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Paper 86
Entered: March 5, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BIONTECH SE AND PFIZER INC.,
Petitioners,

v.

MODERNA TX INC.,
Patent Owner.

IPR2023-01358
Patent 10,702,600 B1

Before SHERIDAN K. SNEDDEN, TIMOTHY G. MAJORS, and DAVID COTTA, *Administrative Patent Judges.*

COTTA, *Administrative Patent Judge*

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
35 U.S.C. § 318(a)
Granting the Parties Motions to Seal;
37 C.F.R. § 42.14

I. INTRODUCTION

BioNTech SE and Pfizer Inc. (collectively "Petitioner") filed a Petition to institute an *inter partes* review ("IPR") of claims 1, 2, 4–6, 8–12, 16, 17, 20, 21, and 26 (the "challenged claims") of U.S. Patent No. 10,702,600 B1 ("the '600 patent"). Paper 3 ("Petition" or "Pet."). Moderna Tx, Inc. ("Patent Owner") filed a Preliminary Response. Paper 8 ("Prelim. Resp."). With our prior authorization, Petitioner and Patent Owner also filed respective "Preliminary Statement[s] Regarding Alleged Inconsistent Positions," Paper 14 (Petitioner's Statement) and Paper 11 (Patent Owner's Statement). Those statements address positions taken by Patent Owner previously that, according to Petitioner, are inconsistent with positions taken by Patent Owner in this proceeding. Ex. 2060 (chart of alleged inconsistencies).

We instituted trial on March 6, 2024. Paper 17 ("Inst. Dec."). During trial, Patent Owner filed a Patent Owner Response. Paper 41 ("PO Resp."). Petitioner filed a Reply (Paper 59 ("Pet. Reply")) and Patent Owner filed a Sur-reply (Paper 72 ("PO Sur-reply")). An oral hearing was held on December 10, 2024, and a transcript is of record. Paper 85 ("Tr.").

Unopposed motions to seal also remain pending (Papers 42, 58, 71, and 78). We resolve those motions in Section V below.

We have jurisdiction under 35 U.S.C. § 6(b). After considering the full record developed through trial, we determine that Petitioner has proved by a preponderance of the evidence that the challenged claims are unpatentable. *See* 35 U.S.C. § 316(e). Our reasoning is explained below, and we issue this Final Written Decision under 35 U.S.C. § 318(a).

A. Real Parties-in-Interest

Petitioner identifies BioNTech SE, BioNTech US Inc., BioNTech Manufacturing GmbH, and Pfizer Inc. as the real parties-in-interest. Pet. 3. Patent Owner identifies itself and Moderna US, Inc. as the real parties-in-interest. Paper 6, 1.

B. Related Matters

The parties identify as a related matter the following lawsuit involving the '600 patent (and other patents): *ModernaTX, Inc. et al. v. Pfizer Inc., BioNTech SE, et al.*, 1:22-cv-11378-RGS (D. Mass) (hereafter "Massachusetts Litigation"); Pet. 3; Paper 6, 1.

Petitioner also identifies U.S. Application No. 16/880,829. This application issued in 2021 as U.S. Patent No. 10,933,127 ("the '127 patent"). Pet. 3. Patent Owner states that the '127 patent is also asserted in the Massachusetts Litigation. Paper 6, 1–2 (listing, as related, several other patents and applications). Claims of the '127 patent are challenged in IPR2023-01359 (Paper 6, 1; Pet. 3), for which we issue a Final Written Decision concurrent with this decision.

C. Technology Overview

We provide below a primer on certain background technologies relevant to the '600 patent, the prior art, and the arguments raised by the parties in this case. This is an overview and is not intended to be exhaustive. The citations are principally to overviews of the technology provided by the parties' technical declarants and secondary publications as appropriate.

1. *DNA, RNA, and Protein*

"DNA contains the genetic code that instructs the synthesis of proteins vital to all aspects of life." Ex. 1002 ¶ 21 (declaration of Dr. Daniel O. Griffin); Ex. 2199 ¶ 54 (declaration of Dr. Deborah H. Fuller) (testifying that DNA in the nucleus of cells provides the "blueprint" for making proteins). DNA is usually double-stranded and includes sequences of nucleotides that consist of a phosphate group bonded to a sugar deoxyribose and one of four different nitrogenous bases—adenine (A), guanine (G), cytosine (C), or thymine (T). Ex. 1002 ¶ 21 (citing Ex. 1043, 5–6). In double-stranded DNA, one chain of nucleotides is attached to a "complementary" chain through the process called "base-pairing" with the bases (A) and (T) pairing together and the bases (C) and (G) pairing together and the double-stranded DNA molecule forming the classic double-helix conformation. *Id.*; *see also id.* ¶ 22 ("Different nucleotide sequences in DNA allow it to encode different proteins"); Ex. 2199 ¶ 54 ("These four nucleobases are arranged in specific sequences that, like letters of the alphabet, encode information in the form of genes that the cell can 'read' to make proteins.").

According to Patent Owner's declarant, Dr. Fuller, "the central dogma of biology explains that the genetic flow of information is from DNA to mRNA to protein." Ex. 2199 ¶ 55; *see also id.* ¶ 53 ("Every cell in the body of humans (and other mammals) has the necessary machinery to synthesize proteins"). "A process called transcription turns the double-stranded DNA into a single-stranded polynucleotide called messenger ribonucleic acid ('mRNA')." *Id.* ¶ 55 (explaining that mRNA contains the same A, G, and

C nucleobases, but thymine (T) is replaced by uracil (U)); Ex. 1002 ¶ 22 ("In the case or RNA [(e.g., mRNA)], the nucleotide monomers contain the sugar ribose (rather than deoxyribose), and the nitrogenous base thymine is replaced with uracil.").

mRNA is synthesized from DNA and transported out of the nucleus of the cell into the cell's cytoplasm where the mRNA is then "translate[d]" into the protein that the mRNA encodes. Ex. 2199 ¶¶ 55–56. Figure 3 of Dr. Fuller's declaration is reproduced below.

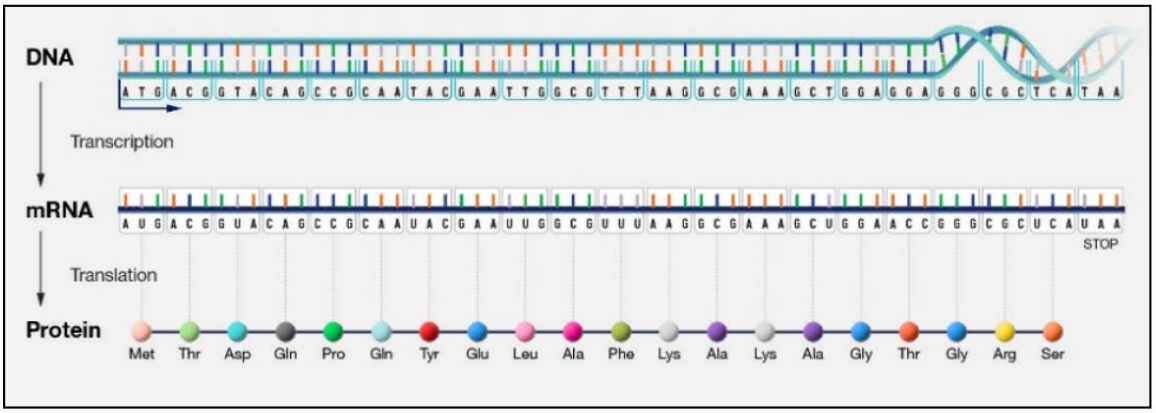


Figure 3. Ex. 2003. Central Dogma of transcription of DNA to mRNA and translation of mRNA to protein.

Id. ¶ 55 (Fig. 3). Figure 3 above is a schematic showing the two-step transcription and translation process wherein DNA is first transcribed to mRNA and mRNA is then translated into protein. *Id.* During translation, "each 'codon' of mRNA, containing three nucleobases, is turned into one amino acid," and the "individual amino acids are joined together in a chain that makes up the protein or polypeptide." *Id.* ¶ 56; *see also id.* ¶ 56 n.2 (explaining that particular "codons" (among 64 possible sequences) correspond to and encode particular amino acids (among the 20 amino

acids), such that "most amino acids are encoded by multiple codon sequences").

2. *Viruses: Coronavirus*

Viruses are infectious organisms that cannot survive and replicate on their own—instead, they infect a host cell and hijack that cell's machinery to create new viral copies of itself, which copies are then released from the host cell to spread within the body. Ex. 1002 ¶ 29 (citing Ex. 1043, 1431). A virus consists of genetic material (either DNA or RNA), a protein coat surrounding the genetic material, and (sometimes) a lipid envelope. *Id.* ¶ 28 (citing Ex. 1043, 1431).

Coronaviruses are a type of enveloped, single-stranded RNA virus. *Id.* ¶ 30 (citing 1079, 1). Betacoronavirus is a genus of coronavirus. *Id.* Coronaviruses, including betacoronavirus, have four main structural proteins: the nucleocapsid (N), membrane protein (M), envelope protein (E), and the spike protein (S). *Id.* ¶ 31; Ex. 2199 ¶ 104. Figure 7 of Dr. Fuller's declaration is reproduced below.

