree with Dr. Krause's assertion that there is a nexus between the claims and the lipid nanoparticles of Spikevax® and Comirnaty®.⁷²⁸

453. As an initial matter, I understand from Dr. Moon's opening declaration that the '127 patent describes only the generic components of a lipid nanoparticle, but is not directed to specific formulations of lipids.⁷²⁹ Moreover, the development of the lipid nanoparticle pre-dates Patent Owner's work.⁷³⁰ I understand from Dr. Moon that the fundamental technology behind lipid nanoparticles—the use of four lipids, including an ionizable cationic lipid—had already existed before 2015.⁷³¹ I further understand that Dr. Moon has opined that, before the patents were filed, Geall demonstrated that lipid nanoparticles with the same claimed lipid nanoparticle compositions were useful for delivering larger molecules such as self-amplifying

⁷²⁷ Ex. 2200 ¶¶ 218-223.

⁷²⁸ Ex. 2200 ¶ 227.

⁷²⁹ Ex. 1004 ¶ 45.

⁷³⁰ Ex. 1004 ¶¶ 19-44.

⁷³¹ Ex. 1004 ¶¶ 35-44.

mRNA.⁷³² The scientific community has also recognized that the pioneering work on lipid nanoparticles was developed by groups such as the University of British Columbia. For example, the Nobel Prize Committee explained:

A second major improvement was made in the lab of Pieter Cullis at the University of British Columbia with the development of ionizable cationic lipids . . . The important discoveries by Cullis team spurred large industrial interest in the development of ionizable lipids. . . . More efficient ionizable cationic lipids were identified in large-scale screening programs in several biotech companies. Consequently, lipid nanoparticles now enable safe and efficient *in vivo* delivery of nucleic acids, including mRNA, into human cells. This advance is of great importance for clinical applications of nucleic acid-based technologies.⁷³³

454. The Gairdner Foundation has likewise recognized Drs. Karikó, Weissman and Cullis: “The work of Drs. Karikó, Weissman and Cullis enabled the rapid availability of highly effective and safe COVID-19 mRNA vaccines, which has become an important tool for the control of COVID-19 pandemic.”⁷³⁴ Thus, to

⁷³² Ex. 1004 ¶¶ 54-57.

⁷³³ Ex. 1124 at 4.

⁷³⁴ Ex. 1113 at 2.

the extent Patent Owner claims that the function, safety or efficacy of Comirnaty® and Spikevax® stems from their use of LNPs to deliver mRNA, I understand this feature to have been known in the prior art.

B. No Satisfaction of a Long-Felt, Unmet Need

455. I disagree with Dr. Krause's opinion that the alleged invention in the '127 patent satisfied a long-felt need.⁷³⁵ First, as explained in Sections VIII.A.1-2, Spikevax®, and Comirnaty® do not embody the challenged claims, and have features that were known in the prior art, including for example the 1-methylpseudouridine modification, the full-length spike protein, and the lipid nanoparticle composition. Thus, there is no nexus between the patents and any satisfaction of long felt need.

456. Additionally, while there was a need for a safe and effective COVID-19 vaccine that first arose with the outbreak of the pandemic in early 2020, the mRNA vaccines were not the only vaccines that met this need. Other vaccines became available in response to the pandemic as well with comparable efficacy and safety. For example, the Spikevax® and Comirnaty® vaccines had comparable efficacy and safety to the protein subunit vaccine developed by Novavax. Specifically, by June 2021, Novavax demonstrated that its vaccine had a favorable

⁷³⁵ Ex. 2200 ¶¶ 165-177.

safety profile and an overall efficacy rate of 90.4% at preventing COVID-19,⁷³⁶ which is comparable to Spikevax®'s efficacy rate of 94.1% and Pfizer/BioNTech's efficacy rate of 95%.⁷³⁷ Further, Novavax's vaccine was shown to be 100% effective at preventing moderate-to-severe disease, 93% effective against predominantly circulating Variants of Concern and Variants of Interest, and 91% effective in high-risk populations.⁷³⁸ On December 20, 2021, the European Medicines Agency granted conditional marketing authorization for Novavax's vaccine.⁷³⁹ And on July 13, 2022, the FDA issued an EUA for Novavax's vaccine for individuals 18 years and older.⁷⁴⁰

457. Dr. Krause further contends that the "foundational technology" described in the '127 patent was quickly adapted for new variants of SARS-CoV-2.⁷⁴¹ It is unclear what Dr. Krause is pointing to in the '127 patent disclosure that

⁷³⁶Ex. 1125 at 1.

