

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 IPR2023-01358
Patent No. 10,702,600

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	12
IV.	GROUND 1: SCHRUM DISCLOSES EVERY LIMITATION OF CLAIMS 1-2, 4-6, 8-12, 16-17, 20-21, AND 26 OF THE '600 PATENT ...	12
A.	Dr. Fuller's Opinions Regarding Ground 1 Were Based on an Incorrect Premise	13
B.	Claim 1: "A composition, comprising: 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."	15
1.	Dr. Fuller Fails to Rebut My Demonstration that Schrum Discloses Each Limitation of Claim 1	17
2.	Schrump Discloses the Elements of Claim 1 as Arranged in the Claim	23
3.	A POSA Would Readily Envisage the Limitations of Claim 1 Based upon Schrum's Teachings	31
C.	Claim 2: "The composition of claim 1, wherein the open reading frame encodes a BetaCoV S protein."	33
D.	Claim 4: "The composition of claim 1, wherein the mRNA further comprises a 5' untranslated region (UTR) and a 3' UTR."	35
E.	Claim 5: "The composition of claim 4, wherein the mRNA further comprises a poly(A) tail."	38
F.	Claim 6: "The composition of claim 4, wherein the mRNA further comprises a 5' cap analog."	40
G.	Claim 8: "The composition of claim 1, wherein the mRNA comprises a chemical modification."	42

H.	Claim 9: “The composition of claim 8, wherein the chemical modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification.”	45
I.	Claim 10: “The composition of claim 8, wherein at least 80% of the uracil in the open reading frame has a chemical modification.”	48
J.	Claim 11: “The composition of claim 1, wherein the lipid nanoparticle comprises an ionizable cationic lipid, a neutral lipid, a sterol, and a PEG-modified lipid.”	50
K.	Claim 12: “The composition of claim 11, wherein the lipid nanoparticle comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.”	52
L.	Claim 16: “A composition, comprising: a messenger ribonucleic acid (mRNA) comprising a 5’ untranslated region (UTR), an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit, a 3’ UTR, and a poly(A) tail, formulated in a lipid nanoparticle that comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.”	54
	1. Dr. Fuller Fails to Rebut My Demonstration that Schrum Discloses Each Limitation of Claim 16	56
	2. Schrum discloses the elements of claim 16 as they are arranged in the claim	56
	3. A POSA would have at once envisaged the claimed arrangement of claim 16 from Schrum.	58
M.	Claim 17: “The composition of claim 16, wherein the open reading frame encodes a Beta CoV S protein.”	59
N.	Claim 20: “The composition of claim 16, wherein at least 80% of the uracil in the open reading frame has a chemical modification.”	60
O.	Claim 21: “The composition of claim 20, wherein the chemical modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification.”	63
P.	Claim 26: “A lipid nanoparticle, comprising: a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit; wherein the lipid nanoparticle comprises 20-60% ionizable cationic lipid, 5-	

25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.”	66
1. Dr. Fuller Fails to Rebut My Demonstration that Schrum Discloses Each Limitation of Claim 26	68
2. Schrum discloses the elements of claim 26 as they are arranged in the claim	68
3. A POSA would have at once envisaged the claimed arrangement of claim 26 from Schrum.	69
V. GROUND 2: THE COMBINATION OF SCHRUM IN VIEW OF GEALL DISCLOSES ALL OF THE LIMITATIONS OF CLAIMS 1-2, 4-6, 8-12, 16-17, 20-21, AND 26	70
A. Claim 1: “A composition, comprising: 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.”	71
1. Schrum and Geall Disclose Every Element of Claim 1	71
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) <i>No “Skepticism” of mRNA Vaccines</i>	78
2) <i>Clinical Trials of mRNA Vaccines Encoding for Infectious Disease Immunogens Do Not Demonstrate Skepticism</i>	88
3) <i>By October 2015, mRNA Vaccines Had Known Advantages Over Other Vaccine Modalities, Including Other Nucleic Acid Vaccines</i>	95
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	103

1)	<i>The SARS-CoV S Protein Was a Known, Protective Immunogen</i>	105
2)	<i>By October 2015, S Protein-Based Vaccines Had Already Proven to Be Protective</i>	111
3)	<i>Concerns with Enhanced Disease Would Not Have Dissuaded a POSA from Using a Betacoronavirus S Protein as a Vaccine Immunogen</i>	118
4)	<i>The “Full-Length” S Protein Had Known Advantages as a Vaccine Immunogen</i>	135
c.	A POSA Would Have Been Motivated to Formulate Immunogen-Encoding mRNA in Lipid Nanoparticles and Would Reasonably Expect to Do So Successfully	140
1)	<i>By October 2015, Lipid Nanoparticles Were a Well-Known Delivery Approach for mRNA</i>	141
2)	<i>By October 2015, Lipid Nanoparticles Had Already Been Shown to Improve mRNA Vaccine Potency</i>	144
d.	[REDACTED]	
	[REDACTED]	
	[REDACTED]	
	[REDACTED]	
	[REDACTED]	
B.	Claim 2: “The composition of claim 1, wherein the open reading frame encodes a BetaCoV S protein.”	171
C.	Claim 4: “The composition of claim 1, wherein the mRNA further comprising a 5' untranslated region (UTR) and a 3' UTR.”	173
D.	Claim 5: “The composition of claim 4, wherein the mRNA further comprises a poly(A) tail.”	174

E.	Claim 6: “The composition of claim 4, wherein the mRNA further comprises a 5’ cap analog.”	176
F.	Claim 8: “The composition of claim 1, wherein the mRNA comprises a chemical modification.”	178
G.	Claim 9: “The composition of claim 8, wherein the chemical modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification.”	183
H.	Claim 10: “The composition of claim 8, wherein at least 80% of the uracil in the open reading frame has a chemical modification.”	185
I.	Claim 11: “The composition of claim 1, wherein the lipid nanoparticle comprises an ionizable cationic lipid, a neutral lipid, a sterol, and a PEG-modified lipid.”	187
J.	Claim 12: “The composition of claim 11, wherein the lipid nanoparticle comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.”	188
K.	Claim 16: “A composition, comprising: a messenger ribonucleic acid (mRNA) comprising a 5’ untranslated region (UTR), an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit, a 3’ UTR, and a poly(A) tail, formulated in a lipid nanoparticle that comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.”	190
	1. Schrum and Geall Disclose Every Element of Claim 16	191
	2. A POSA Would Have Been Motivated To Combine Schrum And Geall With A Reasonable Expectation Of Success	191
L.	Claim 17: “The composition of claim 16, wherein the open reading frame encodes a Beta CoV S protein.”	193
M.	Claim 20: “The composition of claim 16, wherein at least 80% of the uracil in the open reading frame has a chemical modification.”	195
N.	Claim 21: “The composition of claim 20, wherein the chemical modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification.”	196
O.	Claim 26: “A lipid nanoparticle, comprising: a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit; wherein	

	the lipid nanoparticle comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.”	199
1.	Schrump and Geall Disclose Every Element of Claim 26	199
2.	A POSA would have been motivated to combine Schrum and Geall with a reasonable expectation of success	200
VI.	GROUND 3: THE COMBINATION OF SCHRUMP IN VIEW OF YANG DISCLOSES ALL OF THE LIMITATIONS OF CLAIMS 1-2, 4-6, 8-12, 16-17, 20-21, AND 26	202
A.	Claim 1: “A composition, comprising: 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.”	202
1.	Schrump and Yang Disclose Every Element of Claim 1	203
2.	A POSA would have been motivated to combine the teachings of Schrum and Yang with a reasonable expectation of success	206
B.	Claim 2: “The composition of claim 1, wherein the open reading frame encodes a BetaCoV S protein.....	212
C.	Claim 4: “The composition of claim 1, wherein the mRNA further comprises a 5' untranslated region (UTR) and a 3' UTR.”	213
D.	Claim 5: “The composition of claim 4, wherein the mRNA further comprises a poly(A) tail.”	213
E.	Claim 6: “The composition of claim 4, wherein the mRNA further comprises a 5' cap analog.”	214
F.	Claim 8: “The composition of claim 1, wherein the mRNA comprises a chemical modification.”	214
G.	Claim 9: “The composition of claim 8, wherein the chemical modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification.”	214
H.	Claim 10: “The composition of claim 8, wherein at least 80% of the uracil in the open reading frame has a chemical modification.”	215

I.	Claim 11: “The composition of claim 1, wherein the lipid nanoparticle comprises an ionizable cationic lipid, a neutral lipid, a sterol, and a PEG-modified lipid.”	215
J.	Claim 12: “The composition of claim 11, wherein the lipid nanoparticle comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.”	215
K.	Claim 16: “A composition, comprising: a messenger ribonucleic acid (mRNA) comprising a 5’ untranslated region (UTR), an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit, a 3’ UTR, and a poly(A) tail, formulated in a lipid nanoparticle that comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.”	215
1.	Schrum and Yang Disclose Every Element of Claim 16	216
2.	A POSA would have been motivated to combine Schrum and Yang with a reasonable expectation of success	216
L.	Claim 17: “The composition of claim 16, wherein the open reading frame encodes a Beta CoV S protein.”	219
M.	Claim 20: “The composition of claim 16, wherein at least 80% of the uracil in the open reading frame has a chemical modification.”	220
N.	Claim 21: “The composition of claim 20, wherein the chemical modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification.”	220
O.	Claim 26: “A lipid nanoparticle, comprising: a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit; wherein the lipid nanoparticle comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.”	220
1.	Schrum and Yang Disclose Every Element of Claim 26	221
2.	A POSA would have been motivated to combine Schrum and Yang with a reasonable expectation of success	221
VII.	GROUND 4: THE COMBINATION OF SCHRUM IN VIEW OF ALTMAYER DISCLOSES ALL OF THE LIMITATIONS OF CLAIMS 1-2, 4-6, 8-12, 16-17, 20-21, AND 26	223

A.	Claim 1: “A composition, comprising: 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.”	223
1.	Schrum and Altmeyer Disclose Every Element of Claim 1 ...	224
2.	A POSA would have been motivated to combine Schrum and Altmeyer with a reasonable expectation of success	227
B.	Claim 2: “The composition of claim 1, wherein the open reading frame encodes a BetaCoV S protein.”	232
C.	Claim 4: “The composition of claim 1, wherein the mRNA further comprises a 5' untranslated region (UTR) and a 3' UTR.”	233
D.	Claim 5: “The composition of claim 4, wherein the mRNA further comprises a poly(A) tail.”	233
E.	Claim 6: “The composition of claim 4, wherein the mRNA further comprises a 5' cap analog.”	233
F.	Claim 8: “The composition of claim 1, wherein the mRNA comprises a chemical modification.”	233
G.	Claim 9: “The composition of claim 8, wherein the chemical modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification.”	234
H.	Claim 10: “The composition of claim 8, wherein at least 80% of the uracil in the open reading frame has a chemical modification.”	234
I.	Claim 11: “The composition of claim 1, wherein the lipid nanoparticle comprises an ionizable cationic lipid, a neutral lipid, a sterol, and a PEG-modified lipid.”	234
J.	Claim 12: “The composition of claim 11, wherein the lipid nanoparticle comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.”	234
K.	Claim 16: “A composition, comprising: a messenger ribonucleic acid (mRNA) comprising a 5' untranslated region (UTR), an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit, a 3' UTR, and a poly(A) tail, formulated in a lipid nanoparticle that comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.”	235

1.	Schrump and Altmeyer Disclose Every Element of Claim 16 .	235
2.	A POSA would have been motivated to combine Schrump and Altmeyer with a reasonable expectation of success	236
L.	Claim 17: “The composition of claim 16, wherein the open reading frame encodes a Beta CoV S protein.”	238
M.	Claim 20: “The composition of claim 16, wherein at least 80% of the uracil in the open reading frame has a chemical modification.”	239
N.	Claim 21: “The composition of claim 20, wherein the chemical modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification.”	239
O.	Claim 26: “A lipid nanoparticle, comprising: a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit; wherein the lipid nanoparticle comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.”	239
1.	Schrump and Altmeyer Disclose Every Element of Claim 26 .	240
2.	A POSA would have been motivated to combine Schrump and Altmeyer with a reasonable expectation of success	240
VIII.	THERE ARE NO OBJECTIVE INDICIA THAT SUPPORT THE NON-OBVIOUSNESS OF THE ’600 PATENT	242
A.	Nexus.....	243
1.	Spikevax® and Comirnaty® Do Not Embody the Challenged Claims.....	243
a.	Two-Proline Mutation.....	244
b.	mRNA Structural Features	248
c.	Lipid Nanoparticle Composition	250
2.	Many features of SpikeVax®, and Comirnaty® were known in the prior art	251
a.	1-methylpseudouridine Modification	251
b.	Full-length Spike Protein	254
c.	Lipid Nanoparticle Composition	254

B.	No Satisfaction of a Long-Felt, Unmet Need	256
C.	No Failure of Others or Skepticism.....	259
1.	mRNA was viewed as a promising platform for vaccines.	259
2.	Researchers were not skeptical that the S protein could be used as an antigen in an mRNA betacoronavirus vaccine.....	259
3.	No Failure of Others Supports the Validity of the Challenged Claims.....	259
D.	No Unexpected Results.....	260
E.	No Praise	262
IX.	CONCLUSION	263
	APPENDIX A – LIST OF MATERIALS CONSIDERED.....	265

I. INTRODUCTION

1. I have previously submitted a declaration in this proceeding, relating to U.S. Patent No. 10,702,600 (“the ’600 patent”). I understand that the Board has instituted an inter partes review for the ’600 patent.

2. I further understand that Dr. Deborah H. Fuller has submitted a declaration relating to the ’600 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, IPR2023-01358, Declaration of Dr. Deborah H. Fuller.

² For example, Ex. 2199 ¶ 497 and ¶ 312.

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 IPR2023-01358, 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 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.

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.

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

⁴ Paper No. 17 (Institution Decision IPR2023-01358) at 31-32.

⁵ Paper No. 17 (Institution Decision IPR2023-01358) at 31-32.

⁶ Ex. 2199 ¶¶ 42-46.

⁷ Ex. 2199 ¶ 42.

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 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 ’600 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 ¶ 159.

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 '600 patent, it would not affect the opinions I have expressed with respect to the '600 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 '600 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 ¶ 160.

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 ’600 patent expressly referring to a full-length Spike protein.¹⁸ For example, Dr. Fuller refers to how the ’600 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 ’600 patent’s disclosure of amino acid sequences for a full-length spike protein for a vaccine support her argument.²⁰ For example, she points to Table 12, listing “GenBank Accession” numbers for “*Full-*

¹⁷ Ex. 1002 ¶ 49.

¹⁸ Ex. 2199 ¶ 170.

¹⁹ Ex. 2199 ¶ 170 (quoting Ex. 1001) (emphases added).

²⁰ Ex. 2199 ¶¶ 165-167.

length Spike Glycoprotein Amino Acid Sequences (*Homo sapiens* strains).”²¹ But

Dr. Fuller fails to explain why the ’600 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 ’600 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.

²¹ Ex. 2199 ¶ 167 (citing Ex. 1001, Table 12) (emphasis added).

3. S Protein Subunit

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 ’600 patent are invalid.

IV. GROUND 1: SCHRUM DISCLOSES EVERY LIMITATION OF CLAIMS 1-2, 4-6, 8-12, 16-17, 20-21, AND 26 OF THE ’600 PATENT

28. In Section VIII of my previous declaration, I explained that each of the limitations of claims 1-2, 4-6, 8-12, 16-17, 20-21, and 26 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.

²² Ex. 2199 ¶¶ 172-187.

²³ Ex. 1002 § VIII.

²⁴ Ex. 2199 § X.

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 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?

. . .

²⁵ Ex. 1104 at 213:10-12.

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.

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 '600 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

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

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], [] 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 '600 patent at issue in this proceeding, as I previously explained²⁹ and reiterate in response to Dr. Fuller's opinions below.

B. Claim 1: “A composition, comprising: a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a

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.”).

²⁸ Ex. 1104 at 213:1-4.

²⁹ Ex. 1002 § VIII.

**betacoronavirus (BetaCoV) S protein or S protein subunit
formulated in a lipid nanoparticle.”**

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 mRNA compositions encoding an immunogen (like the BetaCoV S protein), and the use of these compositions for vaccination.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 ’600 patent—a BetaCoV S protein.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

³⁰ Ex. 1002 § VIII.1.

³¹ Ex. 2199 ¶¶ 237-260.

³² Ex. 2199 ¶¶ 237-260.

³³ Ex. 2199 ¶¶ 237-260.

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 '600 patent that Dr. Fuller contends to not be disclosed by Schrum is the BetaCoV S protein antigen. And contrary to Dr. 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," 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,

³⁴ Ex. 2199 ¶¶ 261-308.

³⁵ Ex. 1002 ¶¶ 70-73.

³⁶ Ex. 1002 ¶ VIII.1.

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 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

³⁷ Ex. 2199 ¶¶ 240-244.

³⁸ Ex. 1009 ¶ 342 (emphasis added).

³⁹ Ex. 1009 ¶ 342.

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 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

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.").

⁴¹ Ex. 1009 ¶ 342.

⁴² Ex. 2199 ¶¶ 245-252.

⁴³ Ex. 2199 ¶ 247.

cannot disclose each limitation of a patent claim without including a working example.⁴⁴

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

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.”).

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

⁴⁶ Ex. 1031 at 227.

⁴⁷ Ex. 1002 ¶ 72 n.118.; Ex. 1002 ¶ 73 (“A POSA would understand that mRNA encoding the spike protein of a SARS-CoV would necessarily disclose an open

43. I also note that Dr. Fuller’s opinion is inconsistent with the specification of the ’600 patent, which does not provide any data showing that any of the contemplated BetaCoV S proteins “actually result[] in a ‘structural protein **forming a spike.**’”⁴⁸ Instead, the specification of the ’600 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 ’600 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 ’600 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

reading frame, which is the portion of the mRNA that encodes the protein/polypeptide of interest.”).

⁴⁸ Ex. 2199 ¶ 246 (emphasis added).

⁴⁹ Ex. 1001 at 8:4-6.

⁵⁰ Ex. 2199 ¶ 298.

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, 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.

⁵¹ Ex. 2199 ¶ 252.

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.

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 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.

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

47. Dr. Fuller also asserts that Schrum does not disclose every element of claim 1 as arranged in the claim.⁵⁷ Contrary to Dr. Fuller’s opinion, Schrum does so.

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

⁵⁷ Ex. 2199 ¶¶ 261-301.

48. As I explain in my opening declaration, Schrum discloses a vaccine made up of mRNA encoding an immunogen.⁵⁸ 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.⁵⁹ Thus, a POSA reading Schrum would be directed to Geall's disclosure of immunogens, which includes the SARS-CoV S protein.⁶⁰

49. 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 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

⁵⁸ Ex. 1002 ¶¶ 68-69 (citing Ex. 1009 ¶ 342).

⁵⁹ 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.

⁶⁰ Ex. 1002 ¶ 72 (citing Ex. 1010 at 16:6-7; 19:26-29).

the very bottom of page 19, Coronavirus in the very last sentence, the spike protein.⁶¹

50. 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.”⁶²

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 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

⁶¹ Ex. 2114 at 68:3-20.