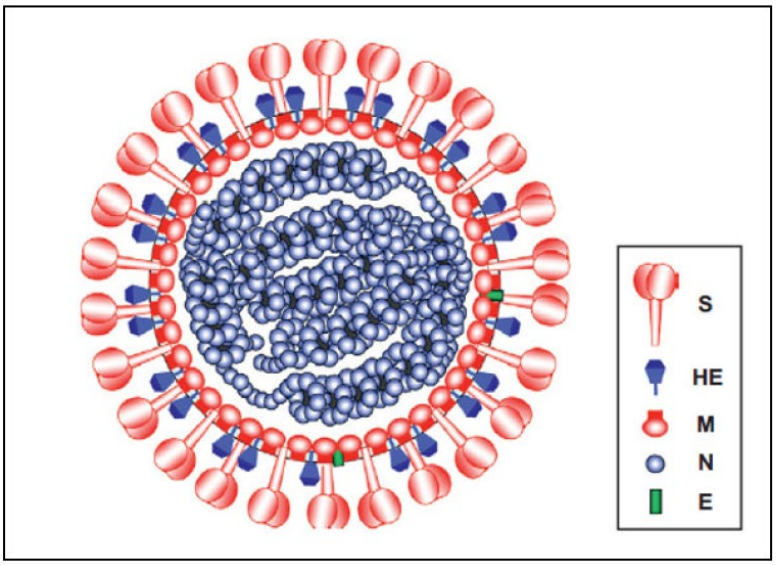


Figure 7. Ex. 2009, Fig. 3E. A betacoronavirus. S = spike protein. HE = hemagglutinin-esterase protein. M = membrane glycoprotein. N = nucleocapsid protein. E = envelope protein.

Ex. 2199 ¶ 105 (citing Ex. 2009, (Fig. 3E)). Figure 7 above shows an illustrative betacoronavirus viral particle, including positive-stranded RNA within the particle and surrounded by various viral proteins (N, M, E, and S). *Id.* (testifying that an envelope composed of the M, E, and S proteins surrounds the RNA and N protein).[1]

According to Dr. Griffin, the S protein "protrudes from the envelope and forms trimers (or, 'spikes') on the outer surface of the virus particle." Ex. 1002 ¶ 31. "Spike proteins mediate viral binding to and fusion with the target host cell." *Id.* (citing Ex. 1080, 1954); Ex. 2199 ¶ 122 ("The spike protein on a live betacoronavirus mediates entry of the betacoronavirus into

[1] Some betacoronaviruses include another surface protein called the homodimeric hemagglutinin-esterase (HE) glycoprotein. Ex. 2199 ¶ 105 (citing Ex. 2009, 812).

the host cell, causing infection and disease."). Moreover, Dr. Fuller explains, "the spike protein is composed of two protein subunits: the S1 subunit and the S2 subunit," where "the S1 subunit binds to a receptor on the host cell's surface, and the S2 subunit mediates fusion between the viral and host cell membranes." Ex. 2199 ¶ 122 (citing Ex. 2135, 468); *see also id.* (testifying that the S1 subunit includes the receptor-binding domain (RBD) and the S2 subunit includes the transmembrane (TM) and cytoplasmic (CP) domains) (citing Ex. 2135, Fig. 3a).

3. *Immune System*

The immune system helps protect the body from foreign pathogens, including viruses. Ex. 1002 ¶ 32.

As Dr. Griffin explains, the immune system can be characterized as including both "innate" and "adaptive" immune systems. *Id.* The innate immune system (e.g., macrophages that engulf bacteria or foreign particles) is not specific to a particular infectious agent, whereas the adaptive immune system "adapts to fight specific infections." *Id.* ¶¶ 32–33. "The primary components of the adaptive immune system are B-cells and T-cells," which are types of white blood cells. *Id.* ¶ 33 (citing Ex. 1043, 1364). B-cells can "recognize[] and bind[] to a particular structure on the surface of a pathogen (known as an antigen)," such that, "when a pathogen (like a virus) invades," B-cells that recognize the antigen can activate and "produce large amounts of a type of protein called an antibody." *Id.* The antibodies can recognize and bind the antigen and then neutralize the pathogen. *Id.* (citing Ex. 1043, 1364, 1375–76, 1384). T-cells are also part of the adaptive immune system and include receptors that can recognize polypeptides presented by an

antigen-presenting cell. *Id.* ¶ 34 (citing Ex. 1078, 138–41 ("T cells detect the presence of an intracellular pathogen because the infected cells display on their surface peptide fragments of the pathogen's proteins."), 336–37; Ex. 1043, 1392–93).

"Fundamental to the adaptive immune system is an immunological memory that allows T cells and B cells to remember a particular antigen," allowing the body's immune system to respond faster if it later encounters the antigen, such as a virus or viral protein. Ex. 1002 ¶ 35 (citing Ex. 1043, 1370–71); *see* Ex. 2199 ¶ 47 (testifying that antibodies "can bind to certain antigens (like a lock-and-key mechanism)" and, because the immune system has "memory" (e.g., due to a prior exposure to a virus/antigen), the body "readily produces . . . antigen-specific antibodies which bind to the antigen" on a virus, marking the virus for destruction) (citing Ex. 2001, S5–S7).

4. *Vaccines*

"To combat infections, including viral infections, scientists have long turned to vaccines, which can harness the body's immune system" and "prepare the body to protect itself from future exposure" to the virus or other pathogen. Ex. 1002 ¶ 36; Ex. 2199 ¶ 47.

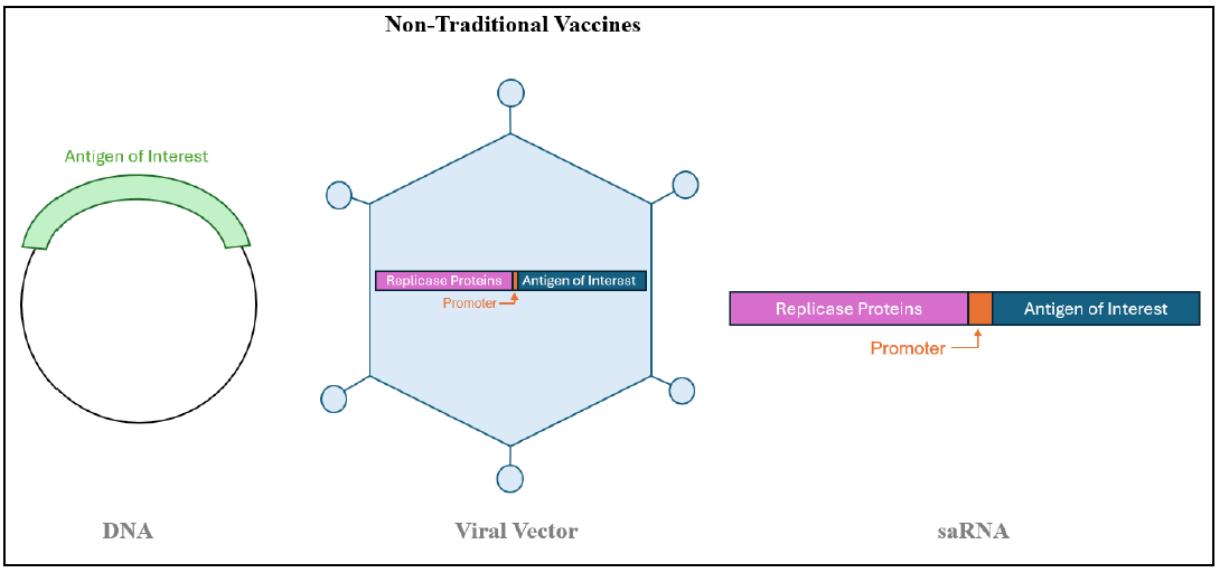
"Traditional vaccines worked by presenting the immune system with a weakened or inactivated piece of the pathogen (i.e., an antigen)." Ex. 1002 ¶ 36; Ex. 1078, 698–99. An antigen is "also called an 'immunogen.'" Ex. 2099 ¶ 48 (citing Ex. 2001, S5–S6); *see also id.* ¶¶ 49–51 (testifying that traditional vaccines used antigens derived directly from the pathogen (e.g., virus) and commonly used live-attenuated (weakened), inactivated (dead), and protein (e.g., subunit or single antigen) vaccines; citing, for example, the

live-attenuated vaccines developed against smallpox in the late 18th century, as well as the vaccines against polio and measles). Presentation of the antigen "stimulates the body's adaptive immune system to make antibodies against that specific antigen" and, because the immune system retains a "memory," if the body is exposed later to the virus/antigen, the body uses its memory "to more efficiently make antibodies against that virus." Ex. 1002 ¶ 36 (citing Ex. 1043, 1369–71; Ex. 1078, 699–700).