⁷³⁷ Ex. 2200 ¶ 199.

⁷³⁸ Ex. 1125 at 1-2.

⁷³⁹ Ex. 1107 at 6.

⁷⁴⁰ Ex. 1127 at 1.

⁷⁴¹ Ex. 2200 ¶ 177.

was foundational to creating the SARS-CoV-2 vaccines. These COVID-19 vaccines were combating a virus that did not exist in 2015, using proprietary lipid nanoparticle formations, and each company's own mRNA technology. Moreover, in my opinion, mRNA vaccines are not the only technology that can be adapted quickly to immunize against variant strains of SARS-CoV-2. For example, by October 3, 2023, the FDA authorized Novavax's vaccine for XBB.1.5,⁷⁴² just three weeks after its authorization for Patent Owner's and Pfizer/BioNTech's vaccine for the same SARS-CoV-2 variant.⁷⁴³ Additionally, on June 14, 2024, Novavax filed for FDA approval of its Covid-19 vaccine targeting the JN.1 variant.⁷⁴⁴ This occurred shortly after Patent Owner's filing for approval of a vaccine against the same variant, on June 7, 2024.⁷⁴⁵

C. No Failure of Others or Skepticism

1. mRNA was viewed as a promising platform for vaccines.

⁷⁴² Ex. 1111 at 1.

⁷⁴³ Ex. 1110 at 1.

⁷⁴⁴ Ex. 1126 at 1.

⁷⁴⁵ Ex. 1122 at 1.

458. For the reasons explained in Section V.A.2.a, by 2015, mRNA was viewed as a promising platform for vaccines. I thus disagree with Dr. Krause's argument that a POSA would have been skeptical of using mRNA for a vaccine.⁷⁴⁶

2. Researchers were not skeptical that the S protein could be used as an antigen in an mRNA betacoronavirus vaccine

459. For the reasons explained in Section V.A.2.b, researchers had long established that the spike protein could be used effectively in a vaccine. I thus disagree with Dr. Krause's argument that researchers would have been skeptical of using a spike protein.⁷⁴⁷

3. No Failure of Others Supports the Validity of the Challenged Claims

460. For the reasons explained in Section V.A.2.a, others had successfully testing the use of mRNA vaccines, including for infectious diseases. I thus disagree with Dr. Krause's argument that the purported failure of others supports the validity of the Challenged Claims.⁷⁴⁸

⁷⁴⁶ Ex. 2200 ¶¶ 178-186.

⁷⁴⁷ Ex. 2200 ¶¶ 187-192.

⁷⁴⁸ Ex. 2200 ¶¶ 193-199.

D. No Unexpected Results

461. I disagree with Dr. Krause's argument that results of the experiments shown in the '127 patent were "unexpected."⁷⁴⁹

462. *First*, Dr. Krause contends that it was surprising Patent Owner's vaccine proved immunogenic, citing self-serving statements from the patent.⁷⁵⁰ But as explained in Section V.H, before October 2015, researchers had tested mRNA, including modified mRNA, for infectious diseases. Moreover, lipid nanoparticles of the same compositions and ratios had been successfully used with siRNA, and, in fact, had been approved for the drug Onpattro for polyneuropathy caused by hATTR amyloidosis in adults.⁷⁵¹

463. *Second*, Dr. Krause argues that "the degree of success shown by [Patent Owner]'s inventions was surprising and unexpected," including the 94% efficacy rate.⁷⁵² But that vaccine is not described in the '127 patent and was created approximately five years after the '127 patent filing date. As explained in Section VIII.A.2, many generic features of the claims, including the modified mRNA, the

⁷⁴⁹ Ex. 2200 ¶¶ 200-207.

⁷⁵⁰ Ex. 2200 ¶ 201.

⁷⁵¹ Ex. 1128 at 1.

⁷⁵² Ex. 2200 ¶¶ 202-205.

spike protein, and the lipid nanoparticles, were long-established in the prior art as components for mRNA vaccines. And the specific components of the Comirnaty® and Spikevax® vaccines were proprietary and developed by third parties. Indeed, before the COVID-19 pandemic, there were already numerous clinical trials that had demonstrated the efficacy of mRNA vaccines, including those described in Section V.A.2.a.2. Moreover, as explained in Section VIII.A.1, many unclaimed features are tied to their efficacy and safety, such as the 2P mutation.