⁶² Ex. 1002 ¶¶ 74-75 (citing Ex. 1009 ¶ 397) (emphases added).

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.

51. 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.”⁶³ 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.”⁶⁴ Paragraph 397 then expressly knits together these two closely related sections.

52. 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.⁶⁵ I disagree with Dr. Fuller’s opinion. The first

⁶³ Ex. 1009 ¶ 340.

⁶⁴ Ex. 1009 ¶ 378.

⁶⁵ Ex. 2199 ¶ 263.

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.⁶⁶

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

53. Schrum reinforces that immunogen-encoding mRNA may be formulated in a lipid nanoparticle for use as a vaccine.⁶⁷ 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*.”⁶⁸ And, Schrum

⁶⁶ Ex. 1009 ¶ 340 (emphases added).

⁶⁷ Ex. 1002 ¶¶ 74-75 (citing Ex. 1009 ¶ 397).

⁶⁸ Ex. 1002 ¶ 56 (citing Ex. 1009 ¶ 378) (emphases added).

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*.”⁶⁹ A POSA would have understood therefore that mRNA encoding an immunogen—an “mRNA of the invention”—can be formulated using lipid nanoparticles, as Paragraph 378 of Schrum instructs.

54. 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.”⁷⁰ 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 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.

55. 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-

⁶⁹ Ex. 1009 ¶ 340 (emphases added).

⁷⁰ Ex. 1002 ¶ 87 (citing Ex. 1009 ¶¶ 995, 999).

amplifying mRNA and non-amplifying mRNA.⁷¹ There is no question, however, that Schrum discloses non-amplifying mRNA, including non-amplifying mRNA encoding an immunogen for use as a vaccine.⁷² 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.

56. In her declaration, Dr. Fuller further argues that Geall discloses “hundreds of immunogens [that] cover a wide variety of targets.”⁷³ Geall, however, includes a discrete section on coronaviruses, and within that section, discloses only one immunogen: a spike protein (as shown below).⁷⁴ 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.

⁷¹ Ex. 2199 ¶¶ 268-269.

⁷² Ex. 1009 ¶ 342 (“[The] . . . mmRNA of the invention may encode an immunogen.”).

⁷³ Ex. 2199 ¶¶ 272-273.

⁷⁴ Ex. 1010 at 19:26-29.

57. Dr. Fuller criticizes both Schrum and Geall for lacking working examples or “data” regarding mRNA encoding betacoronavirus immunogens.⁷⁵ 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.⁷⁶ 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.”⁷⁷ Because Schrum discloses that “an immune response may be elicited by delivering a lipid nanoparticle,” and “the lipid nanoparticle may be formulated for use in a vaccine,”⁷⁸ 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 ’600 patent (as well as claim 1 of the related ’127 patent) does not require any particular level of immune response.

⁷⁵ Ex. 2199 ¶¶ 275-278.

⁷⁶ Ex. 1009 ¶¶ 6-8, ¶ 995.

⁷⁷ Ex. 1019 at 1319.

⁷⁸ Ex. 1009 ¶ 397.

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

58. Dr. Fuller writes that “a POSA would not have at once envisaged the claimed arrangement of claim 1 of the '600 patent from Schrum (including via any alleged incorporation of Geall) for at least the reasons discussed above in Section X.A.2 [*i.e.*, Dr. Fuller's opinion that Schrum does not disclose the limitations of Claim 1 as arranged].”⁷⁹ I disagree, as, in my opinion, a POSA would have envisaged the arrangement of Claim 1 based on Schrum's teachings.

59. 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.

60. 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.⁸⁰ I disagree. The only “selection” the POSA must make

⁷⁹ Ex. 2199 ¶ 305.

⁸⁰ Ex. 2199 ¶¶ 305-307.

from Schrum's disclosure is which immunogen to incorporate into the LNP-encapsulated mRNA vaccine it describes.

61. 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."⁸¹ 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.⁸² 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 (MHV), and Porcine transmissible gastroenteritis virus (TGEV). *The coronavirus immunogen may be a spike polypeptide.*⁸³

With respect to coronavirus, there are no other immunogens listed, and a POSA would at once envisage a mRNA vaccine encoding the betacoronavirus spike

⁸¹ Ex. 2199 ¶ 306.

⁸² For example, Ex. 1010 at 19:1-29.

⁸³ Ex. 1010 at 19:26-29 (emphases added).

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.

62. Dr. Fuller asserts that a POSA would have no reason to focus on lipid nanoparticles as delivery systems for mRNA.⁸⁴ 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.”⁸⁵ Certainly, a POSA would have at once envisaged what Schrum discloses expressly in combination – i.e., the use of lipid nanoparticles to deliver the mRNA vaccine.

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

63. As I explained in my opening declaration⁸⁶ and for the reasons explained in claim 1, Section IV.B, Schrum discloses each limitation of claim 2. In

⁸⁴ Ex. 2199 ¶ 307.

⁸⁵ Ex. 1009 ¶ 397 (emphases added).

⁸⁶ Ex. 1002 § VIII.2.

response, Dr. Fuller makes four arguments. I disagree with each.

64. **First**, Dr. Fuller asserts that Schrum does not anticipate claim 2 for the same reason that it does not anticipate claim 1.⁸⁷ For the reasons explained in claim 1, Section IV.B, I disagree.

65. **Second**, Dr. Fuller asserts that Schrum does not disclose the requirement of “wherein the open reading frame encodes a BetaCoV S protein.”⁸⁸ 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.⁸⁹

66. **Third**, Dr. Fuller asserts that I cannot show that Schrum discloses every element of claim 2 arranged in the same way as claim 2.⁹⁰ For the reasons explained in claim 1, Section IV.B, I disagree. Schrum discloses a LNP-mRNA vaccine and

⁸⁷ Ex. 2199 ¶ 311.

⁸⁸ Ex. 2199 ¶ 312.

⁸⁹ 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.

⁹⁰ Ex. 2199 ¶¶ 313-315.

incorporates Geall by reference, which teaches the S-protein as an immunogen for a betacoronavirus vaccine.⁹¹

67. **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.⁹² For the reasons laid out above, and with respect to claim 1, I disagree.

D. Claim 4: “The composition of claim 1, wherein the mRNA further comprises a 5' untranslated region (UTR) and a 3' UTR.”

68. As I explained in my opening declaration⁹³ 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.

69. **First**, Dr. Fuller asserts that I do not address how claim 1, from which claim 4 depends, is met.⁹⁴ For the reasons explained in my opening declaration,⁹⁵ I disagree.

⁹¹ Ex. 1009 ¶¶ 342, 397.

⁹² Ex. 2199 ¶ 316.

⁹³ Ex. 1002 § VIII.3.

⁹⁴ Ex. 2199 ¶¶ 321-322.

⁹⁵ Ex. 1002 §§ VIII.1, 3.

70. ***Second***, Dr. Fuller asserts that I do not explain how Schrum discloses every element of claim 4 as arranged in the claim.⁹⁶ I disagree. As explained in my opening declaration with respect to claim 1, Schrum (incorporating Geall) discloses an mRNA encoding a spike protein and encapsulated in a lipid nanoparticle.⁹⁷ 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 can contain signal sequences directing the mRNA to certain locations within a cell so that it is translated in the appropriate cellular location.⁹⁸ 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.”⁹⁹ The '600 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.”¹⁰⁰

⁹⁶ Ex. 2199 ¶¶ 323-324.

⁹⁷ Ex. 1002 § VIII.1.

⁹⁸ Ex. 1002 ¶¶ 26-27.

⁹⁹ Ex. 1009 ¶ 61. *See also* Ex. 1009 ¶ 904 (method for making modified mRNA including 5' and 3' UTRs).

¹⁰⁰ Ex. 1001 at 42:3-5 (emphases added).

Indeed, as explained in my opening declaration with respect to claim 4, Schrum discusses several such examples of mRNA comprising UTRs.¹⁰¹ 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.

71. **Third**, Dr. Fuller asserts that I do not explain how a POSA would have at once envisaged the claimed arrangement of claim 4.¹⁰² 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.¹⁰³ 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 4.

¹⁰¹ Ex. 1002 § VIII.3.

¹⁰² Ex. 2199 ¶¶ 325-326.

¹⁰³ Ex. 1002 ¶¶ 26-27.

E. Claim 5: “The composition of claim 4, wherein the mRNA further comprises a poly(A) tail.”

72. As I explained in my opening declaration¹⁰⁴ and for the reasons explained in claims 1 and 4, Sections IV.B and IV.D, Schrum discloses this limitation. I thus disagree with Dr. Fuller’s opinions to the contrary.

73. *First*, Dr. Fuller asserts that I do not address how claims 1 and 4, from which claim 5 depends, are met.¹⁰⁵ For the reasons explained in my opening declaration,¹⁰⁶ I disagree.

74. *Second*, Dr. Fuller asserts that I do not explain how Schrum discloses every element of claim 5 as arranged in the claim.¹⁰⁷ I disagree. As explained in my opening declaration with respect to claim 1, Schrum (incorporating Geall) discloses an mRNA encoding a spike protein and encapsulated in a lipid nanoparticle.¹⁰⁸ And as further explained in my opening declaration, a POSA would have understood that mature eukaryotic mRNA transcripts contain a poly A tail that

¹⁰⁴ Ex. 1002 § VIII.4.

¹⁰⁵ Ex. 2199 ¶¶ 330-331.

¹⁰⁶ Ex. 1002 §§ VIII.1, 3-4.

¹⁰⁷ Ex. 2199 ¶¶ 332-333.

¹⁰⁸ Ex. 1002 § VIII.1.

plays a role in mRNA stability and the regulation of protein translation.¹⁰⁹ The '600 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*."¹¹⁰ Indeed, as explained in my opening declaration with respect to claim 5, Schrum discusses such examples of mRNA comprising poly(A) tails.¹¹¹ Thus, given that Schrum discloses mRNA, a POSA would have understood that the mRNA comprises a poly(A) tail as arranged in the claim.

75. **Third**, Dr. Fuller asserts that I do not explain how a POSA would have at once envisaged the claimed arrangement of claim 5.¹¹² As explained in Sections IV.B.3 and IV.D, a POSA would have at once envisaged the elements of claims 1 and 4. 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

¹⁰⁹ Ex. 1002 ¶¶ 26-27.

¹¹⁰ Ex. 1001 at 42:3-5 (emphases added).

¹¹¹ Ex. 1002 § VIII.4.

¹¹² Ex. 2199 ¶¶ 334-335.

protein would contain a poly-A tail, consistent with the the additional limitation of claim 5.

F. Claim 6: “The composition of claim 4, wherein the mRNA further comprises a 5' cap analog.”

76. As I explained in my opening declaration¹¹³ and for the reasons explained in claims 1 and 4, Sections IV.B and IV.D, Schrum discloses this limitation. I thus disagree with Dr. Fuller’s opinions to the contrary.

77. *First*, Dr. Fuller asserts that I do not address how claims 1 and 4, from which claim 6 depends, are met.¹¹⁴ For the reasons explained in my opening declaration,¹¹⁵ I disagree.

78. *Second*, Dr. Fuller asserts that I do not explain how Schrum discloses every element of claim 6 as arranged in the claim.¹¹⁶ I disagree. As explained in my opening declaration with respect to claim 1, Schrum (incorporating Geall) discloses an mRNA encoding a spike protein and encapsulated in a lipid

¹¹³ Ex. 1002 § VIII.5.

¹¹⁴ Ex. 2199 ¶¶ 339-340.

¹¹⁵ Ex. 1002 §§ VIII.1, 3, 5.

¹¹⁶ Ex. 2199 ¶¶ 341-342.

nanoparticle.¹¹⁷ And as further explained in my opening declaration, a POSA would have understood that mature eukaryotic mRNA transcripts contain a 5' cap, which stabilize mRNA and align it on the ribosome appropriately for translation.¹¹⁸ The '600 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."¹¹⁹ Indeed, as explained in my opening declaration with respect to claim 6, Schrum discusses such examples of mRNA comprising 5' cap analog.¹²⁰ 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.

79. **Third**, Dr. Fuller asserts that I do not explain how a POSA would have at once envisaged the claimed arrangement of claim 6.¹²¹ I disagree. As explained in Section IV.B.3 and IV.D., a POSA would have at once envisaged the elements of claims 1 and 4. Moreover, for the reasons explained in the paragraph above given that Schrum discloses mRNA, a POSA would have further understood that Schrum

¹¹⁷ Ex. 1002 § VIII.1.

¹¹⁸ Ex. 1002 ¶¶ 26-27.

¹¹⁹ Ex. 1001 at 42:3-5 (emphases added).

¹²⁰ Ex. 1002 § VIII.5.

¹²¹ Ex. 2199 ¶¶ 343-344.

discloses a mRNA comprising a 5' cap analog. 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 5' cap analog, consistent with the the additional limitation of claim 6.

G. Claim 8: "The composition of claim 1, wherein the mRNA comprises a chemical modification."

80. As I explained in my opening declaration¹²² 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.

81. *First*, Dr. Fuller asserts that I do not address how claim 1, from which claim 8 depends, is met.¹²³ For the reasons explained in my opening declaration,¹²⁴ I disagree.

82. *Second*, Dr. Fuller asserts that I do not explain how Schrum discloses every element of claim 8 as arranged in the claim.¹²⁵ I disagree. As explained in

¹²² Ex. 1002 § VIII.6.

¹²³ Ex. 2199 ¶¶ 348-349.

¹²⁴ Ex. 1002 §§ VIII.1, 6.

¹²⁵ Ex. 2199 ¶¶ 350-351.

my opening declaration with respect to claim 1, Section IV.B, Schrum (incorporating Geall) discloses an mRNA encoding a spike protein and encapsulated in a lipid nanoparticle, and that the mRNA may be modified.¹²⁶ And, as explained in my opening declaration with respect to claim 8, Schrum discusses examples of chemically modified mRNA resulting in successful protein expression.¹²⁷ 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 8. Moreover, the examples of the '600 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.”¹²⁸ Dr. Fuller further states that Geall reported ineffective results when using chemical modifications for self-amplifying mRNA.”¹²⁹ Irrespective of Geall’s disclosure, a POSA still would have understood that Schrum discloses that non-amplifying

¹²⁶ Ex. 1002 § VIII.1; Ex. 1009 ¶ 586.

¹²⁷ Ex. 1002 § VIII.6.

¹²⁸ Ex. 1001 at 21:6-7.

¹²⁹ Ex. 2199 ¶¶ 352-354, 357.

mRNA achieved high levels of protein expression with modified nucleotides, as explained in my opening declaration.¹³⁰

83. *Third*, Dr. Fuller asserts that I do not explain how a POSA would have at once envisaged the claimed arrangement of claim 8.¹³¹ 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 LNPs, 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 an LNP-encapsulated mRNA vaccine encoding the betacoronavirus S protein could utilize the modified mRNA Schrum exemplifies, consistent with the additional limitation of claim 8.

¹³⁰ Ex. 1002 § VIII.6.

¹³¹ Ex. 2199 ¶¶ 355-356.

H. Claim 9: “The composition of claim 8, wherein the chemical modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification.”

84. As I explained in my opening declaration¹³² and for the reasons explained in claims 1 and 8, Sections IV.B and IV.G, Schrum discloses this limitation. I thus disagree with Dr. Fuller’s opinions to the contrary.

85. *First*, Dr. Fuller asserts that I do not address how claims 1 and 8, from which claim 9 depends, are met.¹³³ For the reasons explained in my opening declaration,¹³⁴ I disagree.

86. *Second*, Dr. Fuller asserts that I do not explain how Schrum discloses every element of claim 9 as arranged in the claim.¹³⁵ As explained in my opening declaration with respect to claim 1, Schrum (incorporating Geall) discloses an mRNA encoding a spike protein and encapsulated in a lipid nanoparticle, and that the mRNA may be modified.¹³⁶ And, as explained in my opening declaration with respect to claim 8, Schrum discusses examples of modified mRNA resulting in

¹³² Ex. 1002 § VIII.7.

¹³³ Ex. 2199 ¶¶ 361-362.

¹³⁴ Ex. 1002 §§ VIII.1, 6-7.

¹³⁵ Ex. 2199 ¶¶ 363-364.

¹³⁶ Ex. 1002 § VIII.1; Ex. 1009 ¶ 586.

successful protein expression.¹³⁷ Moreover, as I explained with respect to claim 9 of my opening declaration, Schrum provides examples of successful production of protein *in vitro* and *in vivo* after administration of N1-methylpseudouridine-modified mRNA.¹³⁸ Indeed, Schrum notes that “exemplary nucleobases and nucleosides having a modified uracil include . . . N1-methyl-pseudouridine.”¹³⁹ Thus, given Schrum’s disclosure of modified mRNA for use in LNP-encapsulated vaccines, 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 9. Moreover, the examples of the ’600 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.”¹⁴⁰

¹³⁷ Ex. 1002 § VIII.6.

¹³⁸ Ex. 1002 § VIII.7.

¹³⁹ Ex. 1009 ¶ 283.

¹⁴⁰ Ex. 1001 at 21:6-7.

87. Dr. Fuller further states that Geall reported ineffective results when using chemical modifications for self-amplifying mRNA.”¹⁴¹ 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.¹⁴²

88. **Third**, Dr. Fuller asserts that I do not explain how a POSA would have at once envisaged the claimed arrangement of claim 9 from Schrum.¹⁴³ As explained in Sections IV.B.3 and IV.G, a POSA would have at once envisaged the elements of claims 1 and 8. Moreover, for the reasons explained in the paragraph above, given that Schrum discloses modified mRNA encoding a betacoronavirus S protein for use in LNP-encapsulated vaccines, 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 could contain the 1-methylpseudouridine modification Schrum exemplifies, consistent with the the additional limitation of claim 9.

¹⁴¹ Ex. 2199 ¶¶ 365, 368.

¹⁴² Ex. 1002 § VIII.6.

¹⁴³ Ex. 2199 ¶¶ 366-367.

I. Claim 10: “The composition of claim 8, wherein at least 80% of the uracil in the open reading frame has a chemical modification.”

89. As I explained in my opening declaration¹⁴⁴ and for the reasons explained in claims 1 and 8, Sections IV.B and IV.G, Schrum discloses this limitation. I thus disagree with Dr. Fuller’s opinions to the contrary.

90. **First**, Dr. Fuller asserts that I do not address how claims 1 and 8, from which claim 10 depends, are met.¹⁴⁵ For the reasons explained in my opening declaration,¹⁴⁶ I disagree.

91. **Second**, Dr. Fuller asserts that I do not explain how Schrum discloses every element of claim 10 as arranged in the claim.¹⁴⁷ As explained in my opening declaration with respect to claim 1, Schrum (incorporating Geall) discloses an mRNA encoding a spike protein and encapsulated in a lipid nanoparticle, and that the mRNA may be modified.¹⁴⁸ And, as explained in my opening declaration with respect to claim 8, Schrum discusses examples of modified mRNA resulting in

¹⁴⁴ Ex. 1002 § VIII.8.

¹⁴⁵ Ex. 2199 ¶¶ 372-373.

¹⁴⁶ Ex. 1002 § VIII.1, 6, 8.