More recently, scientists have developed "[n]on-traditional vaccines (e.g., DNA, viral vectors, self-amplifying RNA, and mRNA)," which "include nucleic acids that contain the genetic information required for the body's own cells to make the antigen of interest." Ex. 2199 ¶ 53; *see also* Ex. 1002 ¶ 37 ("In the 1990s, a new category of vaccines gained acceptance: nucleic acid vaccines. Unlike traditional vaccines, which directly contain an antigen, nucleic acid vaccines contain DNA or mRNA *encoding* an antigen.") (citing, *e.g.*, Ex. 1014[2] (describing immunization of mice using liposome-entrapped mRNA encoding viral nucleoprotein to generate an anti-influenza cytotoxic T lymphocyte response)). Thus, nucleic acid "vaccines rely on the subject's own cellular machinery" that is responsible for making proteins to make the antigen/immunogen. Ex. 1002 ¶ 37; Ex. 2199 ¶ 53.

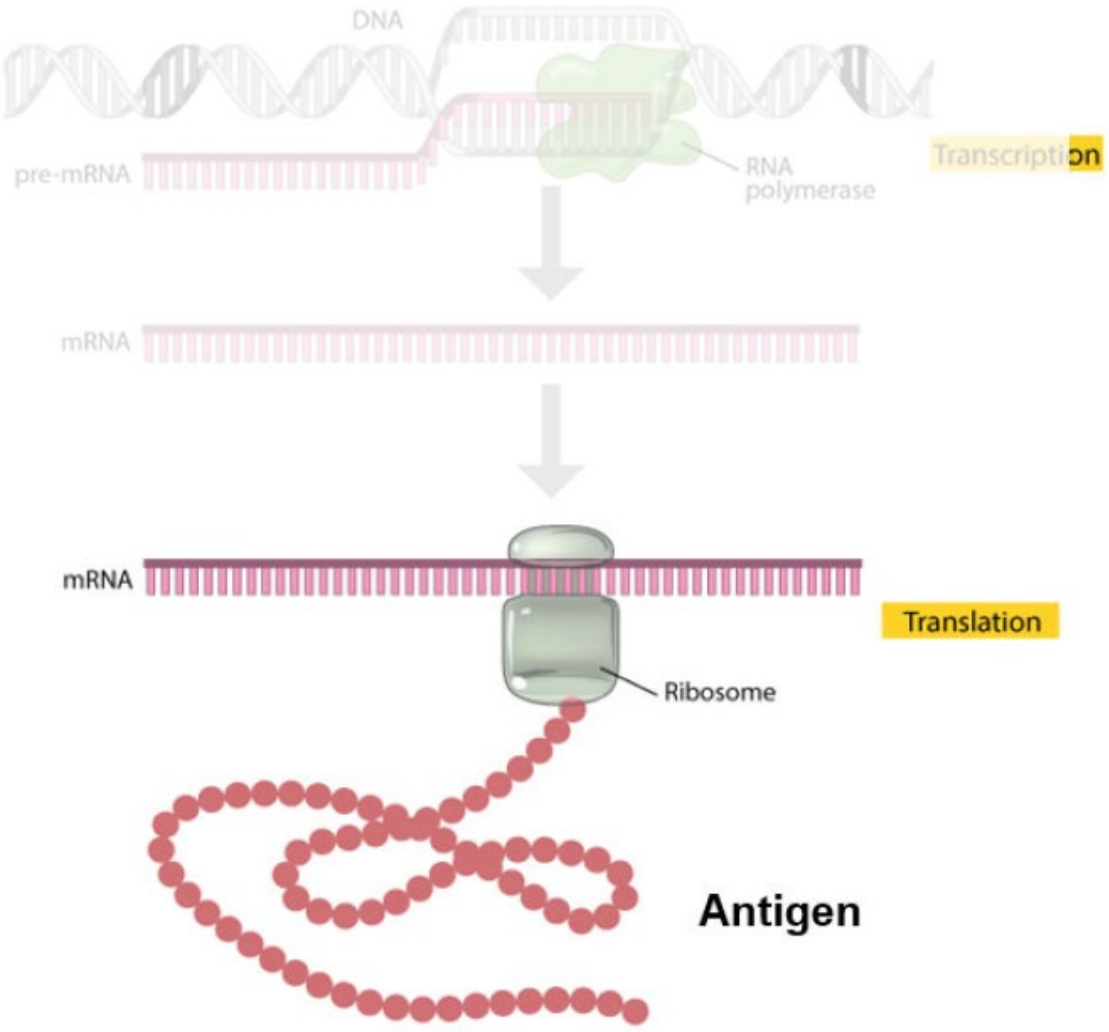
Figure 4 from Dr. Fuller's declaration is reproduced below, depicting three "[n]on-traditional vaccines."

[2] Frédéric Martinon et al., *Induction of virus-specific cytotoxic T lymphocytes in vivo by liposome-entrapped mRNA*, 23 Eur. J. Immunol., 1719–1722 (1993).



Ex. 2199 ¶ 60 (Fig. 4 (caption omitted)). The figure above is an illustration of DNA, viral vector, and self-amplifying RNA (saRNA) vaccines. *Id.* A DNA vaccine includes genetic information for the antigen of interest (green); the DNA is delivered to the cells where it enters the nucleus, mRNA that encodes for the antigen of interest is transcribed from the DNA, and that mRNA then leaves the nucleus for the cytoplasm where it is translated into protein (i.e., the antigen). *Id.* ¶¶ 58–60 (testifying that the first DNA vaccine clinical trial was initiated in 1995 for influenza); Ex. 1002 ¶ 38.

Unlike DNA vaccines, an mRNA vaccine "skip[s]" the transcription steps because mRNA delivered to the cells can be directly translated in the cytoplasm into the antigen encoded by that mRNA. Ex. 1002 ¶¶ 38–39 (citing Ex. 1019, 1321; Ex. 1018, Fig. 1); Ex. 2199 ¶ 71 ("Once (and if) the mRNA enters the host cell cytoplasm, the cell's machinery (i.e., the ribosome) will translate it into the antigen of interest without any intervening steps."). This process is depicted in the image below.



Ex. 1002 ¶¶ 38–39 (adapting image from Ex. 1018, Fig. 1). The image above shows a direct translation of mRNA into the antigen of interest, and transcription steps where mRNA is prepared from DNA are greyed out. *Id.*

Viral vector and saRNA vaccines include genetic information for the antigen of interest as well as genetic information that encodes for non-structural viral "replicase" proteins. Ex. 2099 ¶¶ 61–63 (explaining that viral vectors contain an "engineered" virus (e.g., one derived from the Semliki Forest virus ("SFV")) that acts as a vector for genetic material of another virus (i.e., the antigen of interest)), 67 (explaining that saRNA

vaccines are not delivered in viral particles like viral vector vaccines, and instead are delivered "naked" or in delivery vehicles such as liposomes or polymeric nanoparticles). Figure 4 of Dr. Fuller's declaration (above) shows viral vector and saRNA vaccines that include sequences of nucleic acids (i.e., RNA) related to the replicase proteins (pink), a sub-genomic promoter (orange), and the antigen (dark blue segment). By using the cell's own machinery to produce replicase proteins, these vaccines produce more copies of the RNA, leading to amplified production of the antigen. Ex. 2199 ¶¶ 62 ("The replicase machinery allows the viral vector to replicate to produce more copies of its RNA."), 69–70 ("The ability of saRNA to replicate within the cell gives rise to many copies of the sub-genomic RNA, which, in turn, leads to 'amplifi[ed]' production of the antigen.") (citing, *e.g.*, 1010, 12:1–27 ("The overall results of this sequence of transcriptions is a huge amplification in the number of the introduced replicon RNAs and so the encoded immunogen becomes a major polypeptide product of the cells.")).

D. The '600 Patent

The '600 patent is titled "Betacoronavirus mRNA Vaccine." Ex. 1001, code (54) (capitalization omitted). The '600 issued from an application filed February 28, 2020. *Id.* at code (22). The '600 patent further claims priority to several other, earlier-filed applications, including non-provisional applications filed in 2017 and 2018. *Id.* at code (63). The '600 patent also claims priority to nine provisional applications, the earliest of which were filed October 22, 2015. *Id.* at code (60).

According to the '600 patent, "[r]espiratory disease is a medical term that encompasses pathological conditions affecting the organs and tissues

that makes gas exchange possible in higher organisms." *Id.* at 1:27–32 (explaining that such disease includes, for example, conditions of the upper respiratory tract, bronchi, alveoli, and the nerves and muscles that affect breathing). Further, the patent explains, "[r]espiratory disease is a common and significant cause of illness and death around the world." *Id.* at 1:35–37.

The '600 patent provides, as background, an overview of various viruses and the respiratory diseases that such viruses may cause. *Id.* at 1:27–3:9. The '600 patent identifies, among other viruses, Parainfluenza virus type 3 (PIV3), Respiratory Syncytial Virus (RSV), and Betacoronaviruses (BetaCoVs). *Id.* Regarding Betacoronaviruses, the '600 patent states:

> Betacoronviruses (BetaCoVs) are one of four genera of coronaviruses of the subfamily Coronavirinae in the family Coronaviridae . . . . They are enveloped, positive-sense, single-stranded RNA viruses of zoonotic origin. . . . The BetaCoVs of the greatest clinical importance concerning humans are OC43 and HKU1 of the A lineage, SARS-CoV of the B lineage, and MERS-CoV of the C lineage.