464. **Third**, Dr. Krause asserts that the lack of antibody dependent enhancement was surprising.⁷⁵³ For the reasons explained in Section V.A.2.b, the lack of antibody dependent enhancement would not have been surprising to researchers.

465. **Fourth**, Dr. Krause asserts that successful use of the full-length S protein was unexpected.⁷⁵⁴ For the reasons explained in Section V.A.2.b.4, the use of the full-length S protein would not have been surprising to researchers.

E. No Praise

466. In my opinion, there is no praise that would support the non-obviousness of the '127 patent. In his declaration, Dr. Krause contends that “[o]thers

⁷⁵³ Ex. 2200 ¶¶ 206-207.

⁷⁵⁴ Ex. 2200 ¶ 208.

in the field have praised and recognized the great success of [Patent Owner]’s COVID-19 vaccine design.”⁷⁵⁵ But the evidence that Dr. Krause identifies does not show praise for Patent Owner’s patented invention.⁷⁵⁶ Indeed, Dr. Krause has not pointed to any specific praise of the ’127 patent, let alone widespread praise by respected scientists. Instead, Dr. Krause focuses on the COVID-19 vaccine. However, COVID-19 did not even exist until almost five years after the patents were filed, and the relevant vaccines therefore relate to a virus that did not even exist in 2015.

467. Moreover, as explained in Sections VIII.A.1-2, the success of the mRNA vaccines was attributable either to unclaimed features or those known in the prior art. Even the articles upon which Dr. Krause cites to support that fact. For example, in the article titled “Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults,”⁷⁵⁷ cited by Dr. Krause, the authors emphasized that “[t]he mRNA-1273 vaccine was codeveloped by researchers at the NIAID Vaccine Research Center and Moderna in Cambridge, Massachusetts” and underscores the importance of the 2P mutation:

⁷⁵⁵ Ex. 2200 ¶ 209.

⁷⁵⁶ Ex. 2200 ¶¶ 209-214.

⁷⁵⁷ Ex. 2200 ¶ 212 (citing Ex. 2035).

This vaccine encodes a stabilized version of the SARS CoV-2 full-length spike glycoprotein trimer, S-2P, which has been modified to include two proline substitutions at the top of the central helix in the S2 subunit. The mRNA is encapsulated in lipid nanoparticles at a concentration of 0.5 mg per milliliter and diluted with normal saline to achieve the final target vaccine concentrations.⁷⁵⁸

IX. CONCLUSION

468. For the reasons stated above and in my opening declarations, it remains my opinion that Schrum, Schrum in view of Geall, Schrum in view of Yang, and Schrum in view of Altmeyer disclose the limitations of claims 1-3, 6-9, 11-13, 17-18, and 20 of the '127 patent.

469. I declare under penalty of perjury that the foregoing is true and correct. I also hereby declare that all statements made herein on my 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.

⁷⁵⁸ Ex. 2035 at 2428.

Reply Declaration of Daniel O. Griffin, M.D., Ph.D.
Patent No. 10,933,127

Executed on: August 30, 2024

By: 
Daniel O. Griffin, M.D., Ph.D.

APPENDIX A – LIST OF MATERIALS CONSIDERED

Exhibit No.	Document
Ex. 1002	Declaration of Daniel O. Griffin, M.D., Ph.D. and associated exhibits therein
Ex. 1004	Declaration of James J. Moon, Ph.D. and associated exhibits therein
Ex. 1013	Jon A. Wolff et al., <i>Direct gene transfer into mouse muscle in vivo</i> , 247 Science 1465 (1990)
Ex. 1026	Patent Sublicense Agreement Between Cellscript, LLC and ModernaTx, Inc.
Ex. 1103	Daniel O. Griffin et al., <i>Cytokine storm of a different flavor: the different cytokine signature of SARS-CoV-2 the cause of COVID-19 from the original SARS outbreak</i> , Journal of Global Antimicrobial Resistance, 24 Journal of Global Antimicrobial Resistance 90 (2021)
Ex. 1104	Deposition of Deborah Fuller, Ph.D., and exhibits cited therein, dated August 2, 2024
Ex. 1105	Deposition of Philip Krause, M.D., and exhibits cited therein, dated August 14, 2024
Ex. 1106	Eric M. Slimko and Henry A. Lester, <i>Codon optimization of Caenorhabditis elegans GluCl ion channel genes for mammalian cells dramatically improves expression levels</i> , 127 Journal of Neuroscience Methods 75 (2003)
Ex. 1107	European Medicines Agency, Nuvaxovid (available at https://www.ema.europa.eu/en/medicines/human/EPAR/nuvaxovid)
Ex. 1108	Frank Liang et al., <i>Efficient Targeting and Activation of Antigen-Presenting Cells In Vivo after Modified mRNA Vaccine Administration in Rhesus Macaques</i> , 25(12) Mol Ther. 2635 (2017)
Ex. 1109	Fei Song et al., <i>Middle East Respiratory Syndrome Coronavirus Spike Protein Delivered by Modified Vaccinia Virus Ankara Efficiently Induces Virus-Neutralizing Antibodies</i> , 87(21) J. of Virology 11950 (2013)
Ex. 1110	FDA, FDA Takes Action on Updated mRNA COVID-19 Vaccines to Better Protect Against Currently Circulating Variants (Sept. 11, 2023) (available at https://www.fda.gov/news-