¹⁴⁷ Ex. 2199 ¶¶ 374-375.

¹⁴⁸ Ex. 1002 § VIII.1; *see also* 1009 ¶ 586.

successful protein expression.¹⁴⁹ Moreover, as I explain with respect to claim 10 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.”¹⁵⁰ 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 10. Additionally, the examples of the ’600 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.”¹⁵¹

92. Dr. Fuller further states that Geall reported ineffective results when using chemical modifications for self-amplifying mRNA.”¹⁵² 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

¹⁴⁹ Ex. 1002 § VIII.6.

¹⁵⁰ Ex. 1002 § VIII.8.

¹⁵¹ Ex. 1001 at 21:6-7.

¹⁵² Ex. 2199 ¶ 376, 379.

nucleotides, as explained in my opening declaration.¹⁵³

93. **Third**, Dr. Fuller asserts that I do not explain how a POSA would have at once envisaged the claimed arrangement of claim 10 of from Schrum.¹⁵⁴ As explained in Section IV.B.3 and IV.G, a POSA would have at once envisaged the elements of claims 1 and 8. Moreover, for the reasons explained in the paragraph above given that Schrum discloses modified mRNA encoding a spike protein encapsulated in a lipid nanoparticle, 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 could contain modifications of at least 80% of its uracil residues, consistent with the the additional limitation of claim 10.

J. Claim 11: "The composition of claim 1, wherein the lipid nanoparticle comprises an ionizable cationic lipid, a neutral lipid, a sterol, and a PEG-modified lipid."

94. As I explained in my opening declaration¹⁵⁵ 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.

¹⁵³ Ex. 1002 § VIII.6.

¹⁵⁴ Ex. 2199 ¶¶ 377-378.

¹⁵⁵ Ex. 1002 § VIII.9.

95. **First**, Dr. Fuller asserts that I do not address how claim 1, from which claim 11 depends, is met.¹⁵⁶ For the reasons explained in my opening declaration,¹⁵⁷ 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.¹⁵⁸ I disagree. As explained in my opening declaration with respect to claim 1, Schrum discloses an mRNA encoding a spike protein and encapsulated in a lipid nanoparticle.¹⁵⁹ And as I explain with respect to claim 11 of my opening declaration, Schrum's examples with lipid nanoparticles include the claimed composition—"an ionizable cationic lipid, a neutral lipid, a sterol, and a PEG-modified lipid."¹⁶⁰

97. Thus, given that Schrum discloses mRNA encapsulated in a lipid nanoparticle, and examples of the lipid nanoparticle of the claimed composition, a POSA would have understood the mRNA to be encapsulated in a lipid nanoparticle in the claimed composition, as arranged in the claim.

¹⁵⁶ Ex. 2199 ¶¶ 383-384.

¹⁵⁷ Ex. 1002 §§ VIII.1, 9.

¹⁵⁸ Ex. 2199 ¶¶ 385-386.

¹⁵⁹ Ex. 1002 § VIII.1.

¹⁶⁰ Ex. 1002 § VIII.9.

98. **Third**, Dr. Fuller asserts that I do not explain how a POSA would have at once envisaged the claimed arrangement of claim 11.¹⁶¹ 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 encapsulated in a lipid nanoparticle, and examples of the lipid nanoparticle in the claim composition, a POSA would have further understood that Schrum discloses a mRNA encapsulated in a lipid nanoparticle of the claimed composition. Thus, a POSA would have at once envisaged that the LNP utilized in Schrum's disclosure of a LNP-encapsulated mRNA vaccine encoding a betacoronavirus S protein could comprise an ionizable cationic lipid, a neutral lipid, a sterol, and a PEG-modified lipid, consistent with the additional limitation of claim 11.

K. Claim 12: "The composition of claim 11, wherein the lipid nanoparticle comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid."

99. As I explained in my opening declaration¹⁶² and for the reasons explained in claims 1 and 11, Sections IV.B and IV.J, Schrum discloses this limitation. I thus disagree with Dr. Fuller's opinions to the contrary.

¹⁶¹ Ex. 2199 ¶¶ 387-388.

¹⁶² Ex. 1002 § VIII.10.

100. **First**, Dr. Fuller asserts that I do not address how claims 1 and 11, from which claim 12 depends, are met.¹⁶³ For the reasons explained in my opening declaration,¹⁶⁴ I disagree.

101. **Second**, Dr. Fuller asserts that I do not explain how Schrum discloses every element of claim 12 as arranged in the claim.¹⁶⁵ As explained in my opening declaration with respect to claim 1, Schrum discloses an mRNA encoding a spike protein and encapsulated in a lipid nanoparticle.¹⁶⁶ And as I explain with respect to claim 11 of my opening declaration, Schrum's examples with lipid nanoparticles include the claimed composition—"an ionizable cationic lipid, a neutral lipid, a sterol, and a PEG-modified lipid."¹⁶⁷ Moreover, as I explain with respect to claim 12 of my opening declaration, Schrum's examples with lipid nanoparticles satisfy the claimed composition and ranges."¹⁶⁸ Thus, given that Schrum discloses mRNA encapsulated in a lipid nanoparticle, and examples of the lipid nanoparticle of the

¹⁶³ Ex. 2199 ¶¶ 392-393.

¹⁶⁴ Ex. 1002 §§ VIII.1, 9-10.

¹⁶⁵ Ex. 2199 ¶¶ 394-395.

¹⁶⁶ Ex. 1002 § VIII.1

¹⁶⁷ Ex. 1002 § VIII.9.

¹⁶⁸ Ex. 1002 § VIII.10.

claimed composition and ranges, a POSA would have understood the mRNA to be encapsulated in a lipid nanoparticle in the claimed composition and ranges, as arranged in the claim.

102. **Third**, Dr. Fuller asserts that I do not explain how a POSA would have at once envisaged the claimed arrangement of claim 12.¹⁶⁹ As explained in Section IV.B.3 and IV.J, 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 mRNA encapsulated in a lipid nanoparticle, and examples of the lipid nanoparticle in the claim composition and ranges, a POSA would have further understood that Schrum discloses a mRNA encapsulated in a lipid nanoparticle of the claimed composition and ranges. Thus, a POSA would have at once envisaged that the LNP utilized in Schrum's disclosure of a LNP-encapsulated mRNA vaccine encoding a betacoronavirus S protein could comprise 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid, consistent with the additional limitation of claim 12.

L. Claim 16: "A composition, comprising: a messenger ribonucleic acid (mRNA) comprising a 5' untranslated region (UTR), an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit, a 3' UTR, and a poly(A) tail, formulated in a lipid nanoparticle that comprises 20-60% ionizable cationic lipid,

¹⁶⁹ Ex. 2199 ¶¶ 396-397.

5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.”

103. As explained in my opening declaration, Schrum discloses each limitation of claim 16.¹⁷⁰

104. Dr. Fuller does not dispute the majority of my explanation of Schrum’s disclosures. That is, Dr. Fuller does not dispute that Schrum teaches mRNA compositions encoding an immunogen (like the BetaCoV S protein), and the use of these compositions for vaccination.¹⁷¹ 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.¹⁷²

105. Instead, Dr. Fuller argues that Schrum does not disclose the immunogen

¹⁷⁰ Ex. 1002 § VIII.11.

¹⁷¹ Ex. 1002 ¶¶ 68-73; Ex. 2199 ¶ 229; 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.

¹⁷² Ex. 1002 ¶¶ 74-76; Ex. 2199 ¶ 229.

of the claims of the '600 patent—a BetaCoV S protein.¹⁷³ As explained below, I disagree.

106. Dr. Fuller further alleges that Schrum does not disclose the elements of claim 16 as they are arranged in the claim, and that a POSA would not have at once envisaged the claimed arrangement of claim 16 from Schrum.¹⁷⁴ 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 16**

107. As discussed above, the only limitation of claim 16 of the '600 patent that Dr. Fuller contends to be not disclosed by Schrum is the BetaCoV S protein antigen. 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,” 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.¹⁷⁵

**2. Schrum discloses the elements of claim 16 as they are
arranged in the claim**

¹⁷³ Ex. 2199 ¶¶ 408-409.

¹⁷⁴ Ex. 2199 ¶¶ 407-414.

¹⁷⁵ Ex. 1002 § VIII.11.

108. Dr. Fuller also asserts that Schrum does not disclose every element of claim 16 as arranged in the claim.¹⁷⁶ Contrary to Dr. Fuller's opinion, Schrum does so.

109. As explained in my opening declaration,¹⁷⁷ Schrum (incorporating Geall) discloses a vaccine made up of mRNA with a 3' and 5' UTR, and a poly(A) tail encoding an immunogen, and formulating the mRNA vaccine in a lipid nanoparticle system that encompasses the claimed composition and ranges, as arranged in the claim. In particular, building on its disclosures of mRNA vaccines encapsulated by lipid nanoparticles, Schrum 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."¹⁷⁸ A POSA would have understood that the mRNA vaccines disclosed in Schrum could be delivered using the lipid nanoparticles disclosed in the examples.

110. 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,

¹⁷⁶ Ex. 2199 ¶¶ 407-409.

¹⁷⁷ Ex. 1002 ¶¶ 68-69, 72 (citing Ex. 1009 ¶ 342).

¹⁷⁸ Ex. 1002 ¶ 94 (citing claim 12, Ex. 1009 ¶¶ 995, 999).

and a poly(A) tail.¹⁷⁹ Indeed, the '600 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.”¹⁸⁰ And, as explained in my opening declaration, Schrum discusses examples of mRNA comprising those components resulting in successful protein expression.¹⁸¹ 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 16 from Schrum.

111. Dr. Fuller writes that “a POSA would not have at once envisaged the claimed arrangement of claim 16 of the '600 patent from Schrum (including via any alleged incorporation of Geall) for at least the reasons discussed in Section X.A.3, Section X.C, Section X.D, Section X.J, and Section X.K.2.”¹⁸² In particular, Dr. Fuller refers back to her opinions relating to Schrum’s disclosure of each limitation of claim 16, as arranged therein, including the SARS-CoV S protein, the lipid nanoparticle composition and ranges, and the mRNA components.

¹⁷⁹ Ex. 1002 ¶¶ 26-27.

¹⁸⁰ Ex. 1001 at 42:3-5 (emphases added).

¹⁸¹ 1002 § VIII.11.

¹⁸² Ex. 2199 ¶ 413.

112. I disagree with her opinions in that section for the reasons discussed above in Section IV.L.2.

M. Claim 17: “The composition of claim 16, wherein the open reading frame encodes a Beta CoV S protein.”

113. As I explained in my opening declaration¹⁸³ and for the reasons explained in claim 16, Section IV.L, Schrum discloses each limitation of claim 17. In response, Dr. Fuller makes four arguments. I disagree with each.

114. *First*, Dr. Fuller asserts that Schrum does not anticipate claim 17 for the same reason that it does not anticipate claim 16.¹⁸⁴ For the reasons explained in claim 16, I disagree.¹⁸⁵

115. *Second*, Dr. Fuller asserts that Schrum does not disclose the requirement of “wherein the open reading frame encodes a BetaCoV S protein.”¹⁸⁶ For the reasons explained in claim 16, Section IV.L, I disagree with Dr. Fuller’s

¹⁸³ Ex. 1002 § VIII.12.

¹⁸⁴ Ex. 2199 ¶¶ 417-418.

¹⁸⁵ 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.

¹⁸⁶ Ex. 2199 ¶ 419.

opinion, as Schrum incorporates Geall, which expressly discloses the use of the S-protein as an immunogen for a betacoronavirus vaccine.¹⁸⁷

116. **Third**, Dr. Fuller asserts that I cannot show that Schrum discloses every element of claim 17 arranged in the same way as claim 17.¹⁸⁸ For the reasons explained with respect to claim 16, I disagree. Schrum discloses a mRNA vaccine with specific mRNA components (5' and 3' UTR, poly(A) tail) encapsulated in a lipid nanoparticle of the claimed composition and ranges, and incorporates Geall by reference, which teaches the S-protein as an immunogen for a betacoronavirus vaccine.

117. **Fourth**, Dr. Fuller asserts that a POSA would not have at once envisaged claim 17 for at least the reasons discussed regarding why Schrum does not disclose each element of claim 17 as arranged in the claim.¹⁸⁹ For the reasons explained in the paragraph above, and with respect to claim 16, I disagree.

N. Claim 20: “The composition of claim 16, wherein at least 80% of

¹⁸⁷ 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.

¹⁸⁸ Ex. 2199 ¶¶ 420-423.

¹⁸⁹ Ex. 2199 ¶ 425.

the uracil in the open reading frame has a chemical modification.”

118. As I explained in my opening declaration¹⁹⁰ and for the reasons explained in claim 16, Section IV.L, Schrum discloses this limitation. I thus disagree with Dr. Fuller’s opinions to the contrary.

119. *First*, Dr. Fuller asserts that I do not address how claim 16, from which claim 20 depends, is met.¹⁹¹ For the reasons explained in my opening declaration,¹⁹² I disagree.

120. *Second*, Dr. Fuller asserts that I do not explain how Schrum discloses every element of claim 20 as arranged in the claim.¹⁹³ As explained in my opening declaration with respect to claim 16, Section IV.L, Schrum discloses a mRNA vaccine (that may be modified) with specific mRNA components (5’ and 3’ UTR, poly(A) tail) and incorporates Geall by reference, which teaches the S-protein as an immunogen for a betacoronavirus vaccine. .¹⁹⁴ Moreover, as I explain with respect to claim 20 of my opening declaration, Schrum further explains that in the disclosed

¹⁹⁰ Ex. 1002 § VIII.13.

¹⁹¹ Ex. 2199 ¶¶ 429-430.

¹⁹² Ex. 1002 §§ VIII.11, 13.

¹⁹³ Ex. 2199 ¶¶ 431-432.

¹⁹⁴ Ex. 1002 § VIII.11.

mRNA, “at least 80%, at least 90%, or 100% of the uracil in the nucleic acid may be replaced with a modified uracil.”¹⁹⁵ Schrum further discusses examples of modified mRNA resulting in successful protein expression.¹⁹⁶ 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 20. Additionally, the examples of the '600 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.”¹⁹⁷ Dr. Fuller further states that Geall reported “ineffective results when using chemical modifications for self-amplifying mRNA.”¹⁹⁸ Irrespective of Geall’s disclosure, a POSA still would have understood that Schrum discloses that non-amplifying

¹⁹⁵ Ex. 1002 § VIII.13.

¹⁹⁶ Ex. 1002 § VIII.6.

¹⁹⁷ Ex. 1001 at 21:6-7.

¹⁹⁸ Ex. 2199 ¶¶ 433, 436.

mRNA achieved high levels of protein expression with modified nucleotides, as explained in my opening declaration.¹⁹⁹

121. *Third*, Dr. Fuller asserts that I do not explain how a POSA would have at once envisaged the claimed arrangement of claim 16.²⁰⁰ As explained in Section IV.L.3, a POSA would have at once envisaged the elements of claim 16. Moreover, for the reasons explained in the paragraph above, 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 at once envisaged that the mRNA utilized in Schrum's disclosure of a LNP-encapsulated mRNA vaccine encoding a betacoronavirus S protein could contain modifications of at least 80% of its uracil residues, consistent with the additional limitation of claim 20.

O. Claim 21: "The composition of claim 20, wherein the chemical modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification."

122. As I explained in my opening declaration²⁰¹ and for the reasons explained in claims 16 and 20, Sections IV.L and IV.N, Schrum discloses this

¹⁹⁹ Ex. 1002 § VIII.13.

²⁰⁰ Ex. 2199 ¶¶ 434-435.

²⁰¹ Ex. 1002 § VIII.14.

limitation. I thus disagree with Dr. Fuller's opinions to the contrary.

123. **First**, Dr. Fuller asserts that I do not address how claims 16 and 20, from which claim 21 depends, are met.²⁰² For the reasons explained in my opening declaration,²⁰³ I disagree.

124. **Second**, Dr. Fuller asserts that I do not explain how Schrum discloses every element of claim 21 as arranged in the claim.²⁰⁴ As explained in my opening declaration with respect to claim 16, Schrum discloses a mRNA vaccine (that may be modified) with specific mRNA components (5' and 3' UTR, poly(A) tail) and encapsulated in a lipid nanoparticle of the claimed composition and ranges and incorporates Geall by reference, which teaches the S-protein as an immunogen for a betacoronavirus vaccine.²⁰⁵ 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."²⁰⁶ Additionally, as I explained with respect to claim 21 of my

²⁰² Ex. 2199 ¶¶ 440-441.

²⁰³ Ex. 1002 §§ VIII.11, 13-14.

²⁰⁴ Ex. 2199 ¶¶ 442-443.

²⁰⁵ Ex. 1002 § VIII.11.

²⁰⁶ Ex. 1002 § VIII.13.

opening declaration, Schrum provides examples of successful production of protein *in vitro* and *in vivo* after administration of N1-methylpseudouridine-modified mRNA.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, that 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 additional limitation of claim 21. Moreover, the examples of the ’600 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

125. 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-

²⁰⁷ Ex. 1002 § VIII.14.

²⁰⁸ Ex. 1009 ¶ 283.

²⁰⁹ Ex. 1001 at 21:6-7.

²¹⁰ Ex. 2199 ¶¶ 444, 447.

amplifying mRNA achieved high levels of protein expression with modified nucleotides, as explained in my opening declaration.²¹¹

126. *Third*, Dr. Fuller asserts that I do not explain how a POSA would have at once envisaged the claimed arrangement of claim 21.²¹² As explained in Sections IV.L.3 and IV.N, a POSA would have at once envisaged the elements of claims 16 and 20. 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 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 could contain modifications of at least 80% of its uracil residues with the the 1-methylpseudouridine modification Schrum exemplifies, consistent with the the additional limitation of claim 21.

P. Claim 26: "A lipid nanoparticle, comprising: a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit; wherein the lipid nanoparticle comprises 20-60%

²¹¹ Ex. 1002 § VIII.13.

²¹² Ex. 2199 ¶¶ 445-446.

ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.”

127. As explained in my opening declaration,²¹³ Schrum discloses each limitation of claim 26.

128. Dr. Fuller does not dispute the majority of my explanation of Schrum’s disclosures. That is, Dr. Fuller does not dispute that Schrum teaches mRNA compositions encoding an immunogen (like the BetaCoV S protein), and the use of these compositions for vaccination.²¹⁴ Nor does Dr. Fuller dispute that Schrum teaches encapsulating mRNA encoding the immunogen in lipid nanoparticle systems in the claimed composition and ranges, including for mRNA vaccine applications.²¹⁵

129. Instead, Dr. Fuller argues that Schrum does not disclose the immunogen of the claims of the ’600 patent—a BetaCoV S protein.²¹⁶ As explained below, I

²¹³ Ex. 1002 § VIII.15.

²¹⁴ Ex. 1002 § VIII.15; Ex. 2199 ¶ 229; 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.

²¹⁵ Ex. 1002 § VIII.15; Ex. 2199 ¶ 229.

²¹⁶ Ex. 2199 ¶¶ 450-452.

disagree.