Id. at 2:47–57. The '600 patent notes the prior reported outbreaks of MERS-CoV between 2012 and 2015. *Id.* at 2:60–3:5. Further, the '600 patent reports that SARS "emerged in China in 2002 and spread to other countries before [being] brought under control." *Id.* at 3:4–6. However, "[b]ecause of a concern for reemergence or a deliberate release of the SARS coronavirus, vaccine development was initiated." *Id.* at 3:6–8.

In summarizing the invention, the '600 patent states:

> Provided herein are ribonucleic acid (RNA) vaccines that build on the knowledge that RNA (e.g., messenger RNA (mRNA)) can safely direct the body's cellular machinery to produce nearly any protein of interest, from native proteins to

> antibodies and other entirely novel protein constructs that can have therapeutic activity inside and outside of cells. The RNA (e.g., mRNA) vaccines of the present disclosure may be used to induce a balanced immune response against hMPV, PIV, RSV, MeV, and/or BetaCoV (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKUl), or any combination of two or more of the foregoing viruses, comprising both cellular and humoral immunity, without risking the possibility of insertional mutagenesis[.]

Id. at 3:24–37. According to the '600 patent, "[t]he RNA (e.g., mRNA) vaccines have superior properties in that they produce much larger antibody titers and produce responses earlier than commercially available anti-viral therapeutic treatments." *Id.* at 3:56–59. Moreover, the '600 patent explains, "[u]nlike traditional vaccines, which are manufactured ex vivo and may trigger unwanted cellular responses, RNA (e.g., mRNA) vaccines are presented to the cellular system in a more native fashion." *Id.* at 3:64–3:67.

More specifically, the '600 patent states that, in embodiments, the BetaCoV is, for example, MERS-CoV or SARS-CoV, and the vaccine comprises at least one mRNA polynucleotide that encodes a BetaCoV antigenic polypeptide. *Id.* at 7:15–23. The encoded BetaCoV polypeptide may be a structural protein such as a spike protein (S) or a subunit or immunogenic fragment thereof. *Id.* at 7:25–28; *see also id.* at 213:57–214:10 (Example 23, mouse study using an mRNA vaccine encoding MERS-CoV spike protein and subunit), 214:11–214:66 (Example 24, rabbit study using mRNA vaccine encoding MERS-CoV spike protein). The '600 patent also discloses that the vaccine may comprise the mRNA polynucleotide formulated in a cationic lipid nanoparticle. *Id.* at 4:1–5.

E. Challenged Claims

The '600 patent includes 26 claims, of which claims 1, 2, 4–6, 8–12, 16, 17, 20, 21, and 26 are challenged here. Claim 1 is illustrative of the subject matter of the challenged claims and is reproduced below.

> 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.

Ex. 1001, 737:26–29.

F. Asserted Grounds of Unpatentability

Petitioner asserts that claims 1, 2, 4–6, 8–12, 16, 17, 20, 21, and 26 would have been unpatentable on the following grounds:

Claim(s) Challenged	35 U.S.C. §[3]	Reference(s)/Basis
1, 2, 4–6, 8–12, 16, 17, 20, 21, 26	102(a)	Schrum[4]
1, 2, 4–6, 8–12, 16, 17, 20, 21, 26	103	Schrum, Geall[5]

[3] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112–29, 125 Stat. 284, 285–88 (2011), revised 35 U.S.C. §§ 102, 103 effective March 16, 2013. Petitioner asserts that the earliest date to which the '600 patent claims priority is October 22, 2015. Pet. 2–3. Patent Owner does not dispute this. Because that date falls after the effective date of the applicable AIA amendments, we apply the AIA versions of §§ 102 and 103 here.

[4] de Fougerolles et al., US 2013/0266640 A1, publ. Oct. 10, 2013 (Ex. 1009 ("Schrum")). Because the parties refer to this reference as "Schrum" rather than by the name of the first listed author, we do the same.

[5] Geall, WO 2012/006369 A2, publ. Jan. 12, 2012 (Ex. 1010 ("Geall")).

Claim(s) Challenged	35 U.S.C. §[3]	Reference(s)/Basis
1, 2, 4–6, 8–12, 16, 17, 20, 21, 26	103	Schrum, Yang[6]
1, 2, 4–6, 8–12, 16, 17, 20, 21, 26	103	Schrum, Altmeyer[7]

Petitioner relies on the declarations of Dr. Daniel O. Griffin (Exs. 1002 and 1159), Dr. James J. Moon (Exs. 1004 and 1161), Mr. Christopher Bakewell (Ex. 1163), and Dr. L. Ross Pierce (Ex. 1164). Patent Owner relies on the declarations of Mr. James E. Malackowski (Ex. 2197), Dr. Warren Chan (Ex. 2198), Dr. Deborah H. Fuller (Ex. 2199), and Dr. Philip Krause (Ex. 2200). The deposition testimony of the above declarants is also of record. Exs. 2114 and 2253 (Griffin transcripts); Exs. 2113 and 2254 (Moon transcripts); Ex. 2256 (Pierce transcript); Ex. 2255 (Bakewell transcript); Ex. 1104 (Fuller transcript); Ex. 1105 (Krause transcript); Ex. 1152 (Chan transcript); Ex. 1157 (Malackowski transcript).[8]

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[6] Zhi-yong Yang et al., *A DNA vaccine induces SARS coronavirus neutralization and protective immunity in mice*, 428 Nature 561–564 (Apr. 1, 2004) (Ex. 1011 ("Yang")).

[7] Altmeyer et al., WO 2005/118813 A2, publ. Dec. 15, 2005 (Ex. 1012 ("Altmeyer")).

[8] The record in this case is extraordinarily voluminous, including more than 500 exhibits and declarations from 8 different witnesses spanning hundreds of pages (the Fuller Declaration, for example, is 458 pages long and the Griffin Declarations are a combined 352 pages long). Our ability to review the record is complicated by the parties' copious use of blanket citations. *See e.g.*, PO Resp. 26 (citing Ex. 2199 §§ XI.B–XI.J, XI.L–XI.N); Pet. Reply 23 (citing Ex. 1164 ¶¶ 1–76), 27 (citing Ex. 1163 ¶¶ 1–154). Neither party moved to strike any argument here as involving an improper incorporation-by-reference, although Patent Owner mentions Rule 42.6(a)(3) in a footnote arguing that Petitioner's "citations to large expert declaration sections should be disregarded." PO Sur-reply 5 n.4 (citing 37 C.F.R.

II. ANALYSIS

A. Legal Principles

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3)).

A claim is unpatentable under 35 U.S.C. § 103 if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the relevant art. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective indicia of nonobviousness when presented. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). Moreover, "[a]n obviousness determination requires finding both that a skilled artisan would have been

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§ 42.6(a)(3)). Although we do not call out here, or elsewhere in this Decision, each instance of blanket citation or incorporation by reference, we considered only arguments raised in the briefing and evidence identified by the parties with specificity. 37 C.F.R. § 42.6(a)(3). We endeavored to consider all of the evidence and argument properly called to our attention but note that it was not our responsibility to make the parties' cases for them. *See, DeSilva v. DiLeonardi*, 181 F.3d 865, 866-67 (7th Cir. 1999) (Incorporation by reference "is a pointless imposition on the court's time. A brief must make all arguments accessible to the judges, rather than ask them to play archeologist with the record.").

motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *CRFD Rsch., Inc. v. Matal*, 876 F.3d 1330, 1340 (Fed. Cir. 2017) (internal quotation marks omitted).

B. Level of Ordinary Skill in the Art

Petitioner describes a person of ordinary skill in the art ("POSA" or "skilled artisan") as follows:

> [A] research team with (1) 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.

Pet. 15 (citing Ex. 1002 ¶ 11; Ex. 1004 ¶ 16).

Patent Owner contends that "a POSA would have had an M.D. and/or Ph.D in immunology, virology, biochemistry, chemistry, or a related discipline, and three or more years of work experience in such fields, and would have been part of a team including biochemists, chemists, drug delivery scientists, and/or clinicians." PO Resp. 3–4.

The parties agree that the POSA would have included, or been part of, a research team. Pet. 15; PO Resp. 4. The parties also propose that the POSA would have experience and expertise in similar subject matter. For example, Petitioner proposes that the POSA would have expertise in vaccines and/or virology while Patent Owner proposes that the POSA would

have expertise in virology and have been part of a team including clinicians and/or biochemists. *Id.* Similarly, the parties agree that the POSA would have expertise in drug delivery. Petitioner's definition is more explicit or specific in certain respects compared to Patent Owner's definition. For example, Petitioner proposes expertise in the field of nucleic acids including nucleic acid therapeutics. Patent Owner, nevertheless, contends that its definition also includes "expertise in nucleic acids among the listed disciplines." PO Resp. 4.