Exhibit No.	Document
	events/press-announcements/fda-takes-action-updated-mrna-covid-19-vaccines-better-protect-against-currently-circulating)
Ex. 1111	FDA, Novavax COVID-19 Vaccine, Adjuvanted (last updated Oct. 17, 2023) (available at https://www.fda.gov/vaccines-blood-biologics/coronavirus-covid-19-cber-regulated-biologics/novavax-covid-19-vaccine-adjuvanted)
Ex. 1113	Gairdner, Pieter Cullis, (available at https://www.gairdner.org/winner/pieter-cullis) (last accessed Aug. 26, 2024)
Ex. 1114	Gavi, Taming the spike: How Jason McLellan helped turn the tide of the pandemic (May 16, 2022) (available at https://www.gavi.org/vaccineswork/taming-spike-how-jason-mclemmell-helped-turn-tide-pandemic)
Ex. 1115	Himani Bisht et al., <i>Severe acute respiratory syndrome coronavirus spike protein expressed by attenuated vaccinia virus protectively immunizes mice</i> , 101(17) Biological Sciences 6641 (2004)
Ex. 1116	History of Vaccines, The Future of Immunization: The Development of HIV Vaccines (available at https://historyofvaccines.org/vaccines-101/future-immunization/development-hiv-vaccines) (last accessed Aug. 26, 2024)
Ex. 1117	Ingmar Hoerr et al., <i>In vivo application of RNA leads to induction of specific cytotoxic T lymphocytes and antibodies</i> , 30 Eur. J. Immunol. 1 (2000)
Ex. 1118	Kapil Bahl et al., <i>Preclinical and Clinical Demonstration of Immunogenicity by mRNA Vaccines against H10N8 and H7N9 Influenza Viruses</i> , 25(6) Mol Ther. 1316 (2017)
Ex. 1119	Lorna Leal et al., <i>Phase I clinical trial of an intranodally administered mRNA-based therapeutic vaccine against HIV-1 infection</i> , 32(17) AIDS 2533 (2018)
Ex. 1121	Matteo Vergati et al., <i>Strategies for cancer vaccine development</i> , 2010.1 Journal of Biomedicine and Biotechnology 596432 (2010)
Ex. 1122	Moderna, Moderna Files FDA Application for the JN.1 Targeting COVID-19 Vaccine (June 7, 2024) (available at https://investors.modernatx.com/news/news-