130. Dr. Fuller further alleges that Schrum does not disclose the elements of claim 26 as they are arranged in the claim, and that a POSA would not have at once envisaged the claimed arrangement of claim 16 from Schrum.²¹⁷ 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 26**

131. As discussed above, the only limitation of claim 26 of the '600 patent that Dr. Fuller contends to be not disclosed by Schrum is the BetaCoV S protein antigen. 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," 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.²¹⁸

**2. Schrum discloses the elements of claim 26 as they are
arranged in the claim**

²¹⁷ Ex. 2199 ¶¶ 453-464.

²¹⁸ Ex. 1002 § VIII.15.

132. Dr. Fuller also asserts that Schrum does not disclose every element of claim 26 as arranged in the claim.²¹⁹ Contrary to Dr. Fuller’s opinion, Schrum does so.

133. As explained in claim 1, Section IV.B.2, Schrum discloses a vaccine made up of mRNA encoding an immunogen, and formulating the mRNA vaccine in a lipid nanoparticle system that encompasses the claimed composition and ranges, as arranged in the claim. In particular, building on its disclosures of mRNA vaccines encapsulated by lipid nanoparticles, Schrum 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.”²²⁰ A POSA would have understood that the mRNA vaccines disclosed in Schrum could be delivered using the lipid nanoparticles disclosed in the examples.

3. A POSA would have at once envisaged the claimed arrangement of claim 26 from Schrum.

134. Dr. Fuller writes that “a POSA would not have at once envisaged the claimed arrangement of claim 26 of the ’600 patent from Schrum (including via any alleged incorporation of Geall).”²²¹

²¹⁹ Ex. 2199 ¶¶ 453-460.

²²⁰ Ex. 1002 ¶ 94 (citing claim 12, Ex. 1009 ¶¶ 995, 999).

²²¹ Ex. 2199 ¶¶ 461-464.

135. In particular, Dr. Fuller refers back to her opinions relating to Schrum's disclosure of each limitation of claim 26, 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.P.2.

V. GROUND 2: THE COMBINATION OF SCHRUM IN VIEW OF GEALL DISCLOSES ALL OF THE LIMITATIONS OF CLAIMS 1-2, 4-6, 8-12, 16-17, 20-21, AND 26

136. In Section IX of my previous declaration, I explained that each of the limitations of claims 1-2, 4-6, 8-12, 16-17, 20-21, and 26 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.²²² 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.

137. 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 Ground 1,²²³ and makes a host of additional arguments as to why a POSA would

²²² Ex. 1002 § IX.

²²³ *E.g.*, Ex. 2199 ¶¶ 467-68.

allegedly disregard and not credit the teachings of the prior art, including in Schrum and Geall.²²⁴ 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 composition, comprising: 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.”

138. 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 an LNP-encapsulated mRNA encoding an immunogen with Geall’s teaching that the immunogen of an RNA vaccine may be a betacoronavirus S protein with a reasonable expectation of doing so. 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

139. I have previously explained that Schrum in view of Geall teaches every limitation of claim 1.²²⁵

²²⁴ *E.g.*, Ex. 2199 ¶¶ 510-667.

²²⁵ Ex. 1002 § IX.1.

140. **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.²²⁶ 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.

141. **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.²²⁷ 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 vaccine²²⁸.

142. 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

²²⁶ Ex. 2199 ¶¶ 469-495.

²²⁷ Ex. 2199 ¶¶ 496-501.

²²⁸ 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.

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.²²⁹ 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.

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

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

144. 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, and would reasonably have expected to do so successfully, in view of well-known methods of synthesizing mRNA, already known in the art.²³⁰

²²⁹ Ex. 1010 at 19:26-29.

²³⁰ Ex. 1002 ¶¶ 112-116.

145. Dr. Fuller does not meaningfully dispute my analysis in her declaration.²³¹ 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.²³² 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 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.”²³³

146. 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

²³¹ Ex. 2199 ¶ 508 (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.).

²³² 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.”).

²³³ Ex. 1104 at 51:22-52:9 (emphases added).

the plain teachings of Schrum and Geall, which disclose an mRNA vaccine encoding a betacoronavirus S protein formulated in a lipid nanoparticle.²³⁴ Dr. Fuller identifies eight purported reasons as to why “a POSA would not have had a reasonable expectation of success of October 2015.”²³⁵

147. 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 (as relevant to the ’127 patent). For example, Dr. Fuller alleges that “to the extent mRNA was being considered in the clinical context, it was much more likely to be used for cancer applications than for infectious disease vaccines.”²³⁶ 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 composition of claim 1. In my opinion it would not have done so.

²³⁴ *See, e.g.*, Ex. 2199 ¶ 509.

²³⁵ Ex. 2199 ¶ 509.

²³⁶ Ex. 2199 ¶ 509.

148. 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 composition 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-encoding mRNA vaccine) in a lipid nanoparticle delivery system. Patent Owner's own scientific publications [REDACTED] further confirm my own opinions.²³⁷

²³⁷ 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

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

149. 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 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."²³⁸ 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

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.

²³⁸ 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.").

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.”²³⁹

150. 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.

151. 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.
- 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*

152. 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

²³⁹ Ex. 1104 at 212:18-213:4 (emphases added).

of efficacy concerns in general and lack of any proven clinical success.”²⁴⁰ Dr. Krause offers a similar opinion.²⁴¹ I disagree. Moreover, Dr. Fuller’s deposition testimony and Dr. Fuller’s and Krause’s cited references undermine this contention.

153. As early as 1990, scientists demonstrated that mRNA administered to mice successfully induced protein production.²⁴² 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.²⁴³ Dr. Fuller recognized 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.”²⁴⁴

154. In subsequent years, several other groups of researchers continued to research mRNA therapeutics and vaccines, making significant progress. For

²⁴⁰ Ex. 2199 ¶ 510.

²⁴¹ *E.g.*, Ex. 2200 ¶ 179.

²⁴² Ex. 1013 at 1.

²⁴³ Ex. 1014 at 1.

²⁴⁴ Ex. 1104 at 74:15-75:2.

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.”²⁴⁵

155. 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.”²⁴⁶ Notably, the lipid nanoparticles used in Novartis’s RSV vaccine study contained the same lipids, in the same ratios, as those claimed in the ’600 patent.²⁴⁷ 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.²⁴⁸

156. Based on these significant developments, Dr. Fuller agreed that “*/b/y*

²⁴⁵ Ex. 1117 at 5.

²⁴⁶ Ex. 2021 at 14604.

²⁴⁷ Ex. 2021 at 14608.

²⁴⁸ Ex. 2025 at 1210.

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.”²⁴⁹

157. 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.

158. **Petsch (Ex. 2025)**. Drs. Fuller and Krause rely on Petsch as supporting skepticism of mRNA vaccines;²⁵⁰ 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***

²⁴⁹ Ex. 1104 at 212:18-213:4 (emphases added).

²⁵⁰ *E.g.*, Ex. 2199 ¶ 530; Ex. 2200 ¶ 71.

*protective effects similar to those of a licensed influenza
vaccine in pigs.*²⁵¹

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.”²⁵² Dr. Fuller, however, omits the next sentence of Petsch, in which the authors confirm that they answer the posed question in the affirmative, writing that they have “validated the mRNA vaccine approach for a B cell-dependent mode of protection against an infectious disease, influenza.”²⁵³ [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

159. *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.

²⁵¹ Ex. 2025 at 1210 (emphases added).

²⁵² Ex. 2199 ¶ 530 (citing Ex. 2025 at 1210-1211).

²⁵³ Ex. 2025 at 1211.

²⁵⁴ [REDACTED]

[REDACTED]

[REDACTED]

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."²⁵⁵ 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 development and protein replacement therapy."²⁵⁶ 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***.²⁵⁷ 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,"²⁵⁸ contradicting Dr. Fuller's contention that the authors'

²⁵⁵ For example, Ex. 2199 ¶ 73 (quoting Ex. 2027), ¶ 513.

²⁵⁶ Ex. 2027 at 261 (emphases added).

²⁵⁷ 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)

²⁵⁸ Ex. 2027 at 267.

conclusions relied on “knowledge of the inventions described in the ’600 patent.”²⁵⁹

160. *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 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.”²⁶⁰ 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,”²⁶¹ she does not address the article’s description of other sources of mRNA funding, such as \$52 million-dollar contract from the Gates foundation.²⁶²

161. *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

²⁵⁹ Ex. 2199 ¶ 513.

²⁶⁰ Ex. 2028 at 193.

²⁶¹ Ex. 2199 ¶¶ 515 (quoting Ex. 2028 at 193).

²⁶² Ex. 2028 at 196.

still in its infancy.”²⁶³ 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 of infectious and non-infectious diseases.”²⁶⁴ 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.”²⁶⁵ Geall 2013 was published two years before the 2015 priority date of the ’600 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.”²⁶⁶

²⁶³ For example, Ex. 2199 ¶ 544 (quoting Ex. 1016 at 156).

²⁶⁴ Ex. 1016 at 3 (emphases added).

²⁶⁵ Ex. 1016 at 5.

²⁶⁶ Ex. 1016 at 2-3 (emphases added).

162. *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. 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."²⁶⁷ She further explained that "about seven or eight years ago [*i.e.*, around 2014-2015], mRNA vaccines started to take the lead."²⁶⁸

²⁶⁷ Ex. 1100 at 1.

²⁶⁸ 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 '600 patent.

163. 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 deliver mRNA into cells*.”²⁶⁹ 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.).²⁷⁰ 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.

164. ***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

²⁶⁹ Ex. 1100 at 2 (emphases added).

²⁷⁰ Ex. 1100 at 2. *See* Ex. 1104 at 88:15–89:4, 101:16–103:2.

cells and those nucleic acids could express something and
maybe provoke an immune response.²⁷¹

165. 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*

166. 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.²⁷² 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 '600 patent require no such thing.²⁷³

²⁷¹ Ex. 1104 at 212:18–213:4.

²⁷² See Ex. 2199 ¶¶ 512–26. 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.

²⁷³ Again, the claims of the '600 patent are directed only to a composition.

167. 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 2-3 years, and Phase III clinical trials can take another 2-4 years.²⁷⁴ 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.

168. 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:

169. *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.²⁷⁵ The study found that participants who received intradermal or intramuscular vaccines through a needle-

²⁷⁴ Ex. 1134 at 2-4.

²⁷⁵ Ex. 2046 at 1.

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 candidate vaccine can induce boostable functional antibodies against a viral antigen when administered with a needle-free device.”²⁷⁶

170. 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.”²⁷⁷ The ’600 patent, however, does not require the vaccine to be delivered in a syringe as opposed to a needle free injector. 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.”²⁷⁸ The study further concluded that the results of this clinical study “could lay the foundation to expand this novel vaccine platform to other infectious diseases where rapid supply is critical.”²⁷⁹ Thus, the

²⁷⁶ Ex. 2046 at 1.

²⁷⁷ Ex. 2199, ¶ 522.

²⁷⁸ Ex. 2046 at 9.

²⁷⁹ Ex. 2046 at 9.

CureVac rabies clinical trial demonstrates the field remained optimistic about mRNA vaccines.

171. *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.

172. 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.²⁸⁰ 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.

173. The specific studies cited in Dr. Fuller's declaration also do not demonstrate skepticism of mRNA vaccines. For example, Dr. Fuller cites a 2019

²⁸⁰ Ex. 1116 at 2–3.

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.”²⁸¹ 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.”²⁸² 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.”²⁸³

174. 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 ’600 patent.²⁸⁴ By contrast, the Phase I study for iHIVARNA started in June 2015, the results of which reflect optimism about mRNA vaccines.²⁸⁵ Reporting on the Phase I results, Lorna et al. observed that “iHIVARNA vaccination was feasible, harmless and well tolerated,

²⁸¹ Ex. 2199 ¶ 523 (citing Ex. 2044).

²⁸² Ex. 2044 at 2, 9.

²⁸³ Ex. 2044 at 2, 9.

²⁸⁴ Ex. 2044 at 2.

²⁸⁵ Ex. 1119 at 2534.

was able to induce moderate HIV-specific immune responses and transiently increased caHIV-RNA expression and ultrasensitive plasma viremia.”²⁸⁶ The study further noted that the Phase I study “support[s] further exploration of iHIVARNA in the currently ongoing phase II clinical trial.”²⁸⁷ 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.

175. *AGS-004 Autologous HIV-1 RNA*. Dr. Fuller also cites a different HIV therapeutic vaccine (“AGS-004”).²⁸⁸ 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 receiving ART [antiretroviral therapy]” and “a robust expansion in the numbers of HIV-specific CTL in the CD28+/CD45RA – CTL compartment.”²⁸⁹ Although “no antiviral effect was seen,” the authors still concluded that “[i]t is conceivable that

²⁸⁶ Ex. 1119 at 2542.

²⁸⁷ Ex. 1119 at 2542.

²⁸⁸ Ex. 2199 ¶ 524.

²⁸⁹ Ex. 2043 at 8.

the boosted HIV-specific CD8⁺ T-cell responses observed could translate into an important clinical effect in another setting.”²⁹⁰ 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.

176. **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.

177. 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, 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.²⁹¹ Similarly, as I

²⁹⁰ Ex. 2043 at 2, 9.

²⁹¹ Ex. 1121 at 8-9.

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.²⁹² 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*

178. Dr. Fuller asserts that by 2015, the promise of DNA, viral vector, and self-amplifying mRNA vaccines would have outweighed mRNA vaccines.²⁹³

179. 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

²⁹² Ex. 1002 ¶¶ 38-40.

²⁹³ Ex. 2199 ¶¶ 533-547, 832-835, 840-844.

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.

180. 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.

181. 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."²⁹⁴ In particular, 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

²⁹⁴ Ex. 1019 at 1319.

pandemic situation. In fact, Dr. Fuller confirmed many of these advantages of mRNA vaccines at her deposition.²⁹⁵

- 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

182. The field was particularly excited about mRNA vaccines because they did not require transporting the cargo nucleic acid across the nuclear membrane.²⁹⁶ 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 transported across the nuclear membrane.²⁹⁷ This was considered a more efficient process for expressing the antigen.²⁹⁸

²⁹⁵ Ex. 1104 at 187:11-190:3.

²⁹⁶ 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”).

²⁹⁷ Ex. 2005 at 1.

²⁹⁸ Ex. 1019 at 1; Ex. 2005 at 1.

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

183. 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.²⁹⁹

184. 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.”³⁰⁰ 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 not possible.”³⁰¹ Petsch et al. similarly recognized that “[u]nlike plasmid DNA, mRNA poses no danger of genomic integration and there remain no selective

²⁹⁹ Ex. 1130 at 2.

³⁰⁰ Ex. 1019 at 1.

³⁰¹ Ex. 2005 at 2118.

markers (e.g., antibiotic resistance genes) in the final vaccine product.”³⁰² 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.”³⁰³

185. 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”³⁰⁴ 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 suppressor genes.”³⁰⁵ Dr. Fuller also points to Yang’s results in 2005 as supporting use of DNA vaccines over mRNA vaccines.³⁰⁶ But for the reasons explained in

³⁰² Ex. 2025 at 1215.

³⁰³ Ex. 1117 at 1.

³⁰⁴ Ex. 2199 ¶ 60 (citing Ex. 2132) (emphases added).

³⁰⁵ Ex. 2132 at 781.

³⁰⁶ Ex. 2199 ¶ 844.

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.

186. 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.”³⁰⁷ 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.”³⁰⁸ 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.

187. Finally, Dr. Fuller misleadingly alleges that “DNA vaccines were considered to have several advantages *over mRNA* including safety, stability, and immunogenicity.”³⁰⁹ For that statement, however, she cites a different portion of her

³⁰⁷ Ex. 1020 at 1; Ex. 2199 ¶¶ 833-835 (citing Ex. 1020).

³⁰⁸ Ex. 2199 ¶ 833-835 (quoting Ex. 1020).

³⁰⁹ Ex. 2199 ¶ 840 (emphases added).

declaration, which discusses an article comparing DNA vaccines with *traditional* vaccines, not mRNA vaccines.³¹⁰

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

188. 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.”³¹¹ In contrast, mRNA vaccines obviate this problem, as mRNA vaccines do not use delivery 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

189. 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

³¹⁰ Ex. 2199 ¶ 840; *see also* ¶ 535–538 (citing Ex. 2132); Ex. 2132 at 781.

³¹¹ Ex. 2005 at 2118.

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.³¹²

190. 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.³¹³

³¹² Ex. 1019 at 1.

³¹³ Ex. 1138 at 5.

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

191. 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.³¹⁴ I disagree.

192. 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.³¹⁵ 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 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."³¹⁶

³¹⁴ See Ex. 2199 ¶¶ 548-620.

³¹⁵ Ex. 1002 ¶¶ 112-116.

³¹⁶ Ex. 1031 at 229.

193. 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 2015.³¹⁷ And while the claims of the '600 patent only recite a composition, Dr. Fuller appears to impose an artificial requirement that a POSA need also reasonably expect to successfully induce an immune response using such an mRNA vaccine.³¹⁸ Even were Dr. Fuller's view of the '600 patent's claims correct, however, a POSA would have reasonably expected to induce an immune response using an mRNA vaccine encoding for a betacoronavirus S protein, as I have previously explained.³¹⁹

194. 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.³²⁰ 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.

³¹⁷ Ex. 1002 ¶ 115.

³¹⁸ *E.g.*, Ex. 2199 ¶ 562.

³¹⁹ *E.g.*, Ex. 1002 ¶ 110; *see also* Ex. 1002 § IX.1.

³²⁰ Ex. 2199 ¶ 572.

195. 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

196. Dr. Fuller writes in her declaration, “In 2015, the field was exploring antigens other than the spike protein for coronavirus vaccines.”³²¹ 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 composition 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.³²² Regardless, Dr. Fuller fails to

³²¹ Ex. 2199 ¶ 607.

³²² 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”

197. 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].”³²³ 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.³²⁴ 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.”³²⁵

³²³ Ex. 1132 at 9804 (emphases added).

³²⁴ Ex. 1132 at 9808.

³²⁵ Ex. 1132 at 9808.

198. 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,”³²⁶ 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.”³²⁷ Based on those results, the authors concluded that the N, M, and E proteins “thus . . . were not significant protective antigens.”³²⁸

199. 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

³²⁶ 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.

³²⁷ Ex. 1132 at 9808-9809.

³²⁸ Ex. 1132 at 9808.

due and had shown its efficacy at producing an immunostimulatory response.³²⁹ 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.”³³⁰ 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.”³³¹

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

200. 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.

201. 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:

³²⁹ See Ex. 1002 ¶ 47, 110, 112, 143–146, 183–184.

³³⁰ Ex. 1031 at 227.

³³¹ 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.³³²

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.³³³

202. 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

³³² Ex. 1104 at 40:13-17.

³³³ 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.³³⁴

³³⁴ 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

203. 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.”³³⁵

204. 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.”³³⁶ 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.”³³⁷ Yang’s demonstration of effective immunostimulatory results *in vivo* following administration of a nucleic acid vaccine encoding the SARS-CoV spike protein

³³⁵ Ex. 2137 at 797.

³³⁶ Ex. 1011 at 561.