We do not consider the differences between the parties' definitions to be material; we would reach the same result under either definition. Petitioner's description of a POSA is consistent with the subject matter of the '600 patent and with the prior art of record. And the additional detail in Petitioner's definition is helpful. Accordingly, we adopt Petitioner's definition. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001). In applying Petitioner's definition of the POSA, we make one addition resulting from the fact that Petitioner's definition does not specify a duration of work experience. Where Petitioner's definition specifies work experience, we consider the duration of such experience to be three or more years (consistent with Patent Owner's suggested duration).[9]

[9] We applied this same POSA definition at institution and invited the parties to address it during trial to the extent material to their arguments. Inst. Dec. 31–32. Although Patent Owner contends that some of its experts have more experience than Petitioner's in some areas (e.g., developing nucleic acid vaccines), Patent Owner did not propose any new definition or argue that Petitioner's experts were unqualified to testify from the POSA's perspective. *See, e.g.*, PO Resp. 3–6 (asserting that "[Patent Owner's] technical experts satisfy [Patent Owner's], Petitioners', and the Board's definitions, [and]

C. Claim Construction

We interpret a claim "using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b)." 37 C.F.R. § 42.100(b) (2020). Under this standard, we construe the claim "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." *Id.*

Petitioner proposes that, for purposes of this proceeding, the claims should be given the claim constructions advanced by Patent Owner and adopted by the district court in the Massachusetts Litigation. Pet. 21. Petitioner, thus, proposes that the claims be construed as follows:

- **betacoronavirus**: "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**: a "spike protein," which is "a structural protein forming a spike."
- **open reading frame**: "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**: "a mammal."

Id.; *see also* Ex. 1035 (district court's order on claim construction).

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their opinions remain the same under each, and the arguments herein apply under each"); Tr. 52:1–14 (arguing the differences in the respective backgrounds of the parties' experts comes down to a "credibility determination").

Patent Owner states that it agrees "the Board should adopt the constructions of 'betacoronavirus,' 'open reading frame,' and 'subject' from the district court litigation." PO Resp. 6–7 (citation omitted). Patent Owner additionally proposes that we should construe three terms. First, Patent Owner proposes that we construe the term "mRNA" to mean "messenger ribonucleic acid" and to exclude "saRNA or components necessary for viral replication." *Id.* at 7. Second, Patent Owner proposes that we construe the term "S protein" to mean "a full-length spike protein where the spike protein is a structural protein forming a spike." *Id.* at 7–8. Third, Patent Owner proposes that we construe the term "S protein subunit" to mean the "S1 or S2 subunit." *Id.* at 8. We address each of the terms the parties have identified for construction in turn.

1. *"Betacoronavirus"*

The parties do not dispute the meaning of the term "betacoronavirus." Absent any apparent dispute, we do not find it necessary to further interpret this term. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))); *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011). Notwithstanding the above, consistent with the parties' agreed construction, we note that the term "betacoronavirus" covers a broad genus of viruses, including, for example, SARS-CoV and MERS CoV. Ex. 1001, 3:29–41 (listing example BetaCoVs); Ex. 1029, 810 (taxonomic tree identifying BetaCoV genus and lineages).

2. "S protein"

The parties agree that the term "S protein" refers to "a structural protein forming a spike." Pet. 21; PO Resp. 7. We adopt this construction. The arguments provided by the parties present two additional claim construction issues relating to the construction of the term "S protein." First, the parties dispute whether the term "S protein" should be limited to a "full length S protein." Second, the parties dispute whether the "S protein" must actually form a spike. We address each of these two issues in turn.

a) Is "S protein" limited to "full length S protein"?

Patent Owner proposes that we add to the agreed construction that the "S protein" is a "full-length spike protein." PO Resp. 7–8. According to Patent Owner, this would clarify that "S protein" "does not refer to a subunit . . . or any truncated form" of the spike protein. *Id.*[10] Petitioner opposes this addition, asserting that the term "S protein" should not be limited to a full-length protein. Pet. Reply 3. We agree with Petitioner that the term "S protein" should not be limited to a full-length protein.

Before we begin our analysis, we provide further background regarding the makeup of betacoronavirus spike protein. As Dr. Fuller explains, the spike ('S') protein typically contains 1128–1472 amino acids and is a trimeric glycoprotein that surrounds the surface of the betacoronavirus particle. Ex. 2199 ¶ 121. In the case of the SARS-CoV

[10] The district court's claim construction does not limit the term "S protein" to only the full-length protein and, as argued by Petitioner, Patent Owner apparently did not seek such a construction with the court. Pet. Reply 3 (citing Ex. 1035, 11).

betacoronavirus, it is "predicted to be 1,255 amino acids in length." Ex. 1031, 227; *see also* Ex. 1011, 561 (depicting full-length SARS-CoV S protein as 1,255 amino acids long). "[T]he spike protein is composed of two protein subunits: the S1 subunit and the S2 subunit." Ex. 2199 ¶ 122 (testimony of Dr. Fuller). Together, the S1 and S2 subunits comprise a full-length spike protein. *Id.* Fig. 9B.

The Specification of the '600 patent teaches that, in addition to the S1 and S2 subunits, a spike protein may comprise "immunogenic fragments" of the S protein. *See, e.g.*, Ex. 1001, 7:23–28 ("In some embodiments, at least one antigenic polypeptide is a *betacoronavirus* structural protein. For example, a *betacoronavirus* structural protein may be a spike protein (S), envelope protein (E), nucleocapsid protein (N), membrane protein (M) or ***an immunogenic fragment thereof***.") (emphasis added); *see also id.* at 7:28–33 ("In some embodiments, a betacoronavirus structural protein is a spike protein (S). In some embodiments, a betacoronavirus structural protein is a S1 subunit or a S2 subunit of spike protein (S) or ***an immunogenic fragment thereof***.") (emphasis added); *see also,* Ex. 2199 ¶ 193 (acknowledging potential existence of a "truncated version of a spike protein"); Ex. 1011, 561 (reflecting existence of truncated immunogenic fragments of spike protein).

With this background, we see two possibilities for the meaning of the term "S protein." First, as Patent Owner proposes, it could refer to the full-length S protein only. Second, it could encompass the full-length BetaCoV S protein as well as fragments of that protein. Put another way, in this second case, "S protein" encompasses a genus comprising the full-length S

protein, subunits S1 and S2, and fragments of the S protein, including immunogenic fragments that include some or all portions of the S1 and/or S2 subunits. We now consider which of these two possible constructions is best supported by the evidence of record.

We begin our analysis by considering the language of the claims, which provides support for both possible constructions. The challenged claims recite "a betacoronavirus (BetaCoV) S protein or S protein subunit." Ex. 1001, 737:26–29, 739:25–32. On the one hand, the term "full-length" does not appear anywhere in the challenged claims. *Id.* This supports that the claimed "S protein" is not limited to a full-length S protein. On the other hand, the claims separately recite "S protein" and "S protein subunit." Ex. 1001, 737:30–31; *see also id.* at 737:30–31 (dependent claim 2, reciting "S protein" without reciting "subunit"), 737:32–34 (dependent claim 3 (unchallenged) reciting "S protein subunit selected from an S1 subunit and an S2 subunit"). This suggests that the term "S protein" is distinct from, and does not encompass, "S protein subunits" and thus does not describe a genus. *Wasica Finance GmbH v. Continental Automotive Sys., Inc.*, 853 F.3d 1272, 1288, n.10 (Fed. Cir. 2017) (holding that a construction rendering a claim term "superfluous" is "disfavored")).

We turn now to the Specification. The Specification uses the term "full-length" many times as a modifier for the term "spike protein." *See*, *e.g.*, *id.* at 24:51–25:40 (describing Figures 17–21 as including data relating to "the full-length Spike protein"), 213:57–214:56 (describing Examples 23 and 24, immunogenicity studies that used a vaccine comprising "the full-length Spike protein"), Table 10 (listing "Betacoronavirus Nucleic Acid

Sequence[s]" including sequences identified as "full-length" and "FL" sequences), Table 12 (listing GenBank Accession numbers for "Full-length Spike Glycoprotein Amino Acid Sequences (*Homo sapiens* strain)"). As Petitioner points out this supports that "when the specification refers to a 'full-length Spike (s) protein,' it does so expressly, suggesting that the claim language lacking that qualifier is not so limited." Pet. Reply 3.

In addition, the Specification includes multiple disclosures where the term "S protein" appears to be used to describe a genus. For example, the Specification repeatedly states that its vaccine embodiments may comprise an "RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2)." Ex. 1001, 35:9–35, 35:64–36:24 (repeating this language many times). This also supports that the term "S protein" encompasses "S" (allegedly the full-spike) as well as the S1 and S2 subunits.