Exhibit No.	Document
	details/2024/Moderna-Files-FDA-Application-for-the-JN.1-Targeting-COVID-19-Vaccine/default.aspx)
Ex. 1123	Long S, Prober C, Fischer M (Griffin-Chapter on Tissue Nematodes). Principles and Practice of Pediatric Infectious Diseases, 6th Edition 2020 Expert Consult
Ex. 1124	Nobel Prize, Discoveries concerning nucleoside base modifications that enabled the development of effective mRNA vaccines against COVID-19 (2023) (available at https://www.nobelprize.org/prizes/medicine/2023/advanced-information/)
Ex. 1125	Novavax, Novavax COVID-19 Vaccine Demonstrates 90% Overall Efficacy and 100% Protection Against Moderate and Severe Disease in PREVENT-19 Phase 3 Trial (June 14, 2021) (available at https://ir.novavax.com/press-releases/2021-06-14-Novavax-COVID-19-Vaccine-Demonstrates-90-Overall-Efficacy-and-100-Protection-Against-Moderate-and-Severe-Disease-in-PREVENT-19-Phase-3-Trial)
Ex. 1126	Novavax, Novavax Submits Application to U.S. FDA for Updated Protein-based 2024-2025 Formula COVID-19 Vaccine (June 14, 2024) (available at https://ir.novavax.com/press-releases/2024-06-14-Novavax-Submits-Application-to-U-S-FDA-for-Updated-Protein-based-2024-2025-Formula-COVID-19-Vaccine)
Ex. 1127	Novavax, U.S. FDA Grants Emergency Use Authorization for Novavax COVID-19 Vaccine, Adjuvanted for Individuals Aged 18 and Over (July 13, 2022) (available at https://ir.novavax.com/press-releases/2022-07-13-U-S-FDA-Grants-Emergency-Use-Authorization-for-Novavax-COVID-19-Vaccine%2C-Adjuvanted-for-Individuals-Aged-18-and-Over)
Ex. 1128	ONPATTRO™ Prescribing Label (available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210922s000lbl.pdf)
Ex. 1129	Silke Holtkamp et al., <i>Modification of antigen-encoding RNA increases stability, translational efficacy, and T-cell stimulatory capacity of dendritic cells</i> , 108(13) Gene Therapy 4009 (2006)

Exhibit No.	Document
Ex. 1130	Sofia Stenler et al., <i>Safety and efficacy of DNA vaccines: Plasmids vs. minicircles</i> , 10(5) Human Vaccines & Immunotherapeutics 1306 (2014)
Ex. 1132	Ursula J. Buchholz et al., <i>Contributions of the structural proteins of severe acute respiratory syndrome coronavirus to protective immunity</i> , 101(26) Biological Sciences 9804 (2004)
Ex. 1133	Ugur Sahin et al., <i>mRNA-based therapeutics —developing a new class of drugs</i> , 13 Nature Reviews Drug Discovery 759 (2014)
Ex. 1134	Vaccine Research & Development, How can Covid-19 vaccine development be done quickly and safely? (available at https://coronavirus.jhu.edu/vaccines/timeline#:~:text=Typical%20Timeline,vaccine%20doses%20for%20widespread%20distribution.) (last accessed Aug. 26, 2024)
Ex. 1136	Yiu Wing Kam et al., <i>Antibodies against trimeric S glycoprotein protect hamsters against SARS-CoV challenge despite their capacity to mediate FcγRII-dependent entry into B cells in vitro</i> , 25 Vaccine 729 (2007)
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. 1139	Borys Pedenko et al., <i>SARS-CoV-2 S Glycoprotein Stabilization Strategies</i> , 15 Viruses 557 (2023)
Ex. 1140	Damon Deming et al., <i>Vaccine Efficacy in Senescent Mice Challenged with Recombinant SARS-CoV Bearing Epidemic and Zoonotic Spike Variants</i> , 3(12) plos Medicine 2359 (2006)
Ex. 1141	Daniel O. Griffin and Thomas L. Rothstein, <i>A small CD11b+ human B1 cell subpopulation stimulates T cells and is expanded in lupus</i> , 208(13) J. Exp. Med. 2591 (2011)
Ex. 1142	Daniel O. Griffin et al., <i>Human B1 cells in umbilical cord and adult peripheral blood express the novel phenotype CD20+CD27+CD43+CD70-</i> , 208(1) J. Exp. Med. 67 (2011)
Ex. 1143	Daniel O. Griffin et al., <i>Co-infection with Hepatitis C Virus Increases Mortality in HIV-1 Infected Patients Through Increased Liver-Related Deaths Rather Than By Increasing Malignancy Related Deaths</i> , 7(4) J AIDS and Clin Res 1000558 (2016)
Ex. 1305	Updated Curriculum Vitae of Daniel O. Griffin

Exhibit No.	Document
Ex. 1314	Petsch, B., et al. <i>Protective efficacy of in vitro synthesized, specific mRNA vaccines against influenza A virus infection</i> . Nature biotechnology 30, 1210-1216 (2012).
Ex. 1315	Hattinger, E., et al. <i>Prophylactic mRNA Vaccination against Allergy Confers Long-Term Memory Responses and Persistent Protection in Mice</i> . Journal of Immunology Research 2015, 797421 (2015).
Ex. 2199	Declaration of Deborah H. Fuller, Ph.D. and associated exhibits therein (PROTECTIVE ORDER MATERIAL)
Ex. 2200	Declaration of Philip Krause, M.D. and associated exhibits therein (PROTECTIVE ORDER MATERIAL)