³³⁷ Ex. 1011 at 561.

would have confirmed for a POSA that the S-protein was the leading antigen candidate for a betacoronavirus vaccine.³³⁸

205. 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.”³³⁹ 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.³⁴⁰ Specifically, Altmeyer disclosed that a RNA vaccine encoding the SARS-CoV spike protein induces “[s]pike-specific antibodies” and “SARS CoV-specific antibodies.”³⁴¹

206. 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

³³⁸ Ex. 1002 ¶¶ 143–146.

³³⁹ Ex. 2138.

³⁴⁰ See Ex. 1002 ¶¶ 64–66, 183–184.

³⁴¹ Ex. 1012, ¶ 116.

reduced titers of SARS-CoV in the upper and lower respiratory tracts of mice after challenge.”³⁴²

207. Researchers had also found by 2015 that the S-protein of the MERS coronavirus—another betacoronavirus—was also the “primary target” for vaccine development.³⁴³ 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.”³⁴⁴ 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.”³⁴⁵ 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.”³⁴⁶

³⁴² Ex. 1115 at 6641.

³⁴³ Ex. 1101 at 1.

³⁴⁴ Ex. 1101 at 1.

³⁴⁵ Ex. 1109 at 11950.

³⁴⁶ Ex. 1101 at 7.

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

208. 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.³⁴⁷ 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).”³⁴⁸

209. 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.

210. **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:

³⁴⁷ E.g., Ex. 2199 ¶ 548.

³⁴⁸ Ex. 2199 ¶ 77.

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.*³⁴⁹

Dr. Fuller further confirmed that these different vaccine platforms using a betacoronavirus S protein immunogen all induced an immune response. In fact, she testified that “pretty much every type out there” of SARS-CoV vaccines using the spike proteins induced an immune response.³⁵⁰

211. **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

³⁴⁹ Ex. 1104 at 61:12-62:4 (emphases added).

³⁵⁰ Ex. 1104 at 65:15-20.

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?

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.³⁵¹

212. 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].”³⁵²

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

³⁵¹ Ex. 1101 at 40:10-43:14.

³⁵² Ex. 2199 ¶ 548 (quoting Paper No. 19 (Institution Decision), 53).

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*

214. 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.³⁵³ Dr. Krause similarly contends that a POSA would have been skeptical of using an S protein immunogen because of concerns with vaccine-associated enhanced disease.³⁵⁴ I disagree.

215. **First**, disease enhancement is not a phenomenon unique to betacoronavirus vaccines using an S-protein antigen. Disease enhancement is a

³⁵³ Ex. 2199 ¶ 577.

³⁵⁴ Ex. 2200 ¶¶ 187-191.

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.³⁵⁵ 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.³⁵⁶ If a POSA were dissuaded from designing vaccines

³⁵⁵ 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.”).

³⁵⁶ *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 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]

because of the possibility of disease enhancement, then vaccine development would fully halt.³⁵⁷

216. 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 enhancement of COVID-19 vaccine candidates.³⁵⁸ 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.³⁵⁹ Dr. Fuller also points to the fact that Pfizer and BioNTech

[REDACTED]
[REDACTED]

³⁵⁷ *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[.]”).

³⁵⁸ *See, e.g.*, Ex. 2199 ¶ 599 (citing Ex. 2104); Ex. 2200 ¶¶ 140–141.

³⁵⁹ Ex. 2104 at 8–9.

conducted a preclinical study of their COVID vaccine candidate to demonstrate the lack of disease enhancement.³⁶⁰ 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.

217. *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* 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.”³⁶¹

³⁶⁰ Ex. 2199 ¶ 604.

³⁶¹ Ex. 2199 ¶ 126. [REDACTED]

[REDACTED]

218. 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 of SARS-CoV.”³⁶² 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.”³⁶³ 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

[REDACTED]
[REDACTED]

³⁶² 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.”).

³⁶³ Ex. 1104 at 41:20-42:3.

“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.”³⁶⁴ 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.

219. 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.”³⁶⁵ 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.”³⁶⁶

220. 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.”³⁶⁷ To the contrary, a POSA would have

³⁶⁴ Ex. 1140 at 2359.

³⁶⁵ Ex. 2199 ¶ 579.

³⁶⁶ Ex. 1104 at 252:2-253:1.

³⁶⁷ Ex. 1104 at 253:6-9.

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.³⁶⁸ A POSA would have understood that IFN- γ is a cytokine that is primarily produced by Th1 cells, and thus the results 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.”³⁶⁹ Thus, Dr. Fuller’s statements are thus unsupported by the scientific literature.

221. *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),³⁷⁰ that statement is counterbalanced by the statement that the “full-length S protein of

³⁶⁸ Ex. 1314 at 1211.

³⁶⁹ Ex. 1315 at 2.

³⁷⁰ Ex. 1031 at 229-30.

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.”³⁷¹

222. 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).”³⁷²

223. 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.³⁷³ 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

³⁷¹ Ex. 1031 at 229.

³⁷² 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).”).

³⁷³ See Ex. 2199 ¶ 589, Ex. 2200 ¶ 188 (citing Ex. 2030).

awareness of Jaume, which was published in 2011, did not dissuade them from pursuing S protein based vaccines before the priority date.

224. As an initial matter, a POSA in 2015 would not have concluded that Jaume 2011 demonstrated that its vaccine candidates necessarily would have caused 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.³⁷⁴ The mice received two doses of the vaccine alongside an Alum adjuvant.³⁷⁵ 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.³⁷⁶

225. Instead, Jaume collected serum samples from each group of mice after the immunization, pooled the samples, and heat inactivated them to create antibody

³⁷⁴ Ex. 2030 at 10583-10584, 10589-10590.

³⁷⁵ Ex. 2030 at 10583.

³⁷⁶ 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)).

sera for use in further studies.³⁷⁷ 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 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.³⁷⁸

³⁷⁷ Ex. 2030 at 10583.

³⁷⁸ Ex. 2200 ¶ 161.

226. 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 after somebody’s been vaccinated and then later infected with the virus.”³⁷⁹ 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.³⁸⁰

³⁷⁹ Ex. 1105 at 68:19–21 (emphasis added).

³⁸⁰ Ex. 2030 at 10586-87.

227. 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 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.”³⁸¹ 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.”³⁸²

228. 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

³⁸¹ Ex. 2030 at 10595.

³⁸² Ex. 2030 at 10595 (emphasis added).

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 humans. However, the current absence of suitable preclinical models ***recommends the development of an MVA vaccine delivering MERS-CoV S.***³⁸³

229. Drs. Fuller and Krause also cite the work of Vennema and colleagues in their opinions regarding ADE.³⁸⁴ Vennema describes the observation of enhanced disease after administration of a feline infectious peritonitis virus (“FIPV”) S protein viral vector vaccine.³⁸⁵ 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

³⁸³ Ex. 1109 at 11953 (emphases added).

³⁸⁴ Ex. 2199 ¶¶ 585–586; Ex. 2200 ¶ 190.

³⁸⁵ Ex. 2029 at 1407.

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 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).]³⁸⁶

230. 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.”³⁸⁷

231. 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

³⁸⁶ Ex. 1132 at 9809 (emphases added).

³⁸⁷ Ex. 1109 at 11953.

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-CoV challenge and do not enhance infection* in this animal model.”³⁸⁸

232. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

³⁸⁸ Ex. 1011 at 563 (emphases added).

³⁸⁹ [REDACTED].

233. 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 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."³⁹⁰ 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*."³⁹¹ 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."³⁹² Far from teaching away from the use of a full-length S protein, these statements reflect the authors' uncertainty that the unwelcome

³⁹⁰ Ex. 2199 ¶ 593; *see also* ¶¶ 591–592.

³⁹¹ Ex. 2137 at 797 (emphases added).

³⁹² Ex 2137 at 800–801.

immunogenicity was caused by the use of the full-length S protein. Thus, a POSA 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.

234. Dr. Fuller also assumes from the fact that Martin and colleagues used a truncated S protein vaccine that they were concerned with disease enhancement.³⁹³ 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.³⁹⁴

235. 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."³⁹⁵ 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.

³⁹³ Ex. 2199 ¶¶ 594, 645.

³⁹⁴ *See supra* § V.A.2.b.3.

³⁹⁵ Ex. 2199 ¶ 589.

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

236. Applying her interpretation that “S protein” in the claims of the ’600 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.³⁹⁶ As discussed earlier in this declaration, I disagree that the specification of the ’600 patent supports interpreting “S protein” as meaning only “full-length spike protein.”³⁹⁷ 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.

237. **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.³⁹⁸ 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

³⁹⁶ See, e.g., Ex. 2199 ¶ 595.

³⁹⁷ *Supra* § III.2.

³⁹⁸ 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.

238. **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."³⁹⁹ 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.⁴⁰⁰

239. **Third**, it was known by October 2015 that full-length betacoronavirus S protein vaccines induced stronger antibody responses—a major goal of vaccine administration—than truncated S protein-based vaccines. In July 2015, scientists

³⁹⁹ Ex. 1031 at 229.

⁴⁰⁰ Ex. 1104 at 71:4-10.

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.”⁴⁰¹ 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.”⁴⁰²

240. 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 S protein will have more epitopes, neutralizing antibody*

⁴⁰¹ Ex. 1101 at 2.

⁴⁰² Ex. 1101 at 7.

*epitopes*⁴⁰³ *to target.*⁴⁰⁴

241. 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."⁴⁰⁵ 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[] higher antibody titers than the truncated version.***"⁴⁰⁶ Wang's teachings, as well as

⁴⁰³ While Dr. Fuller contends that a POSA would avoid the full-length spike protein due to concerns with enhanced disease (*e.g.*, Ex. 2199 ¶ 583), 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.)

⁴⁰⁴ Ex. 1104 at 260:9-15 (emphases added).

⁴⁰⁵ Ex. 2199 ¶ 563.

⁴⁰⁶ Ex. 1104 at 260:9-15 (emphases added).

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.

242. 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.⁴⁰⁷ 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."⁴⁰⁸ So, a POSA would recognize that where expression of the full-length betacoronavirus S protein achieved by a nucleic acid vaccine induced a stronger antibody response, then

⁴⁰⁷ 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.").

⁴⁰⁸ Ex. 1104 at 51:22-53:9.

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.

243. **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.⁴⁰⁹ 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.⁴¹⁰ 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.”⁴¹¹

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

244. Dr. Fuller asserts that a POSA would have preferred delivery options

⁴⁰⁹ Ex. 2199 ¶¶ 573-576; Ex. 2200 ¶ 192.

⁴¹⁰ See generally Ex. 1101.

⁴¹¹ Ex. 1104 at 78:5-10.

other than lipid nanoparticles.⁴¹² 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

245. Scientists have long known that naked (*i.e.*, unformulated) mRNA rapidly degrades in the body upon administration.⁴¹³ 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 long since turned to formulating mRNA in delivery vehicles (such as lipid nanoparticles, for instance). Dr. Fuller agreed at deposition; she testified:

⁴¹² Ex. 2199 ¶¶ 93-103, 621.

⁴¹³ *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.”).

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.*⁴¹⁴

246. 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."⁴¹⁵ 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.⁴¹⁶

247. In its examples, Schrum further demonstrates the use of lipid nanoparticles to improve protein expression. In Example 16, for instance, modified

⁴¹⁴ Ex. 1104 at 192:4-11 (emphases added).

⁴¹⁵ Ex. 1009 ¶ 406.

⁴¹⁶ Ex. 2199 ¶ 621 ("[D]elivery carrie[rs] may also be detrimental if the carrier impacts translation of the mRNA.").

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 ’600 patent (50:10:38.5:1.5 (DLin-KC2-DMA:DSPC:Cholesterol PEG-c-DOMG)).⁴¹⁷ 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

G-CSF Protein Expression			
Dose (ug)	Conc (ng/ml)	Dilution Factor	Sample Volume
1	17.73	20x	5 ul
10	1204.82	2500x	0.04 ul
100	4722.20	2500x	0.04 ul

TABLE 29

Factor IX Protein Expression			
Dose (ug)	Conc (ng/ml)	Dilution Factor	Sample Volume
1	36.05	10x	5 ul
10	383.04	10x	5 ul
100*	3247.75	50x	1 ul
100*	11177.20	250x	0.2 ul

248. 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 protein production compared to” administration of mRNA using other lipid-based

⁴¹⁷ Ex. 1009 ¶¶ 995-998 (Example 16).

delivery vehicles.⁴¹⁸ 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.

249. 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*

250. As I have previously explained, Schrum itself teaches a POSA to deliver immunogen-encoding mRNA in a lipid nanoparticle system.⁴¹⁹ 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.

251. 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]."⁴²⁰ Comparing the performance of self-amplifying mRNA vaccines encoding for the respiratory syncytial virus

⁴¹⁸ Ex. 1009 ¶ 997.

⁴¹⁹ Ex. 1009 ¶ 397.

⁴²⁰ Ex. 2021 at 14604.

(“RSV”)—also an infectious disease like SARS-CoV—fusion (“F”) protein⁴²¹ 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)].”⁴²² 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.⁴²³

252. In their 2012 article, Geall et al. explained that the improved immunogenicity resulted from greater protection of the mRNA payload, as well as

⁴²¹ Like the betacoronavirus S protein, the RSV F protein is a surface protein responsible for viral mediation and entry. *E.g.*, Ex. 1001 at 30:60-67.

⁴²² Ex. 2021 at 14606 (brackets in original).

⁴²³ 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].”).

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.”⁴²⁴ Further, “[e]ncapsulation [of RNA into lipid nanoparticles] was also required for efficient delivery of functional RNA into muscle.”⁴²⁵

253. 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.⁴²⁶ 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 vehicle.”⁴²⁷ 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

⁴²⁴ Ex. 2021 at 14605.

⁴²⁵ Ex. 2021 at 14605.

⁴²⁶ Ex. 1104 at 114:6-12.

⁴²⁷ Ex. 1104 at 192:4-11.

lipid nanoparticle system for immunogen-encoding, non-replicating mRNA vaccines (as in Ex. 2021) to achieve similar benefits.

254. 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.”⁴²⁸

255. In her declaration, though, Dr. Fuller attempts to dismiss Geall et al.’s 2012 publication as not relevant to an mRNA vaccine.⁴²⁹ 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 only the antigen.⁴³⁰ The terminology of non-amplifying mRNA (NRM), also known

⁴²⁸ Ex. 2049 at 2.

⁴²⁹ *E.g.*, Ex. 2199 ¶ 633.

⁴³⁰ 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).

as conventional mRNA vaccines, and self-amplifying mRNA (SAM) vaccines, also known as replicons, is commonly used in the scientific literature.

256. 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 '600 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."⁴³¹ The same paper described self-amplifying mRNA as "very large-sized mRNAs."⁴³²

257. 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. 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

⁴³¹ Ex. 1118 at 1321.

⁴³² Ex. 1118 at 1321.

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.⁴³³ 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.

258. 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.

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

 For example, an article authored by several Patent Owner scientists describes how “mRNA vaccines are

⁴³³ Ex. 1004 ¶ 35.

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.”⁴³⁴ 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.”⁴³⁵

260. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

⁴³⁴ Ex. 1108 at 2635.

⁴³⁵ Ex. 1108 at 2635.

[REDACTED]

261. In her declaration, Dr. Fuller identifies purported structural and functional differences between self-amplifying mRNA and non-amplifying mRNA.⁴³⁸ 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.

262. 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-

436 [REDACTED]

437 [REDACTED]

⁴³⁸ Ex. 2199 ¶¶ 477, 483-484.

amplifying mRNA.⁴³⁹ 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.”⁴⁴⁰ 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.”⁴⁴¹ 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]

d. [REDACTED]

⁴³⁹ Ex. 2199 ¶¶ 553-557.

⁴⁴⁰ Ex. 2005 at 2124.

⁴⁴¹ Ex. 2005 at 2124.

⁴⁴² [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

263. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

264. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

443 [REDACTED]

[REDACTED]

[REDACTED]

444 [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

265. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

266. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

267. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

268. [REDACTED]

[REDACTED]

[REDACTED]

269. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

270. [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]

271. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

272. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

b) Scientific Literature Published by Patent
Owner's Scientists

[REDACTED]

[REDACTED]

[REDACTED]

273. [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 '600 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.⁴⁵⁸ 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 (SAM) vaccine platform for pre-pandemic influenza just eight days after release of the viral gene sequence."⁴⁵⁹

274. 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:

⁴⁵⁸ Ex. 1108 at 2635 (emphases added).

⁴⁵⁹ Ex. 1108 at 2635.

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.⁴⁶⁰

275. 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 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"⁴⁶¹ Bahl et al. further notes that "one of

⁴⁶⁰ Ex. 1118 at 1316-17.

⁴⁶¹ Ex. 1118 at 1321.

the major limitations with other nucleic acid-based technologies, such as plasmid DNA, has been translation to higher-order species, such as nonhuman primates.”⁴⁶²

2)

276.

277.

⁴⁶² Ex. 1118 at 1320.

⁴⁶³ *See, e.g.*, Ex. 1132 at 9808; *supra* § V.A.2.b.

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

[REDACTED]
[REDACTED]
[REDACTED]

278. [REDACTED]

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

[REDACTED]

[REDACTED].

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[illegible]

279. [REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

280. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

281. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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

282. 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:

⁴⁶⁹ Ex. 2200 ¶ 129 (emphases added).

[REDACTED]

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.*⁴⁷⁰

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

283. [REDACTED]

[REDACTED]

[REDACTED]

⁴⁷⁰ Ex. 2049 at 2 (emphases added).

[REDACTED]

284. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

285. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

* * *

286. 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 composition of claim 1.

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

287. As I explained in my opening declaration⁴⁷⁸ 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.

288. **First**, Dr. Fuller incorporates the arguments made with respect to claim 1, Section V.A.⁴⁷⁹ For the reasons explained in claim 1, I disagree.

289. **Second**, Dr. Fuller asserts that Schrum in view of Geall does not

⁴⁷⁷ *Supra* § V.A.2.b.

⁴⁷⁸ Ex. 1002 § IX.2.

⁴⁷⁹ Ex. 2199 ¶ 671.

disclose an “open reading frame encodes a BetaCoV S protein.”⁴⁸⁰ For the reasons explained in claim 1, Section V.A, I disagree.⁴⁸¹

290. *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 2.⁴⁸² As I explained in my opening declaration⁴⁸³ and for the reasons explained with respect to claim 1, 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.”⁴⁸⁴ 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

⁴⁸⁰ Ex. 2199 ¶¶ 672-673.

⁴⁸¹ 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.

⁴⁸² Ex. 2199 ¶¶ 674-679.

⁴⁸³ Ex. 1002 § IX.2.

⁴⁸⁴ Ex. 2199 ¶ 679.

size of the spike protein.⁴⁸⁵

C. Claim 4: “The composition of claim 1, wherein the mRNA further comprising a 5' untranslated region (UTR) and a 3' UTR.”

291. As I explained in my opening declaration⁴⁸⁶ and for the reasons explained in claim 1, Section V.A., Schrum discloses this limitation.

292. *First*, Dr. Fuller asserts that I do not address how claim 1, from which claim 4 depends, is met.⁴⁸⁷ For the reasons explained in my opening declaration,⁴⁸⁸ I disagree.