The Specification also includes two working examples of betacoronavirus vaccines. *Id.* at 213:60–214:56 (Examples 23 and 24). One of these examples tested an mRNA vaccine encoding the "full-length Spike (S) protein" and the "S2 subunit (S2)" of MERS-CoV; the other tested an mRNA vaccine encoding "full-length Spike (S) protein." *Id.*; *see also id.* at Figs. 17–21 (graphs and images relating to the immunogenicity tests described in Examples 23 and 24), 24:51–25:39 (text describing Figs. 17–21). Consistent with this disclosure, the Specification provides betacoronavirus nucleotide and amino acid sequences relating only to the full-length spike protein and the S2 subunit. *Id.* at Table 10 (providing full-length and S2 nucleotide sequences), Table 11 (providing amino acid sequences), Table 12 (providing GenBank Accession numbers for full-length

amino acid sequences of various strains of betacoronavirus); Ex. 2199 ¶¶ 166–169 (testimony of Dr. Fuller discussing Tables 10–12 of the '600 patent).

Patent Owner identifies the fact that the '600 patent provides data, nucleotide sequences, and amino acid sequences only for full-length S protein and its S2 subunit as a reason why the "S protein" should be construed as limited to the full-length protein. PO Sur-reply 4 ("because the specification refers to 'full-length Spike (S) protein,' includes figures and data for ***full-length*** spike, and recites only working examples, amino acid sequences, and nucleic acid sequences with ***full-length*** S-protein (or S2 subunit), S-protein should be construed as 'full-length.'").

The focus in the Specification's examples on full-length and S2 subunit spike protein lends some support to Patent Owner's position. However, we are reluctant to limit the scope of the claim to what is disclosed in its working embodiments. *Superguide Corp. v. DirectTV Enterprises, Inc.,* 358 F.3d 870, 875 (Fed. Cir. 2004).

Moreover, the Specification makes clear that truncated spike proteins do not fall outside the scope of its disclosure. *See*, *e.g.,* Ex. 1001, 44:17–25 ("amino acid residues located at the carboxy and amino terminal regions of the amino acid sequence of a peptide or protein may optionally be deleted providing for truncated sequences"); 45:26–48 ("As recognized by those skilled in the art, protein fragments, functional protein domains, and homologous proteins are also considered to be within the scope of polypeptides of interest."); *see also id.* at 4:48–61 (disclosing that, in embodiments, the RNA (e.g., mRNA) vaccine comprises an mRNA

polynucleotide encoding at least one BetaCoV "antigenic polypeptide," and "[h]erein, use of the term 'antigenic polypeptide' encompasses immunogenic fragments of the antigenic polypeptide . . . unless otherwise stated"). And the claims make clear that their scope is not limited by any specific examples in the Specification. For example, some claims expressly recite betacoronavirus S1 subunit, for which no explicit data or examples are provided in the Specification. *See*, *e.g.*, *id.* at 737:32–34, 738:35–37 (dependent claims 3 and 18, specifically reciting the S1 subunit).

Finally, the Specification includes disclosure that Patent Owner contends "use[] 'S protein' interchangeably with full-length spike protein, while distinguishing from subunits." PO Resp. 8. In particular, the Specification states:

> In some embodiments, a betacoronavirus structural protein is a spike protein (S). In some embodiments, a betacoronavirus structural protein is a S1 subunit or a S2 subunit of spike protein (S) or an immunogenic fragment thereof.

Ex. 1001, 7:28–32, 34:60–35:1 (similar), 35:9–12 (similar); 35:64–67 (similar).[11] Considering this passage in isolation, Patent Owner's interpretation that this passage uses the terms "spike protein" and "full-length spike protein" interchangeably is plausible. However, the better

[11] We consider the phrase "immunogenic fragment thereof" in the above passage to modify the term "betacoronavirus structural protein" rather than the "S1 subunit or . . . S2 subunit." This is consistent with the disclosure immediately preceding the quoted passage: "In some embodiments, at least one antigenic polypeptide is a betacoronavirus structural protein. For example, a betacoronavirus structural protein may be a spike protein (S), envelope protein (E), nucleocapsid protein (N), membrane protein (M) or an immunogenic fragment thereof." Ex. 1001, 7:24–30.

interpretation—consistent with the use of the modifier "full length" elsewhere in the Specification (*id.* at 24:51–25:40, 213:57–214:56, Table 10, Table 12) and statements describing "S protein" as including "S, S1 and/or S2" (*id.* at 35:9–35, 35:64–36:24)—is that the first sentence of the passage describes a genus and the second sentence describes non-limiting species within that genus. Accordingly, this passage does little to support Patent Owner's proposed claim construction.

Considering all of the evidence and argument before us, we decline Patent Owner's invitation to add the modifier "full length" to the term "S protein." The evidence supporting each parties' proposed constructions stands in near equipoise. We acknowledge that the claims separately list "S protein" and "S protein subunit" and that the Specification lacks data for an mRNA vaccine that encodes S protein fragments/truncations (excepting the S2 subunit, assuming that qualifies as a fragment/truncation) or that encodes the S1 subunit. Nonetheless, the absence of the modifier "full length" in the claims, the presence of the modifier "full length" in the Specification, and the broader use of the term S protein as a genus that comprises the full length protein and fragments in the Specification, persuades us that the term "S protein" should be not be construed as limited to "full-length S protein."[12]

[12] Our determination that "S protein" should not be construed as limited to the full-length protein is not dispositive because, as discussed in detail (*infra* §§ II.E.2. and II.F), the prior art teaches or suggests the use of full-length S protein. Put another way, we would reach the same ultimate result in this Decision under Patent Owner's proposed construction.

b) Do the claims require that the S protein form a spike?

The parties agree that an "S protein" is "a 'spike protein,' which is 'a structural protein forming a spike.'" Pet. 21 (quoting Ex. 1035 (district court claim construction)); PO Resp. 7. Patent Owner argues that, under the parties' agreed claim construction, Petitioner must show—"whether through evidence from testing or otherwise"—that the S protein expresses itself in the form of a spike. PO Resp. 18. We disagree. There is nothing in the language of the claims that requires that the S protein be expressed, or that the form of expression it takes is that of a spike. *See*, *e.g.,* Ex. 1001, 737:26–29 (claim 1). Although the parties' agreed construction identifies S protein as a protein "forming a spike," this language merely identifies the protein that is encoded by the open reading frame. Accordingly, we do not construe "S protein" to require expression of the encoded protein or any subsequent folding or formation of a spike by said protein.[13]

3. *"Open reading frame"*

No dispute in this proceeding turns on the meaning of "open reading frame." Absent any dispute between the parties as to how this term should be construed, we do not find it necessary to further construe this term. *See*

[13] Notwithstanding this construction of "S protein," if claim 1 were interpreted to require actual protein expression and folding of said protein to form the eponymous "spike," we find that such subject matter is suggested in the prior art and would have been obvious as we discuss below. *See* §§ II.E.2 and II.F. Accordingly, even under such alternative interpretation, the result in this Final Written Decision would not change.

Nidec, 868 F.3d at 1017; *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d at 1361.

4. *"Subject"*

The parties agree that the term "subject" should be construed as it was in the district court litigation (Pet. 21; PO Resp. 6–7), but this term does not appear in any of the challenged claims (Ex. 1001, 737:26–739:2).[14] None of the issues in dispute in this proceeding turn on the meaning of the term "subject." Accordingly, we need not expressly construe the term "subject" in this proceeding.

5. *"mRNA"*

Patent Owner contends that we should construe the term "mRNA" to make clear that it does not encompass self-amplifying RNA (saRNA). We recognize that there is a distinction between mRNA and saRNA. *See*, *e.g.,* Ex. 1001, 40:47–49 ("the mRNA of the invention are not self-replicating RNA and do not include components necessary for viral replication"). However, Petitioner does not rely upon saRNA as meeting the claimed mRNA, and Schrum undisputedly discloses mRNA. *See, e.g.*, PO Resp. 27–28 (arguing, *inter alia*, that Schrum (with or without Geall) does not disclose the claimed S protein as an antigen, but offering no argument or evidence rebutting Petitioner's contention that Schrum describes mRNA-based vaccines); *see, e.g.*, Ex. 1009 ¶¶ 340–342; Ex. 1002 ¶¶ 68–69. Accordingly, we do not find it necessary to expressly construe mRNA. *See Nidec*, 868

[14] The method claims in related IPR2023-01359 recite administering to a "subject." In that case, we found the parties agreed construction helpful in reflecting the scope of the claim (i.e., administration to any mammal).

F.3d at 1017; Tr. 65–66 (Patent Owner's counsel acknowledging "I don't think there's a dispute between the parties on this point" unless Petitioner contends that "Geall disclosed the claimed mRNA").

6. *"S protein subunit"*

Patent Owner contends that "'S protein subunit' should be construed as 'S1 subunit or S2 subunit.'" PO Resp. 9. Petitioner does not challenge this interpretation or propose any alternative. Pet. Reply 3. Although Petitioner did not rely on the prior art's disclosures as meeting the "S protein subunit" language of the challenged claims, we adopt Patent Owner's uncontested interpretation for this Decision, which we find helps illustrate the scope of the claims. PO Resp. 15 n.3; *see also id.* at 44 n.10 ("Petitioners argue obviousness based only on purported teaching of S protein, not subunits.").[15]

D. Overview of the Asserted Prior Art

Petitioner asserts that each of the asserted references below is prior art. Pet. 14–19. Patent Owner does not contest the prior-art status of these references. PO Resp. 9–11.

1. *Schrum (Ex. 1009)*

Schrum is a U.S. patent application that published October 10, 2013. Ex. 1009, code (43). Schrum relates generally to compositions "comprising modified nucleic acid molecules which may encode a protein" and, further,

[15] Our interpretation of "S protein" includes S-protein fragments while our construction of "S protein subunit" includes only the S1 and S2 subunits.

"nucleic acids useful for encoding polypeptides capable of modulating a cell's function and/or activity." Ex. 1009, Abstr.

In summarizing the invention, Schrum teaches that, "[i]n one aspect a method of producing a polypeptide of interest in a mammalian cell or tissue is described." *Id.* ¶ 5. Further, Schrum discloses that "[t]he method comprises contacting the mammalian cell or tissue with a formulation comprising a modified mRNA encoding a polypeptide of interest," and the "formulation may be, but is not limited to, nanoparticles." *Id.*; *see also id.* ¶¶ 58 (abbreviating "modified mRNA" as "mmRNA" and disclosing, e.g., that mmRNA may include nucleoside chemical modifications, such as a "pseudouridine" modification), 26 (listing nucleoside modifications, including 1-methylpseudouridine). Schrum discloses that the "formulations of modified mRNA may comprise a fusogenic lipid [(e.g., DSPC)], cholesterol and a PEG lipid." *Id.* ¶ 8 ("The formulation may have a molar ratio 50:10:38.5:1.5-3.0 (cationic lipid: fusogenic lipid: cholesterol: PEG lipid)"); *see also id.* ¶¶ 35, 38 (describing lipid nanoparticle composition).

Schrum includes a section titled "Activation of the Immune Response: Vaccines." *Id.* ¶¶ 340–350. In that section, Schrum teaches, *inter alia*, that in embodiments, "mRNA molecules may be used to elicit or provoke an immune response in an organism," where the delivered mRNA "may encode an immunogenic peptide or polypeptide." *Id.* ¶ 340. Schrum discloses that the "modified nucleic acid molecules and/or mmRNA . . . may encode an immunogen" that "may activate the immune response." *Id.* ¶ 342.

Schrum further discloses that the mRNA "encoding an immunogen may be delivered to a vertebrate in a dose amount large enough to be

immunogenic to the vertebrate." *Id.* In support, Schrum cites and "incorporate[s] by reference in [its] entirety" Geall (Ex. 1010, herein). *Id.* According to Schrum, the "modified nucleic acid molecules or mmRNA of [the] invention may encode a polypeptide sequence for a vaccine." *Id.* ¶ 343. Schrum teaches that the mmRNA may, as a non-limiting example, "be self-replicating mRNA [and] may encode at least one antigen." *Id.* ¶¶ 344–345; *see also id.* ¶¶ 346 ("[T]he self-replicating modified nucleic acids or mmRNA of the invention may be formulated using methods described herein or known in the art."), 349 ("[T]he modified nucleic acid molecules and mmRNA may encode all or part of a positive-sense or a negative-sense stranded RNA virus genome[.]").

Schrum includes several working examples. In Example 16, for instance, Schrum describes *in vivo* studies where mRNA modified with 5-methylcytosine and pseudouridine, and encoding a protein, was "formulated as lipid nanoparticles [(LNPs)]." *Id.* ¶ 995. The LNP formulations were administered to mice intravenously in various doses and protein expression (for G-CSF and Factor IX) was confirmed. *Id.* ¶¶ 995–999.

2. *Geall (Ex. 1010)*

Geall is an international patent application that published January 12, 2012. Ex. 1010, code (43). Geall relates generally to "RNA encoding an immunogen" that is "delivered to a large mammal" to "elicit an immune response." *Id.* at Abstr.

Geall teaches that "[t]he RNA can be delivered as naked RNA" but, to enhance entry of the RNA into cells and subsequent cellular effects, "the RNA is preferably administered in combination with a delivery system." *Id.*

at 3:25–31. According to Geall, "useful delivery systems of interest" include liposomes, polymer microparticles, and cationic oil-in-water emulsions. *Id.* (disclosing that liposome delivery is preferred).

Geall teaches that "[t]he invention involves *in vivo* delivery of RNA which encodes an immunogen." *Id.* at 12:1. "The RNA can trigger innate immunity pathways and is also translated, leading to expression of the immunogen." *Id.* at 12:1–2. According to Geall, "[t]he RNA is +-stranded, . . . so it can be translated without needing any intervening replication steps such as reverse transcription" and "[p]referred +-stranded RNAs are self-replicating." *Id.* at 12:4–17 (disclosing that, with a preferred self-replicating RNA molecule (or replicon), delivery of the molecule "lead[s] to the production of multiple daughter RNAs").

Geall teaches that RNA molecules used with the invention "encode a polypeptide immunogen." *Id.* at 15:33–34 (disclosing that, after "administration of the RNA the immunogen is translated *in vivo* and can elicit an immune response in the recipient"). According to Geall, "[t]he immunogen may elicit an immune response against a bacterium, a virus, a fungus or a parasite." *Id.* at 15:34–35. Further, Geall teaches, "[t]he immunogen will typically be a surface polypeptide" such as "a spike glycoprotein." *Id.* at 16:6–7.

Geall teaches that, in certain embodiments, "the immunogen elicits an immune response" against one of several listed viruses. *Id.* at 18:12–20:23. Geall identifies "*Coronavirus*" among the listed viruses. *Id.* at 19:26–29. And, more specifically, Geall discloses that "[v]iral immunogens include,

but are not limited to, those derived from a SARS coronavirus" where "[t]he coronavirus immunogen may be a spike polypeptide." *Id.*

3. *Yang (Ex. 1011)*

Yang is an article in Nature magazine, published in April 2004. Ex. 1011, 561. Yang reports on an animal-model study related to DNA vaccination against SARS-CoV. *See generally id.*

Yang notes prior SARS outbreaks arising from SARS-CoV and earlier public health measures to contain such outbreaks. *Id.* at 561. According to Yang, "concerns remain over the possibility of future recurrences" of SARS outbreaks and "[f]inding a vaccine for this virus therefore remains a high priority." *Id.*

Yang describes an animal (i.e., mouse) vaccination model that "examine[d] immune protection against [SARS-CoV] viral replication in the respiratory tract as a measure of vaccine efficacy." *Id.* at 562.

Yang teaches that "DNA 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." *Id.* at 561 ("Gene-based vaccination for the SARS-CoV elicits effective immune responses that generate protective immunity in an animal model."); *see also id.* ("Injection of S, SΔTM and SΔCD expression vectors induced a substantial immune response.").[16] Moreover, "[t]he humoral immune response includes the

[16] In Figure 1, Yang identifies the "structure of the cDNAs used," and shows a full-length S protein (1255 amino acids long), and two truncated versions of the S protein: SΔCD (1242 amino acids), truncating a portion of the

generation of neutralizing antibodies. This humoral immunity alone can inhibit pulmonary viral replication in a murine challenge model and suggests that DNA vaccination with the SARS-CoV S glycoprotein gene results in protective immunity." *Id.* at 563. Yang reports 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, and protection was mediated by a humoral but not a T-cell-dependent immune mechanism." *Id.* at 561; *see also id.* at 562 ("In this analysis, the most potent immunogen, SARS SΔCD, led to $>10^6$-fold reduction in viral load in the lungs compared with a control group injected with vector alone, in which mean viral titres of $>10^8$ were observed[.]").

According to Yang, these "results suggest that antibodies against SARS-CoV S glycoprotein protect against a SARS-CoV challenge and do not enhance infection in this animal model." *Id.* at 563 (discussing a need for future testing of SARS vaccine candidates for immunogenicity, safety, and efficacy in humans).

4. *Altmeyer (Ex. 1012)*

Altmeyer is an international patent application that published December 15, 2005. Ex. 1012, code (43). Altmeyer relates generally to "[n]ucleic acid molecules, polypeptides, immunogenic compositions, vaccines, and methods of making and using the nucleotides and encoded

protein's cytoplasmic domain; and SΔTM (1190 amino acids), deleting the transmembrane and cytoplasmic domains. Ex. 1011, 561–562, Fig. 1.

polypeptides associated with the Spike protein of SARS Corona Virus (SARS CoV)." *Id.* at Abstr.

Altmeyer discloses "DNA and RNA sequences" that "encode Spike polypeptides." *Id.* ¶ 60 (teaching that such sequences hybridize to SEQ ID NOS: 2, 3 & 6, as disclosed, under conditions of moderate or severe stringency). According to Altmeyer, "[t]he polypeptides encoded by these novel nucleic acids are referred to herein as 'Spike polypeptides' or 'Spike proteins.'" *Id.* ¶ 61 ("[T]hese terms refer to a genus of polypeptides that further encompasses proteins having the amino acid sequence of SEQ ID NO: 4 or SEQ ID NO: 7" as well as polypeptides with a "high degree of similarity (at least 90% homology) with such amino acid sequences" and polypeptides and proteins that "are immunoreactive."); *see also id.* ¶¶ 64–67 (describing Spike polypeptides and variants thereof, and their use to prepare antibodies that bind to the Spike polypeptides).