293. *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 4.⁴⁸⁹ I disagree. As explained in my opening declaration with respect to claim 1, Schrum in combination with Geall discloses an mRNA encoding a spike protein and encapsulated in a lipid nanoparticle.⁴⁹⁰ And as further

⁴⁸⁵ Ex. 2021 at 14604.

⁴⁸⁶ Ex. 1002 § IX.3.

⁴⁸⁷ Ex. 2199 ¶¶ 697-698.

⁴⁸⁸ Ex. 1002 §§ IX.1, 3.

⁴⁸⁹ Ex. 2199 ¶¶ 699-700.

⁴⁹⁰ Ex. 1002 § IX.1.

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.⁴⁹¹ 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.”⁴⁹² The ’600 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.”⁴⁹³ Indeed, as explained in my opening declaration with respect to claim 4, Schrum discusses such examples of mRNA comprising UTRs.⁴⁹⁴ A POSA would thus have 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.

D. Claim 5: “The composition of claim 4, wherein the mRNA further

⁴⁹¹ Ex. 1002 ¶¶ 26-27.

⁴⁹² Ex. 1009 ¶ 61. *See also* Ex. 1009 ¶ 904 (method for making modified mRNA including 5’ and 3’ UTRs).

⁴⁹³ Ex. 1001 at 42:3-5 (emphases added).

⁴⁹⁴ Ex. § IX.3.

comprises a poly(A) tail.”

294. As I explained in my opening declaration⁴⁹⁵ and for the reasons explained in claims 1 and 4, Sections V.A. and V.C, Schrum discloses this limitation.

295. *First*, Dr. Fuller asserts that I do not address how claims 1 and 4, from which claim 5 depends, are met.⁴⁹⁶ For the reasons explained in my opening declaration,⁴⁹⁷ 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 5.⁴⁹⁸ As explained in my opening declaration with respect to claim 1, Schrum in combination with Geall discloses an mRNA encoding a spike protein and encapsulated in a lipid nanoparticle.⁴⁹⁹ 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

⁴⁹⁵ Ex. 1002 § IX.4.

⁴⁹⁶ Ex. 2199 ¶¶ 690-691.

⁴⁹⁷ Ex. 1002 §§ IX.1, 3-4.

⁴⁹⁸ Ex. 2199 ¶¶ 692-693.

⁴⁹⁹ Ex. 1002 § IX.1.

regulation of protein translation.⁵⁰⁰ In fact, the '600 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.*”⁵⁰¹ Moreover, as explained in my opening declaration with respect to claim 5, Schrum discusses such examples of mRNA comprising a poly(A) tail.⁵⁰² 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.

E. Claim 6: “The composition of claim 4, wherein the mRNA further comprises a 5’ cap analog.”

297. As I explained in my opening declaration⁵⁰³ and for the reasons explained in claims 1 and 4, Sections V.A. and V.C, Schrum discloses this limitation.

⁵⁰⁰ Ex. 1002 ¶¶ 26-27.

⁵⁰¹ Ex. 1001 at 42:3-5 (emphases added).

⁵⁰² Ex. 1002 § IX.4

⁵⁰³ Ex. 1002 § IX.5.

298. **First**, Dr. Fuller asserts that I do not address how claims 1 and 4, from which claim 6 depends, are met.⁵⁰⁴ For the reasons explained in my opening declaration,⁵⁰⁵ 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 6.⁵⁰⁶ As explained in my opening declaration with respect to claim 1, Schrum in combination with Geall discloses an mRNA encoding a spike protein and encapsulated in a lipid nanoparticle.⁵⁰⁷ And as further explained in my opening declaration, a POSA would have understood that mature eukaryotic mRNA transcripts contain a 5' cap, which stabilize mRNA and align it on the ribosome appropriately for translation.⁵⁰⁸ In fact, the '600 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.”⁵⁰⁹

⁵⁰⁴ Ex. 2199 ¶¶ 697-698.

⁵⁰⁵ Ex. 1002 § IX.1, 3, 5.

⁵⁰⁶ Ex. 2199 ¶¶ 699-700.

⁵⁰⁷ Ex. 1002 § IX.1.

⁵⁰⁸ Ex. 1002 ¶¶ 26-27.

⁵⁰⁹ Ex. 1001 at 42:3-5 (emphases added).

Moreover, as explained in my opening declaration with respect to claim 6, Schrum discusses such examples of mRNA comprising a 5' cap analog.⁵¹⁰ 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.

F. Claim 8: “The composition of claim 1, wherein the mRNA comprises a chemical modification.”

300. As I explained in my opening declaration⁵¹¹ 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 8 depends, is met.⁵¹² For the reasons explained in my opening declaration,⁵¹³ 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

⁵¹⁰ Ex. 1002 § IX.5.

⁵¹¹ Ex. 1002 § IX.6.

⁵¹² Ex. 2199 ¶¶ 704-705.

⁵¹³ Ex. 1002 §§ IX.1, 6.

success to arrive at claim 8.⁵¹⁴ As explained in my opening declaration with respect to claim 1, Schrum in combination with Geall discloses an mRNA encoding a spike protein and encapsulated in a lipid nanoparticle, and that the mRNA can be modified.⁵¹⁵ In fact, Schrum summarizes that its disclosure provides “formulation compositions comprising *modified nucleic acid molecules* which may encode a protein,” such as an immunogen.⁵¹⁶ Moreover, as explained in my opening declaration with respect to claim 8, Schrum discusses examples of modified mRNA resulting in successful protein expression.⁵¹⁷ Thus, given that Schrum discloses modified mRNA, and examples of modified mRNA resulting in successful protein expression, a POSA would have been motivated to use the mRNA with such chemical modifications to express the S-protein with a reasonable expectation of success.

303. *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

⁵¹⁴ Ex. 2199 ¶¶ 706-707.

⁵¹⁵ Ex. 1002 § IX.1.

⁵¹⁶ Ex. 1009 ¶ 4 (emphases added).

⁵¹⁷ Ex. 1002 § IX.6

nucleosides for therapeutic applications of mRNA—not for mRNA vaccines.”⁵¹⁸

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.”⁵¹⁹ 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 modified mRNA as a “promising tool for both gene replacement and *vaccination*.”⁵²⁰

304. Dr. Fuller also cites several articles to argue that there was skepticism regarding modified mRNA for vaccines.⁵²¹ 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

⁵¹⁸ Ex. 2199 ¶ 710.

⁵¹⁹ Ex. 2199 ¶ 713 (quoting Ex. 2118 at 619).

⁵²⁰ Ex. 1022 at 1 (emphasis added). In their 2008 article, Drs. Karikó and Weissman contemplate the coadministration of adjuvant, but the claims of the ’600 patent do not exclude the use of such an adjuvant.

⁵²¹ Ex. 2199 ¶¶ 711-712.

reducing the need for adjuvants.”⁵²² 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.”⁵²³

305. 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 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*.”⁵²⁴ 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

⁵²² Ex. 2199 ¶ 711 (quoting Ex. 2025 at 1215); Fuller contends that the citation to Petsch in the regulatory section does not provide evidence that the field viewed mRNA as promising. For the reasons explained in Section V.A.2.d.1.a, I disagree.

⁵²³ Ex. 2199 ¶ 712 (quoting Ex. 1019 at 1323).

⁵²⁴ Ex. 1009 ¶ 341 (emphases added).

pathways.”⁵²⁵ 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 ’600 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.

306. **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 modification, and (2) Geall’s reported ineffective results when using saRNA with chemical modifications⁵²⁶ 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.⁵²⁷ Moreover, the examples of the ’600 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

⁵²⁵ Ex. 1009 ¶¶ 341-342.

⁵²⁶ Ex. 2199 ¶¶ 714-718.

⁵²⁷ Ex. 1002 § IX.6.

useful according to the invention.”⁵²⁸ 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**.”⁵²⁹ If Dr. Fuller’s argument on that point were credited (and it should not be), 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.

G. Claim 9: “The composition of claim 8, wherein the chemical modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification.”

307. As I explained in my opening declaration⁵³⁰ and for the reasons explained in claims 1 and 8, Sections V.A. and V.F, Schrum discloses this limitation.

308. *First*, Dr. Fuller asserts that I do not address how claims 1 and 8, from which claim 9 depends, are met.⁵³¹ For the reasons explained in my opening declaration,⁵³² I disagree.

⁵²⁸ Ex. 1001 at 21:6-7.

⁵²⁹ Ex. 2199 ¶ 200.

⁵³⁰ Ex. 1002 § IX.7.

⁵³¹ Ex. 2199 ¶¶ 722-723.

⁵³² Ex. 1002 §§ IX.1, 6-7.

309. **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 9.⁵³³ As explained in my opening declaration with respect to claim 1, Schrum in combination with Geall discloses an mRNA encoding a spike protein and encapsulated in a lipid nanoparticle, and that the mRNA can be modified.⁵³⁴ Moreover, as explained in my opening declaration with respect to claim 8, Schrum discusses examples of modified mRNA resulting in successful protein expression.⁵³⁵ And as I explain with respect to claim 9 of my opening declaration, Schrum provides examples of successful production of protein *in vitro* and *in vivo* after administration of N1-methylpseudouridine-modified mRNA.⁵³⁶ Indeed, Schrum notes that “exemplary nucleobases and nucleosides having a modified uracil include . . . 1-methyl-pseudouridine.”⁵³⁷ 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

⁵³³ Ex. 2199 ¶¶ 724-727.

⁵³⁴ Ex. 1002 § IX.1.

⁵³⁵ Ex. 1002 § IX.6.

⁵³⁶ Ex. 1002 § IX.7.

⁵³⁷ Ex. 1009 ¶ 283.

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.

310. 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.⁵³⁸ For the reasons explained in Section V.F, I disagree.

H. Claim 10: “The composition of claim 8, wherein at least 80% of the uracil in the open reading frame has a chemical modification.”

311. As I explained in my opening declaration⁵³⁹ and for the reasons explained in claims 1 and 8, Sections V.A. and V.F, Schrum discloses this limitation.

312. **First**, Dr. Fuller asserts that I do not address how claims 1 and 8, from which claim 10 depends, are met.⁵⁴⁰ For the reasons explained in my opening

⁵³⁸ Ex. 2199 ¶¶ 725-727.

⁵³⁹ Ex. 1002 § IX.8.

⁵⁴⁰ Ex. 2199 ¶¶ 731-732.

declaration,⁵⁴¹ I disagree.

313. **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 10.⁵⁴² As explained in my opening declaration with respect to claim 1, Schrum in combination with Geall discloses an mRNA encoding a spike protein and encapsulated in a lipid nanoparticle, and that the mRNA can be modified.⁵⁴³ Moreover, as explained in my opening declaration with respect to claim 8, Schrum discusses examples of modified mRNA resulting in successful protein expression.⁵⁴⁴ And as I explain with respect to claim 10 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.”⁵⁴⁵ 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 been motivated to use the

⁵⁴¹ Ex. 1002 §§ IX.1, 6, 8.

⁵⁴² Ex. 2199 ¶¶ 733-734.

⁵⁴³ Ex. 1002 § IX.1.

⁵⁴⁴ Ex. 1002 § IX.6.

⁵⁴⁵ Ex. 1002 § IX.8.

mRNA with at least 80% modification of a uracil to express the S-protein with a reasonable expectation of success.

314. 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.⁵⁴⁶ For the reasons explained in Sections V.F, I disagree.

I. Claim 11: “The composition of claim 1, wherein the lipid nanoparticle comprises an ionizable cationic lipid, a neutral lipid, a sterol, and a PEG-modified lipid.”

315. As I explained in my opening declaration⁵⁴⁷ and for the reasons explained in claim 1, Section V.A, Schrum discloses this limitation.

316. **First**, Dr. Fuller asserts that I do not address how claim 1, from which claim 11 depends, is met.⁵⁴⁸ For the reasons explained in my opening declaration,⁵⁴⁹ I disagree.

⁵⁴⁶ Ex. 2199 ¶¶ 735-737.

⁵⁴⁷ Ex. 1002 § IX.9.

⁵⁴⁸ Ex. 2199 ¶¶ 741-742.

⁵⁴⁹ Ex. 1002 §§ IX.1, 9.

317. ***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 11.⁵⁵⁰ As explained in my opening declaration with respect to claim 1, Schrum in combination with Geall discloses an mRNA encoding a spike protein and encapsulated in a lipid nanoparticle, and that the mRNA can be modified.⁵⁵¹ And as I explain in my opening declaration with respect to claim 11, Schrum's examples with lipid nanoparticles include the claimed composition—an ionizable cationic lipid, a neutral lipid, a sterol, and a PEG-modified lipid.⁵⁵²

318. Thus, given that Schrum discloses mRNA encoding a spike protein and encapsulated in a lipid nanoparticle, and examples of the lipid nanoparticle in the claimed composition, a POSA would have been motivated to use the mRNA encapsulated in a lipid nanoparticle in the claimed composition to express the S-protein with a reasonable expectation of success.

J. Claim 12: “The composition of claim 11, wherein the lipid nanoparticle comprises 20-60% ionizable cationic lipid, 5-25%

⁵⁵⁰ Ex. 2199 ¶¶ 743-744.

⁵⁵¹ Ex. 1002 § IX.1.

⁵⁵² Ex. 1002 § IX.9.

neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.”

319. As I explained in my opening declaration⁵⁵³ and for the reasons explained in claims 1 and 11, Schrum discloses this limitation.

320. *First*, Dr. Fuller asserts that I do not address how claims 1 and 11, from which claim 12 depends, are met.⁵⁵⁴ For the reasons explained in my opening declaration,⁵⁵⁵ and Sections V.A and V.I, I disagree.

321. *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 12.⁵⁵⁶ As explained in my opening declaration with respect to claim 1, Schrum in combination with Geall discloses an mRNA encoding a spike protein and encapsulated in a lipid nanoparticle, and that the mRNA can be modified.⁵⁵⁷ And as I explain with respect to claim 11 of my opening declaration, Schrum’s examples with lipid nanoparticles include the claimed composition—an

⁵⁵³ Ex. 1002 § IX.10.

⁵⁵⁴ Ex. 2199 ¶¶ 748-749.

⁵⁵⁵ Ex. 1002 § IX.1, 9-10.

⁵⁵⁶ Ex. 2199 ¶¶ 750-751.

⁵⁵⁷ Ex. 1002 § IX.1

ionizable cationic lipid, a neutral lipid, a sterol, and a PEG-modified lipid.⁵⁵⁸

Moreover, as I explain in my opening declaration with respect to claim 12, Schrum's examples with lipid nanoparticles satisfy the claimed composition and ranges.⁵⁵⁹

Thus, given that Schrum discloses mRNA encapsulated in a lipid nanoparticle, and examples of the lipid nanoparticle in the claimed composition and ranges, a POSA would have been motivated to use the mRNA encapsulated in a lipid nanoparticle of the claimed composition and ranges to express the S-protein, all with a reasonable expectation of success.

K. Claim 16: "A composition, comprising: a messenger ribonucleic acid (mRNA) comprising a 5' untranslated region (UTR), an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit, a 3' UTR, and a poly(A) tail, formulated in a lipid nanoparticle that comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid."

322. Schrum in view of Geall discloses each limitation of claim 16, 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 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

⁵⁵⁸ Ex. 1002 § IX.9.

⁵⁵⁹ Ex. 1002 § IX.10.

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 16

323. I have previously explained that Schrum in view of Geall teaches every limitation of claim 16.⁵⁶⁰

324. For claim 16, 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 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.

2. A POSA Would Have Been Motivated To Combine Schrum And Geall With A Reasonable Expectation Of Success

325. 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

⁵⁶⁰ Ex. 1002 § IX.11.

⁵⁶¹ Ex. 2199 ¶ 775-776; 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.

3' UTR and a poly(A)) tail and encoding an immunogen encapsulated in a lipid nanoparticle of the claimed composition and ranges with Geall's disclosure of an RNA vaccine encoding a betacoronavirus spike protein, and would reasonably have expected to do so successfully to arrive at the composition of claim 16 in view of well-known methods of synthesizing mRNA, already known in the art.⁵⁶²

326. 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.”⁵⁶³ A POSA would have understood that the mRNA vaccines disclosed in Schrum could be delivered using the lipid nanoparticles disclosed in the examples.

327. 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.⁵⁶⁴

⁵⁶² Ex. 1002 § IX.11.

⁵⁶³ Ex. 1002 ¶ 132 (citing claim 12, Ex. 1009 ¶¶ 995, 999).

⁵⁶⁴ Ex. 1002 ¶¶ 128, 130-131.

328. Dr. Fuller does not meaningfully dispute my analysis in her declaration.⁵⁶⁵ 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.”⁵⁶⁶ 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.

* * *

329. Schrum and Geall disclose each element of claim 16. 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 composition the claim successfully.

L. Claim 17: “The composition of claim 16, wherein the open reading frame encodes a Beta CoV S protein.”

330. As I explained in my opening declaration⁵⁶⁷ and for the reasons

⁵⁶⁵ Ex. 2199 ¶ 759.

⁵⁶⁶ Ex. 2199 ¶¶ 509, 759.

⁵⁶⁷ Ex. 1002 § IX.12.

explained in claim 16, Section V.K, Schrum in view of Geall discloses this limitation. I disagree with Dr. Fuller's opinions to the contrary.

331. **First**, Dr. Fuller incorporates the arguments made with respect to claim 16.⁵⁶⁸ For the reasons explained in claim 16, I disagree.

332. **Second**, Dr. Fuller asserts that Schrum in view of Geall does not disclose an "open reading frame encodes a BetaCoV S protein."⁵⁶⁹ For the reasons explained in claim 16, Section V.K, I disagree.⁵⁷⁰

333. **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 17.⁵⁷¹ As I explained in my opening declaration⁵⁷² and for the reasons explained with respect to claim 16, a POSA would have been motivated to combine Schrum with Geall, with a reasonable expectation of success to arrive at

⁵⁶⁸ Ex. 2199 ¶¶ 765-766.

⁵⁶⁹ Ex. 2199 ¶ 767.

⁵⁷⁰ 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.

⁵⁷¹ Ex. 2199 ¶¶ 768-769.

⁵⁷² Ex. 1002 § IX.12.

claim 17.

M. Claim 20: “The composition of claim 16, wherein at least 80% of the uracil in the open reading frame has a chemical modification.”

334. As I explained in my opening declaration⁵⁷³ and for the reasons explained in claim 16, Section V.K, Schrum discloses this limitation.

335. *First*, Dr. Fuller asserts that I do not address how claim 16, from which claim 20 depends, is met.⁵⁷⁴ For the reasons explained in my opening declaration,⁵⁷⁵ I disagree.

336. *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 20.⁵⁷⁶ As explained in my opening declaration with respect to claim 16, Schrum in combination with Geall discloses a mRNA vaccine (that may be modified) with specific mRNA components (5' and 3' UTR, poly(A) tail) encoding a spike protein and encapsulated in a lipid nanoparticle of the claimed

⁵⁷³ Ex. 1002 § IX.13.

⁵⁷⁴ Ex. 2199 ¶¶ 772-773.

⁵⁷⁵ Ex. 1002 §§ IX.11, 13.

⁵⁷⁶ Ex. 2199 ¶¶ 774.

composition and ranges.⁵⁷⁷ 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.”⁵⁷⁸ 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 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.

337. 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.⁵⁷⁹ For the reasons explained in Section V.F, I disagree.

N. Claim 21: “The composition of claim 20, wherein the chemical modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification.”

⁵⁷⁷ Ex. 1002 § IX.11.

⁵⁷⁸ Ex. 1002 § IX.13.

⁵⁷⁹ Ex. 2199 ¶¶ 775-777.

338. As I explained in my opening declaration⁵⁸⁰ and for the reasons explained in claims 16 and 20, Sections V.K and V.M, Schrum discloses this limitation.

339. **First**, Dr. Fuller asserts that I do not address how claims 16 and 20, from which claim 21 depends, are met.⁵⁸¹ For the reasons explained in my opening declaration,⁵⁸² I disagree.

340. **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 21.⁵⁸³ As explained in my opening declaration with respect to claim 16, Schrum in combination with Geall discloses a mRNA vaccine (that may be modified) with specific mRNA components (5' and 3' UTR, poly(A) tail) encoding a spike protein and encapsulated in a lipid nanoparticle of the claimed composition and ranges.⁵⁸⁴ Moreover, as I explain with respect to claim 20 of my opening declaration, Schrum further explains that in the disclosed mRNA, “at least

⁵⁸⁰ Ex. 1002 § IX.14.

⁵⁸¹ Ex. 2199 ¶¶ 781-782.

⁵⁸² Ex. 1002 §§ IX.11, 13-14.

⁵⁸³ Ex. 2199 ¶¶ 783-784.

⁵⁸⁴ Ex. 1002 § IX.11.

80%, at least 90%, or 100% of the uracil in the nucleic acid may be replaced with a modified uracil.”⁵⁸⁵ And as I explain with respect to claim 21 of my opening declaration, Schrum provides examples of successful production of protein *in vitro* and *in vivo* after administration of N1-methylpseudouridine-modified mRNA.⁵⁸⁶ Indeed, Schrum notes that “exemplary nucleobases and nucleosides having a modified uracil include . . . 1-methyl-pseudouridine.”⁵⁸⁷ 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, 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.

341. 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

⁵⁸⁵ Ex. 1002 § IX.13.

⁵⁸⁶ Ex. 1002 § IX.14.

⁵⁸⁷ Ex. 1009 ¶ 283.

there was skepticism regarding modified mRNA for vaccines.⁵⁸⁸ For the reasons explained in Section V.F, I disagree.

O. Claim 26: “A lipid nanoparticle, comprising: a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit; wherein the lipid nanoparticle comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.”

342. Schrum in view of Geall discloses each limitation of claim 26, and a POSA would have had good reason to combine (1) Schrum’s disclosure of an mRNA encoding an immunogen that elicits an immune response and encapsulated in a lipid nanoparticle 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 26

343. I have previously explained that Schrum in view of Geall teaches every limitation of claim 26.⁵⁸⁹

⁵⁸⁸ Ex. 2199 ¶ 786.

⁵⁸⁹ Ex. 1002 § IX.15.

344. For claim 26, 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 there was skepticism regarding mRNA vaccines, and that concerns regarding ADE would have discouraged use of a spike protein.⁵⁹⁰ For the reasons explained in Section V.A, I disagree.⁵⁹¹

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

345. 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 encapsulated in a lipid nanoparticle of the claimed composition and ranges with Geall's disclosure of an RNA vaccine encoding a betacoronavirus spike protein, and would reasonably have expected to do so successfully to arrive at the composition of claim 26 in view of well-known methods of synthesizing mRNA, already known in the art.⁵⁹²

⁵⁹⁰ Ex. 2199 ¶¶ 791-792.

⁵⁹¹ 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.

⁵⁹² Ex. 1002 § IX.15.

346. 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.”⁵⁹³ A POSA would have understood that the mRNA vaccines disclosed in Schrum could be delivered using the lipid nanoparticles disclosed in the examples.

347. Dr. Fuller does not meaningfully dispute my analysis in her declaration.⁵⁹⁴ 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.”⁵⁹⁵ 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.

* * *

⁵⁹³ Ex. 1002 ¶¶ 139 (citing claim 12, Ex. 1009 ¶¶ 995, 999).

⁵⁹⁴ Ex. 2199 ¶ 759.

⁵⁹⁵ Ex. 2199 ¶ 509.

348. Schrum and Geall disclose each element of claim 26. 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 composition of the claim successfully.

VI. GROUND 3: THE COMBINATION OF SCHRUM IN VIEW OF YANG DISCLOSES ALL OF THE LIMITATIONS OF CLAIMS 1-2, 4-6, 8-12, 16-17, 20-21, AND 26

A. Claim 1: "A composition, comprising: 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."

349. In Section X of my previous declaration, I explained that each of the limitations of claims 1-2, 4-6, 8-12, 16-17, 20-21, and 26 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.⁵⁹⁶ 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 many of the opinions discussed above with respect to Grounds 1 and 2. I therefore disagree with Dr. Fuller, and my opinions remain unchanged. Claim 1: "A

⁵⁹⁶ Ex. 1002 § X.

composition, comprising: 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.”

350. 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 an LNP-encapsulated mRNA encoding an immunogen with Yang’s teaching that the immunogen of a nucleic acid 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 Yang Disclose Every Element of Claim 1

351. I have previously explained that Schrum in view of Yang teach every limitation of claim 1.⁵⁹⁷

352. **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.⁵⁹⁸ 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

⁵⁹⁷ Ex. 1002 § X.1.

⁵⁹⁸ Ex. 2199 ¶ 803.

well as the encapsulation of such mRNA in lipid nanoparticles, as explained in Section IV.B.

353. Dr. Fuller further asserts that Yang does not teach delivering a full-length S protein or S protein subunit.⁵⁹⁹ 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."⁶⁰⁰ Yang further discloses that "[i]njection of S, SΔTM and SΔCD expression vectors induced a substantial immune response."⁶⁰¹ 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.⁶⁰²

⁵⁹⁹ Ex. 2199 ¶¶ 804-823.

⁶⁰⁰ Ex. 1011 at 561.

⁶⁰¹ Ex. 1011 at 561 (emphasis added).

⁶⁰² Ex. 1011 at Fig. 1.



354. 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).

355. **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.⁶⁰³ For the reasons explained in 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.

356. **Third**, Dr. Fuller asserts that concerns about disease enhancement undermine Yang's disclosure of a spike protein.⁶⁰⁴ For the reasons explained in

⁶⁰³ Ex. 2199 ¶ 823.

⁶⁰⁴ Ex. 2199 ¶¶ 824-828.

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

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

357. 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 and encapsulated in a lipid nanoparticle with Yang's disclosure of a DNA vaccine encoding a betacoronavirus spike protein, and would reasonably have expected to do so successfully to arrive at the composition of claim 1 in view of well-known methods of synthesizing mRNA, already known in the art.⁶⁰⁵ I disagree with Dr. Fuller's opinions to the contrary.

358. *First*, as explained in Section V.A.2, Dr. Fuller does not meaningfully dispute my analysis in her declaration.⁶⁰⁶ 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."⁶⁰⁷ 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,

⁶⁰⁵ Ex. 1002 ¶¶ X.1.

⁶⁰⁶ Ex. 2199 ¶¶ 829-854.

⁶⁰⁷ Ex. 2199 ¶¶ 509, 831.

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.

359. **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.⁶⁰⁸ I disagree.

360. 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.

⁶⁰⁸ Ex. 2199 ¶¶ 548-570, ¶¶ 836-839.

361. 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 "when 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."⁶⁰⁹ In other words, the DNA vaccine introduces more complexity. To that end, a POSA would be encouraged by the results of a DNA vaccine, and understood that mRNA, which has fewer intervening steps, could similarly succeed.⁶¹⁰

362. 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.⁶¹¹ Dr. Fuller points

⁶⁰⁹ Ex. 2199 ¶ 837.

⁶¹⁰ 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 ¶ 838. 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.

⁶¹¹ Ex. 2199 ¶ 839.

to a study by Brito and Geall et al. demonstrating that DNA vaccines and mRNA vaccines resulted in different immune responses.⁶¹²

363. 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 RSV-F protein.⁶¹³ In doing so, Brito et al. relied on CNE-formulated plasmid DNA encoding the same RSV-F protein as a benchmark.⁶¹⁴ 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.⁶¹⁵

364. 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

⁶¹² Ex. 2199 ¶ 839 (citing Ex. 2005).

⁶¹³ Ex. 2005 at 2118.

⁶¹⁴ Ex. 2005 at 2119.

⁶¹⁵ Ex. 2005 at 2118-19.

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).⁶¹⁶ 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.”⁶¹⁷ The 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. [REDACTED]

[REDACTED]

[REDACTED]

365. *Third*, Dr. Fuller disputes that as of October 2015, mRNA vaccines were known to have significant advantages over DNA vaccines.⁶¹⁹ For the reasons explained in Section V.A.2.a.3, I disagree. In particular, Dr. Fuller points to Martin

⁶¹⁶ Ex. 2005 at 2119.

⁶¹⁷ Ex. 2005 at 2123-24.

[REDACTED]

⁶¹⁹ Ex. 2199 ¶¶ 840-844.

2008's results, which she describes as "promising."⁶²⁰ However, Martin 2008's results do not detract from the advantages of mRNA vaccines, described in Section V.A.2.a.3.

366. **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 vaccines, and that Yang provides data on spike proteins with certain domains removed rather than "full length" spike proteins.⁶²¹ For the reasons explained in claim 1, Section VI.A. I disagree with Dr. Fuller's assertions.

367. **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."⁶²² 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

⁶²⁰ Ex. 2199 ¶ 844.

⁶²¹ Ex. 2199 ¶¶ 845-851.

⁶²² Ex. 2199 ¶¶ 852-854.

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.

* * *

368. 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 composition of claim 1 successfully.

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

369. As I explain in my opening declaration,⁶²³ 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.

370. *First*, Dr. Fuller incorporates the arguments made with respect to claim 1.⁶²⁴ For the reasons explained in claim 1, I disagree.

⁶²³ Ex. 1002 § X.2.

⁶²⁴ Ex. 2199 ¶ 857.

371. **Second**, Dr. Fuller asserts that Schrum in view of Yang does not disclose an “open reading frame encodes a BetaCoV S protein.”⁶²⁵ For the reasons explained in claim 1, Section V.A, I disagree.

372. **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 2.⁶²⁶ I disagree. As I explained in my opening declaration⁶²⁷ and for the reasons explained with respect to claim 1, a POSA would have been motivated to combine Schrum with Yang, with a reasonable expectation of success to arrive at claim 2.

C. Claim 4: “The composition of claim 1, wherein the mRNA further comprises a 5' untranslated region (UTR) and a 3' UTR.”

373. For the reasons explained in Ground 2, claim 4, Section V.C, Schrum discloses this limitation.

D. Claim 5: “The composition of claim 4, wherein the mRNA further comprises a poly(A) tail.”

374. For the reasons explained in Ground 2, claim 5, Section V.D, Schrum discloses this limitation.

⁶²⁵ Ex. 2199 ¶¶ 858-859.

⁶²⁶ Ex. 2199 ¶¶ 860-861.

⁶²⁷ Ex. 1002 § X.2.

E. Claim 6: “The composition of claim 4, wherein the mRNA further comprises a 5' cap analog.”

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

F. Claim 8: “The composition of claim 1, wherein the mRNA comprises a chemical modification.”

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

377. Dr. Fuller also asserts that Yang’s DNA vaccine cannot result in chemically modified mRNA.⁶²⁸ 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.⁶²⁹

G. Claim 9: “The composition of claim 8, wherein the chemical modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification.”

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

⁶²⁸ Ex. 2199 ¶¶ 896-900.

⁶²⁹ Ex. 1002 § X.6.

H. Claim 10: “The composition of claim 8, wherein at least 80% of the uracil in the open reading frame has a chemical modification.”

379. For the reasons explained in Ground 2, claim 10, Section V.H, Schrum discloses this limitation.

I. Claim 11: “The composition of claim 1, wherein the lipid nanoparticle comprises an ionizable cationic lipid, a neutral lipid, a sterol, and a PEG-modified lipid.”

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

J. Claim 12: “The composition of claim 11, wherein the lipid nanoparticle comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.”

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

K. Claim 16: “A composition, comprising: a messenger ribonucleic acid (mRNA) comprising a 5' untranslated region (UTR), an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit, a 3' UTR, and a poly(A) tail, formulated in a lipid nanoparticle that comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.”

382. Schrum in view of Yang discloses each limitation of claim 16, and a POSA would have had good reason to combine (1) Schrum's disclosure of an mRNA with a 5' and 3' UTRs and a poly(A) tail encoding an immunogen and encapsulated in a lipid nanoparticle of the claimed composition and ranges with (2) Yang's

teaching that the immunogen of a DNA 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 Yang Disclose Every Element of Claim 16

383. I have previously explained that Schrum in view of Yang teaches every limitation of claim 16.⁶³⁰

384. For claim 16, 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.⁶³¹ For the reasons explained in Section VI.A, I disagree.

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

385. 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 encapsulated in a lipid nanoparticle of the claimed composition and ranges with (2) Yang's disclosure of a

⁶³⁰ Ex. 1002 § X.11.

⁶³¹ Ex. 2199 ¶ 937.

DNA vaccine encoding a betacoronavirus spike protein, and would reasonably have expected to do so successfully to arrive at the composition of claim 16 in view of well-known methods of synthesizing mRNA, already known in the art.⁶³²

386. 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.”⁶³³ A POSA would have understood that the mRNA vaccines disclosed in Schrum could be delivered using the lipid nanoparticles disclosed in the examples.

387. 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.⁶³⁴

⁶³² Ex. 1002 § X.11.

⁶³³ Ex. 1002 ¶ 166 (citing claim 12, Ex. 1009 ¶¶ 995, 999).

⁶³⁴ Ex. 1002 ¶¶ 162, 164-165.

388. Dr. Fuller does not meaningfully dispute my analysis in her declaration.⁶³⁵ 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.”⁶³⁶ 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.

* * *

389. Schrum and Yang disclose each element of claim 16. 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 composition of the claim successfully.

⁶³⁵ Ex. 2199 ¶¶ 940-941.

⁶³⁶ Ex. 2199 ¶¶ 509, 940-941.

L. Claim 17: “The composition of claim 16, wherein the open reading frame encodes a Beta CoV S protein.”

390. As I explain in my opening declaration,⁶³⁷ and for the reasons explained in claim 16, Section VI.K, Schrum in view of Yang discloses this limitation. I disagree with Dr. Fuller’s opinions to the contrary.

391. **First**, Dr. Fuller incorporates the arguments made with respect to claim 16.⁶³⁸ For the reasons explained in claim 16, Section VI.K, I disagree.

392. **Second**, Dr. Fuller asserts that Schrum in view of Yang does not disclose an “open reading frame encodes a BetaCoV S protein.”⁶³⁹ For the reasons explained in claim 16, Section VI.K, I disagree.

393. **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 17.⁶⁴⁰ As I explained in my opening declaration⁶⁴¹ and for the reasons explained with respect to claim 16, a POSA would have been motivated

⁶³⁷ Ex. 1002 § X.12.

⁶³⁸ Ex. 2199 ¶¶ 945-946.

⁶³⁹ Ex. 2199 ¶ 947.

⁶⁴⁰ Ex. 2199 ¶¶ 948-949.

⁶⁴¹ Ex. 1002 § X.12.

to combine Schrum with Yang, with a reasonable expectation of success to arrive at claim 17.

M. Claim 20: “The composition of claim 16, wherein at least 80% of the uracil in the open reading frame has a chemical modification.”

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

N. Claim 21: “The composition of claim 20, wherein the chemical modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification.”

395. For the reasons explained in Ground 2, claim 21, Section V.N, Schrum discloses this limitation.

O. Claim 26: “A lipid nanoparticle, comprising: a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit; wherein the lipid nanoparticle comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.”

396. Schrum in view of Yang discloses each limitation of claim 26, and a POSA would have had good reason to combine (1) Schrum’s disclosure of an mRNA encoding an immunogen that elicits an immune response and encapsulated in a lipid nanoparticle of the claimed composition and ranges with (2) Yang’s teaching that the immunogen of a DNA 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 Yang Disclose Every Element of Claim 26

397. I have previously explained that Schrum in view of Yang teaches every limitation of claim 26.⁶⁴²

398. For claim 26, 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.⁶⁴³ For the reasons explained in Section V.A, I disagree.

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

399. 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 encoding an immunogen encapsulated in a lipid nanoparticle of the claimed composition and ranges with (2) Yang's disclosure of a DNA vaccine encoding a betacoronavirus spike protein, and would reasonably have expected to do so successfully to arrive at the composition of claim 26 in view of well-known methods of synthesizing mRNA, already known in the art.⁶⁴⁴

⁶⁴² Ex. 1002 § X.15.

⁶⁴³ Ex. 2199 ¶¶ 973-974.

⁶⁴⁴ Ex. 1002 § X.15.

400. 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.”⁶⁴⁵ A POSA would have understood that the mRNA vaccines disclosed in Schrum could be delivered using the lipid nanoparticles disclosed in the examples.

401. Dr. Fuller does not meaningfully dispute my analysis in her declaration.⁶⁴⁶ 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.”⁶⁴⁷ 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.

* * *

⁶⁴⁵ Ex. 1002 ¶ 173 (citing claim 12, Ex. 1009 ¶¶ 995, 999).

⁶⁴⁶ Ex. 2199 ¶¶ 973-974.

⁶⁴⁷ Ex. 2199 ¶¶ 509, 974.

402. Schrum and Yang disclose each element of claim 26. 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 composition of the claim successfully.

VII. GROUND 4: THE COMBINATION OF SCHRUM IN VIEW OF ALTMAYER DISCLOSES ALL OF THE LIMITATIONS OF CLAIMS 1-2, 4-6, 8-12, 16-17, 20-21, AND 26

403. In Section XI of my opening declaration, I explained that each of the limitations of claims 1-2, 4-6, 8-12, 16-17, 20-21, and 26 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 composition, comprising: 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."

404. 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 an LNP-

encapsulated mRNA encoding an immunogen that elicits 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

405. I have previously explained that Schrum in view of Altmeyer teach every limitation of claim 1.⁶⁴⁸

406. *First*, in her declaration, Dr. Fuller asserts that Altmeyer does not disclose mRNA.⁶⁴⁹ 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, 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.

⁶⁴⁸ Ex. 1002 § XI.1.

⁶⁴⁹ Ex. 2199 ¶¶ 980-996. Dr. Fuller does not dispute that Altmeyer discloses RNA.

407. *Second*, Dr. Fuller also asserts that Altmeyer does not disclose a spike protein.⁶⁵⁰ In particular, Dr. Fuller states that Altmeyer fails to specify whether the spike protein is a “full-length spike protein.”⁶⁵¹ 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*.”⁶⁵² Example 5 reports 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.”⁶⁵³ 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.”⁶⁵⁴

⁶⁵⁰ Ex. 2199 ¶¶ 997-999.

⁶⁵¹ Ex. 2199 ¶ 998.

⁶⁵² Ex. 1012 ¶ 97 (emphases added).

⁶⁵³ Ex. 1012 ¶ 116 (emphases added).

⁶⁵⁴ Ex. 1012 ¶ 111 (emphases added).

408. **Third**, Dr. Fuller asserts that Altmeyer does not disclose a structural protein forming a spike.⁶⁵⁵ 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.”⁶⁵⁶ Moreover, for the reasons explained in 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.

409. Dr. Fuller’s statements regarding the purported lack of working examples in Altmeyer are simply incorrect.⁶⁵⁷ As explained in my opening declaration,⁶⁵⁸ 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-

⁶⁵⁵ Ex. 2199 ¶¶ 1000-1003.

⁶⁵⁶ Ex. 1012 ¶ 111.

⁶⁵⁷ Ex. 2199 ¶¶ 1001-1002.

⁶⁵⁸ Ex. 1002 XI.1 (quoting Ex. 1012 ¶ 116).

specific antibodies by immunofluorescence on SARS CoV infected FRHK4 cells (Figure 8.).”⁶⁵⁹

410. Still, Dr. Fuller asserts that it is “not possible to tease apart the individual immune results” that are attributable to the “SFV Spike RNA.”⁶⁶⁰ 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 “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.

411. *Fourth*, Dr. Fuller asserts that concerns about disease enhancement undermine Altmeyer’s disclosure of a spike protein.⁶⁶¹ 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.

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

412. 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

⁶⁵⁹ Ex. 1002 XI.1 (quoting Ex. 1012 ¶ 116).

⁶⁶⁰ Ex. 2199 ¶ 1002.

⁶⁶¹ Ex. 2199 ¶¶ 1004-1008.

an immunogen and encapsulated in lipid nanoparticle, with Altmeyer's disclosure of spike protein, and would reasonably have expected to do so successfully to arrive at the composition of claim 1 in view of well-known methods of synthesizing mRNA, already known in the art.⁶⁶² I disagree with Dr. Fuller's opinions to the contrary.

413. **First**, as explained in Section V.A.2, Dr. Fuller does not meaningfully dispute my analysis in her declaration.⁶⁶³ 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."⁶⁶⁴ 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.

⁶⁶² Ex. 1002 ¶¶ XI.1.

⁶⁶³ Ex. 2199 ¶¶ 1011-1021.

⁶⁶⁴ Ex. 2199 ¶¶ 509, 1011.

414. **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.⁶⁶⁵ I disagree.

415. 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.⁶⁶⁶ 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 an immune response. Those lessons would have been applicable across viral vector and mRNA vaccines.

⁶⁶⁵ Ex. 2199 ¶¶ 1012-1014; 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.

⁶⁶⁶ Ex. 2199 ¶¶ 60-62.

416. 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.⁶⁶⁷ 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."⁶⁶⁸ 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.

417. 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."⁶⁶⁹ In other words, Dr.

⁶⁶⁷ Ex. 2199 ¶¶ 990-992.

⁶⁶⁸ Ex. 2199 ¶ 252.

⁶⁶⁹ Ex. 2199 ¶ 995.

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.

418. 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.

419. *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.⁶⁷⁰ 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.

⁶⁷⁰ Ex. 2199 ¶¶ 1015-1021.

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

420. As I explain in my opening declaration,⁶⁷¹ 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.

421. *First*, Dr. Fuller incorporates the arguments made with respect to claim 1.⁶⁷² For the reasons explained in claim 1, Section VII.A, I disagree.

422. *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.”⁶⁷³ For the reasons explained in claim 1, Section VII.A, I disagree.

423. *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 2.⁶⁷⁴ I disagree. As I explained in my opening

⁶⁷¹ Ex. 1002 § XI.2.

⁶⁷² Ex. 2199 ¶ 1024.

⁶⁷³ Ex. 2199 ¶¶ 1025-1026.

⁶⁷⁴ Ex. 2199 ¶¶ 1027-1028.

declaration⁶⁷⁵ 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 composition of claim 2, with a reasonable expectation of success.⁶⁷⁶

C. Claim 4: “The composition of claim 1, wherein the mRNA further comprises a 5' untranslated region (UTR) and a 3' UTR.”

424. For the reasons explained in Ground 2, claim 4, Section V.C, Schrum discloses this limitation.

D. Claim 5: “The composition of claim 4, wherein the mRNA further comprises a poly(A) tail.”

425. For the reasons explained in Ground 2, claim 5, Section V.D, Schrum discloses this limitation.

E. Claim 6: “The composition of claim 4, wherein the mRNA further comprises a 5' cap analog.”

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

F. Claim 8: “The composition of claim 1, wherein the mRNA comprises a chemical modification.”

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

⁶⁷⁵ Ex. 1002 ¶¶ 183-185.

⁶⁷⁶ Ex. 1002 § XI.2.

428. Dr. Fuller also asserts that Altmeyer does not disclose chemically modified mRNA.⁶⁷⁷ Irrespective of Altmeyer's disclosure, however, a POSA would have understood that Schrum discloses this limitation, and in particular that non-amplifying mRNA achieved high levels of protein expression with modified nucleotides, as explained in my opening declaration.⁶⁷⁸

G. Claim 9: "The composition of claim 8, wherein the chemical modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification."

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

H. Claim 10: "The composition of claim 8, wherein at least 80% of the uracil in the open reading frame has a chemical modification."

430. For the reasons explained in Ground 2, Claim 10, Section V.H, Schrum discloses this limitation.

I. Claim 11: "The composition of claim 1, wherein the lipid nanoparticle comprises an ionizable cationic lipid, a neutral lipid, a sterol, and a PEG-modified lipid."

431. For the reasons explained in Ground 2, Claim 11, Section V.I, Schrum discloses this limitation.

J. Claim 12: "The composition of claim 11, wherein the lipid nanoparticle comprises 20-60% ionizable cationic lipid, 5-25%

⁶⁷⁷ Ex. 2199 ¶¶ 1063-1070.

⁶⁷⁸ Ex. 1002 § XI.6.

neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.”

432. For the reasons explained in Ground 2, Claim 12, Section V.J, Schrum discloses this limitation.

K. Claim 16: “A composition, comprising: a messenger ribonucleic acid (mRNA) comprising a 5’ untranslated region (UTR), an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit, a 3’ UTR, and a poly(A) tail, formulated in a lipid nanoparticle that comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.”

433. Schrum in view of Altmeyer discloses each limitation of claim 16, 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 and encapsulated in an lipid nanoparticle of the claimed composition and ranges with (2) Altmeyer’s teaching that the immunogen 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 16

434. I have previously explained that Schrum in view of Altmeyer teaches every limitation of claim 16.⁶⁷⁹

⁶⁷⁹ Ex. 1002 § XI.11.

435. For claim 16, 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.⁶⁸⁰ 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

436. 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 encapsulated in a lipid nanoparticle of the claimed composition and ranges with (2) Altmeyer's disclosure of a betacoronavirus spike protein to arrive at the composition of claim 16, and would reasonably have expected success in view of well-known methods of synthesizing mRNA, already known in the art.⁶⁸¹

437. 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

⁶⁸⁰ Ex. 2199 ¶ 1107.

⁶⁸¹ Ex. 1002 § XI.11.

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.”⁶⁸²

A POSA would have understood that the mRNA vaccines disclosed in Schrum could be delivered using the lipid nanoparticles disclosed in the examples.

438. 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.⁶⁸³

439. Dr. Fuller does not meaningfully dispute my analysis in her declaration.⁶⁸⁴ 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.”⁶⁸⁵ 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

⁶⁸² Ex. 1002 ¶ 200 (citing claim 12, Ex. 1009 ¶¶ 995, 999).

⁶⁸³ Ex. 1002 ¶¶ 197-199.

⁶⁸⁴ Ex. 2199 ¶¶ 1110-1112.

⁶⁸⁵ Ex. 2199 ¶¶ 509, 1111.

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

* * *

440. Schrum and Altmeyer disclose each element of claim 16. 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 composition of the claim, with a reasonable expectation of success.

L. Claim 17: "The composition of claim 16, wherein the open reading frame encodes a Beta CoV S protein."

441. As I explain in my opening declaration,⁶⁸⁶ and for the reasons explained in claim 16, Section VII.K, Schrum in view of Altmeyer discloses this limitation. I disagree with Dr. Fuller's opinions to the contrary.

442. *First*, Dr. Fuller incorporates the arguments made with respect to claim 16.⁶⁸⁷ For the reasons explained with respect to claim 16, I disagree.

443. *Second*, Dr. Fuller asserts that Schrum in view of Altmeyer does not disclose an "open reading frame encodes a BetaCoV S protein."⁶⁸⁸ For the reasons

⁶⁸⁶ Ex. 1002 § XI.12.

⁶⁸⁷ Ex. 2199 ¶¶ 1115-1116.

⁶⁸⁸ Ex. 2199 ¶ 1117.

explained in claim 16, Section VII.K, I disagree.

444. *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 17.⁶⁸⁹ As I explained in my opening declaration⁶⁹⁰ and for the reasons explained with respect to claim 16, a POSA would have been motivated to combine Schrum with Altmeyer to arrive at the composition of claim 17, with a reasonable expectation of success.

M. Claim 20: “The composition of claim 16, wherein at least 80% of the uracil in the open reading frame has a chemical modification.”

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

N. Claim 21: “The composition of claim 20, wherein the chemical modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification.”

446. For the reasons explained in Ground 2, Claim 21, Section V.N, Schrum discloses this limitation.

O. Claim 26: “A lipid nanoparticle, comprising: a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit; wherein the lipid nanoparticle comprises 20-60%

⁶⁸⁹ Ex. 2199 ¶¶ 1118-1119.

⁶⁹⁰ Ex. 1002 § XI.12.

ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.”

447. Schrum in view of Altmeyer discloses each limitation of claim 26, and a POSA would have had good reason to combine (1) Schrum’s disclosure of an mRNA encoding an immunogen and encapsulated in a lipid nanoparticle of the claimed composition and ranges with (2) Altmeyer’s teaching that the immunogen may be a betacoronavirus S protein, all with a reasonable expectation of success in 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 26

448. I have previously explained that Schrum in view of Altmeyer teaches every limitation of claim 26.⁶⁹¹

449. For claim 26, Dr. Fuller recycles many of her arguments with respect to claim 1, including that Altmeyer focuses on DNA, 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.⁶⁹² 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

⁶⁹¹ Ex. 1002 § XI.15.

⁶⁹² Ex. 2199 ¶ 1140.

450. 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 encapsulated in a lipid nanoparticle of the claimed composition and ranges with Altmeyer's disclosure of a betacoronavirus spike protein, and would reasonably have expected to do so successfully to arrive at the composition of claim 26 in view of well-known methods of synthesizing mRNA, already known in the art.⁶⁹³

451. 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.”⁶⁹⁴ A POSA would have understood that the mRNA vaccines disclosed in Schrum could be delivered using the lipid nanoparticles disclosed in the examples.

452. Dr. Fuller does not meaningfully dispute my analysis in her declaration.⁶⁹⁵ Instead, she refers back to her eight purported reasons as to why “a

⁶⁹³ Ex. 1002 § XI.15.

⁶⁹⁴ Ex. 1002 ¶ 207 (citing claim 12, Ex. 1009 ¶¶ 995, 999).

⁶⁹⁵ Ex. 2199 ¶¶ 1142-1143.

POSA would not have had a reasonable expectation of success of October 2015.”⁶⁹⁶

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.

* * *

453. Schrum and Altmeyer disclose each element of claim 26. 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 composition of claim 26, with a reasonable expectation of success.

VIII. THERE ARE NO OBJECTIVE INDICIA THAT SUPPORT THE NON-OBVIOUSNESS OF THE ’600 PATENT

454. 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

⁶⁹⁶ Ex. 2199 ¶¶ 509, 1144.

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.

455. Dr. Fuller relies on the opinion of Dr. Krause regarding objective indicia of non-obviousness for the '600 patent. Accordingly, I address Dr. Krause's arguments below.

A. Nexus

456. In my opinion, there is no nexus between Spikevax® and Comirnaty® and the claims of the '600 patent. As I explain below, Dr. Krause fails to recognize that the claims of the '600 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

457. 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.

⁶⁹⁷ Ex. 2200 ¶¶ 227-228.

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

458. 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 '600 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

459. 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 confirmation. The 2P mutation stabilizes the

⁶⁹⁸ Ex. 2200 ¶ 232.

⁶⁹⁹ Ex. 2200 ¶ 232.

⁷⁰⁰ Ex. 2200 ¶¶ 232-240.

spike protein in the pre-fusion conformation, maximizing the availability of antibody epitopes and improving vaccine performance.⁷⁰¹

460. 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

461. 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

⁷⁰¹ Ex. 1114 at 1-13.

⁷⁰² Ex. 2142 at 567.

⁷⁰³ Ex. 2142 at 567.

⁷⁰⁴ Ex. 2200 ¶¶ 237-240.

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 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.

462. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

⁷⁰⁵ Ex. 2200 ¶ 238.

[REDACTED]
[REDACTED]
[REDACTED]

463. 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

706 [REDACTED]

⁷⁰⁷ Ex. 1139 at 6.

S vaccines without stabilization . . . confirmed the positive effect of S '2P' stabilization.⁷⁰⁸

464. 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

465. Other elements of the vaccines' mRNA technology that affect protein translation and immunogenicity are not claimed in the '600 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.

466. 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

⁷⁰⁸ Ex. 1139 at 7.

⁷⁰⁹ Ex. 2200 ¶ 231.

⁷¹⁰ Ex. 1129.

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 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

⁷¹¹ Ex. 1129 at 4013.

⁷¹² Ex. 1129 at 4014.

⁷¹³ Ex. 1129 at 4014.

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 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

467. I understand that Comirnaty® and Spikevax® both use specific lipid nanoparticle formulations, which are different from each other and not described in the '600 patent. The choice of particular cationic lipid nanoparticle can have a significant effect on the protein translation and immunogenicity of a mRNA vaccine.⁷¹⁵

468. 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

⁷¹⁴ Ex. 1106 at 75.

⁷¹⁵ Ex. 1004 ¶ 37.

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 ’600 patent to combat a virus that did not exist in 2015. That Pfizer and 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

469. In his report, Dr. Krause contends that there is a nexus to the challenged claims of the ’600 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 ’600 patent.

a. 1-methylpseudouridine Modification

⁷¹⁶ Ex. 2200 ¶ 231.

⁷¹⁷ Ex. 2200 ¶¶ 227, 241-244.

470. As explained in my opening declaration,⁷¹⁸ Drs. Karikó and Weissman made the fundamental discovery that modifying mRNA reduces the innate immune 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

471. 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.

⁷¹⁸ Ex. 1002 ¶ 43.

⁷¹⁹ Ex. 2200 ¶¶ 215-217, 241-242.

⁷²⁰ Ex. 1002 ¶¶ 43, 82.

⁷²¹ Ex. 1021 (published in 2005); Ex. 1022 (published in 2008).

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 and Weissman described modified mRNA was a “promising tool for both gene replacement and *vaccination*.”⁷²³

472. 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

⁷²² Ex. 1023.

⁷²³ Ex. 1022 at 1833 (emphasis added).

⁷²⁴ Ex. 1026.

⁷²⁵ Ex. 1124 at 1 (emphasis added).

⁷²⁶ Ex. 1124 at 8.

b. Full-length Spike Protein

473. As explained above in Section V.A.2.b, use of a full-length spike protein was well-known in the prior art.

474. Thus, to the extent that the success of 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

475. I disagree with Dr. Krause's assertion that there is a nexus between the claims and the lipid nanoparticles of Spikevax® and Comirnaty®.⁷²⁸

476. As an initial matter, I understand from Dr. Moon's opening declaration that the '600 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

⁷²⁷ Ex. 2200 ¶¶ 218-223.

⁷²⁸ Ex. 2200 ¶ 227.

⁷²⁹ Ex. 1004 ¶ 45.

⁷³⁰ Ex. 1004 ¶¶ 19-44.

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 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

⁷³¹ Ex. 1004 ¶¶ 35-44.

⁷³² Ex. 1004 ¶¶ 54-57.

great importance for clinical applications of nucleic acid-based technologies.⁷³³

477. 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 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

478. I disagree with Dr. Krause’s opinion that the alleged invention in the ’600 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

⁷³³ Ex. 1124 at 4.

⁷³⁴ Ex. 1113 at 2.

⁷³⁵ Ex. 2200 ¶¶ 165-177.

nanoparticle composition. Thus, there is no nexus between the patents and any satisfaction of long felt need.

479. 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 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

⁷³⁶Ex. 1125 at 1.

⁷³⁷ Ex. 2200 ¶ 199.

⁷³⁸ Ex. 1125 at 1-2.

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

480. Dr. Krause further contends that the "foundational technology" described in the '600 patent was quickly adapted for new variants of SARS-CoV.⁷⁴¹ It is unclear what Dr. Krause is pointing to in the '600 patent disclosure that 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

⁷³⁹ Ex. 1107 at 6.

⁷⁴⁰ Ex. 1127 at 1.

⁷⁴¹ Ex. 2200 ¶ 177.

⁷⁴² Ex. 1111 at 1.

⁷⁴³ Ex. 1110 at 1.

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.

481. 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

482. 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

⁷⁴⁴ Ex. 1126 at 1.

⁷⁴⁵ Ex. 1122 at 1.

⁷⁴⁶ Ex. 2200 ¶¶ 178-186.

⁷⁴⁷ Ex. 2200 ¶¶ 187-192.

483. For the reasons explained in Section V.A.2.a, others had successfully tested the use of mRNA vaccines, including for infectious diseases. I thus I disagree with Dr. Krause's argument that the purported failure of others supports the validity of the Challenged Claims.⁷⁴⁸

D. No Unexpected Results

484. I disagree with Dr. Krause's argument that results of the experiments shown in the '600 patent were "unexpected."⁷⁴⁹

485. *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.F, 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

⁷⁴⁸ Ex. 2200 ¶¶ 193-199.

⁷⁴⁹ Ex. 2200 ¶¶ 200-207.

⁷⁵⁰ Ex. 2200 ¶ 201.

⁷⁵¹ Ex. 1128 at 1.

486. **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 ’600 patent and was created approximately five years after the ’600 patent filing date. As explained in Section VIII.A.2, many generic features of the claims, including the modified mRNA, the 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.

487. **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.

⁷⁵² Ex. 2200 ¶¶ 202-205.

⁷⁵³ Ex. 2200 ¶¶ 206-207.

488. *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

489. In my opinion, there is no praise that would support the non-obviousness of the '600 patent. In his declaration, Dr. Krause contends that “[o]thers 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 '600 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.

490. 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

⁷⁵⁴ Ex. 2200 ¶ 208.

⁷⁵⁵ Ex. 2200 ¶ 209.

⁷⁵⁶ Ex. 2200 ¶¶ 209-214.

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:

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

491. 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, 2, 4-6, 8-12, 16, 17, 20, 21, and 26 of the '600 patent.

⁷⁵⁷ Ex. 2200 ¶ 212 (citing Ex. 2035).

⁷⁵⁸ Ex. 2035 at 2428.

Reply Declaration of Daniel O. Griffin, M.D., Ph.D.
Patent No. 10,702,600

492. 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.

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)