Altmeyer describes methods of RNA and/or DNA vaccination. *See, e.g.*, *id.* ¶¶ 97–98. According to Altmeyer, "[t]he method also includes administering any combination of nucleic acids encoding Spike polypeptides . . . with or without carrier molecules[] to an individual." *Id.* Altmeyer discloses that the individual is an animal and preferably a mammal, including, a human, mouse, rabbit, etc. *Id.* ("In an especially preferred embodiment, the mammal is a human."). Altmeyer teaches that skilled artisans are "cognizant of the concept, application, and effectiveness of nucleic acid vaccines and nucleic acid vaccine technology" and that this technology "allows the administration of nucleic acids encoding Spike polypeptides, naked or encapsulated, directly to tissues and cells without the

need for production of encoded proteins prior to administration." *Id.* ("Such nucleic acid vaccine technology includes, but is not limited to, delivery of naked DNA and RNA and delivery of expression vectors encoding Spike polypeptides.").

Altmeyer discloses, in Example 5, an example of "RNA immunization" of mice. *Id.* ¶¶ 114–116. In that example, Altmeyer teaches that "[m]ice were immunized intramuscularly with SFV[17] Spike RNA, followed by intraperitoneal (IP) injection of Spike protein at day 14 and at day 35." *Id.* Altmeyer discloses that serum samples from immunized mice "showed the presence of recombinant Spike-specific antibodies." *Id.* (citing Figs. 6–8). According to Altmeyer, "data indicate that the Spike protein expressed in the SFV vector could be successfully immunopurified in its native conformation, and that this purified protein induces high titer anti-SARS antibodies in mice." *Id.*

E. Ground 2: Obviousness over Schrum and Geall[18]

Petitioner asserts that claims 1, 2, 4–6, 8–12, 16, 17, 20, 21, and 26 would have been unpatentable as obvious over the combination of Schrum and Geall. Pet. 38–48.[19] We gave an overview of Schrum and Geall above.

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[17] Altmeyer discloses that "SFV" refers to the Semliki Forest Virus vector. *See, e.g.*, Ex. 1012 ¶ 41.

[18] For the reasons discussed below, we determine that all the challenged claims are unpatentable under Grounds 2 and 3. We exercise our discretion and decline to reach the unpatentability of the challenged claims under Grounds 1 and 4. *See infra* § III.

[19] The Petition supports its challenge to claim 1 with testimony from Drs. Griffin and Moon. Ex. 1002 ¶¶ 67–76, 104–116; Ex. 1004 ¶¶ 58–66,

In the subsections below we provide our analysis of Ground 2, starting with Petitioner's contentions on claim 1.

We then turn to Patent Owner's counterarguments. As a preview of those arguments, Patent Owner contends that Schrum and Geall do not disclose all of claim 1's limitations. PO Resp. 27–28. More specifically, Patent Owner contends that neither reference teaches a "full-length" spike protein or a protein that "forms a spike." *Id.* at 27. Patent Owner then raises several arguments related to whether a POSA would have been motivated to combine Schrum and Geall with a reasonable expectation of success. Such arguments include: (i) that, in a field "skeptical" of mRNA vaccines, there is "no data" in Schrum or Geall for mRNA-LNP vaccines, much less mRNA-LNP vaccines encoding an S protein (*see id.* at 28–33); (ii) that skilled artisans had reasons to avoid the S protein as the immunogen for a vaccine, including because other potential BetaCoV proteins could be used and because the S protein was associated with a "risk of enhanced disease" (*id.* at 40–51); and (iii) that Petitioner's selection of a vaccine comprising an LNP delivery vehicle with an mRNA that encodes a BetaCoV S protein as the payload "smacks of hindsight" against the "myriad options" in the art (*id.* at 51–52). Lastly, Patent Owner argues that objective indicia support the nonobviousness of the challenged claims, including, for example, "significant praise" for Patent Owner's "Spikevax® clinical trials" and

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94–100. Dr. Moon's testimony focuses mostly on the lipid nanoparticle (LNP) elements of the claim and Dr. Griffin's testimony focuses primarily on the remainder of the claim limitations, with both declarants cross-referencing the testimony of the other, as applicable.

"tremendous market success" of the parties' "COVID-19 vaccines Spikevax® and Comirnaty®" that allegedly embody the challenged claims. *Id.* at 58–68.[20]

1. *Petitioner's Contentions for Ground 2: Claim 1*

Petitioner contends that claim 1 would have been obvious over the teachings of Schrum and Geall. Pet. 22–27, 38–42.

According to Petitioner, Schrum discloses methods that include delivering nucleic acids that encode a protein by contacting "the mammalian cell or tissue . . . with a formulation comprising a modified mRNA encoding a polypeptide of interest." Pet. 22–23 (citing Ex. 1009, cover, ¶¶ 3–5, claim 1). And Petitioner points out that Schrum's "formulation" may include a "delivery agent" that may comprise "lipid nanoparticles." Pet. 22–23, 26–27 (citing, *e.g.*, Ex. 1009 ¶¶ 3–5, 6 (disclosing, *inter alia*, "the formulation comprising the modified mRNA is a nanoparticle which may comprise at least one lipid"), 22, 34, 397, 406, 995–1000 (Example 16)), 40

[20] In its arguments against Petitioner's anticipation ground, Patent Owner asserts: "Nor do Petitioners argue Schrum is enabled." Ex. 2199, ¶¶ 261–308, 403–414, 453–464." PO Resp. 13. To the extent this argument has applicability to Petitioner's obviousness grounds, it is an undeveloped argument that we do not further consider. *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1320 (Fed. Cir. 2006) ("A skeletal argument, really nothing more than an assertion, does not preserve a claim."). Insofar as Patent Owner purports to support this threadbare assertion with fifty-plus paragraphs of Dr. Fuller's declaration, that is an improper incorporation-by-reference, contrary to the Board's rules. 37 C.F.R. § 42.6(a)(3). Schrum, in any event, is a published U.S. patent application that is *presumptively* enabled. *In re Antor Media Corp.*, 689 F.3d 1282, 1288 (Fed. Cir. 2012).

(arguing Schrum discloses "identical mRNA and lipid nanoparticle components to that claimed in the '600 patent").

We find that the above-cited teachings of Schrum support Petitioner's contentions and we credit Dr. Griffin's and Dr. Moon's testimony interpreting those disclosures. Ex. 1002 ¶¶ 68–76, 104–116;[21] Ex. 1004 ¶¶ 58, 62–66, 94, 98–100. Accordingly, we find that Schrum teaches or suggests claim 1's preamble (if limiting) and limitation [1.a], which together recite "[a] composition comprising" [1.pre] "a messenger ribonucleic acid (mRNA)" [1.a]. We also find that Schrum teaches limitation [1.c] reciting "formulated in a lipid nanoparticle."[22] Patent Owner provides no argument or evidence to the contrary. *See* PO Resp. 27–28 (arguing that Geall does not disclose "betacoronavirus S protein" but not identifying any other limitations that are allegedly missing in the combination of Schrum and Geall).

According to Petitioner, Schrum also teaches or suggests the use of its mRNA formulations as part of a vaccine to activate an immune response. Pet. 23–26, 38–40. Petitioner cites Schrum's teaching that, in embodiments, "mRNA molecules may be used to elicit or provoke an immune response in

[21] Dr. Griffin's testimony on obviousness incorporates portions of his testimony on anticipation. Although we agree with Dr. Griffin that Schrum (via its incorporation of Geall) discloses each of the limitations recited in claim 1, we do not reach the issue of whether Schrum discloses those limitations arranged as claimed so as to meet the anticipation standard. Accordingly, we neither credit nor discredit Dr. Griffin's testimony on that specific issue.

[22] The bracketed shorthand used here for the claim limitations corresponds to the same shorthand used in the Petition. *See, e.g.*, Pet. 22–27, 38–42.

an organism," and "mRNA molecules to be delivered may encode an immunogenic peptide or polypeptide." Ex. 1009 ¶ 340 (cited at Pet. 23, 38–39). Further, Petitioner contends, Schrum teaches "the modified nucleic acid molecules and mmRNA of the present invention encoding an immunogen may be delivered to a vertebrate in a dose amount large enough to be immunogenic to the vertebrate." Ex. 1009 ¶ 342 (citing Geall (Ex. 1010) and another reference, which Schrum states are "herein incorporated by reference in their entirety") (cited at Pet. 23–24, 39); *see also,* Ex. 1009 ¶ 397 ("In one embodiment, the lipid nanoparticle may be formulated for use in a vaccine such as, but not limited to, against a pathogen"); Pet. Reply 5–6 ("[A] POSA would have understood that empty LNPs are not used as vaccines, and must include a payload like mRNA.") (citing, *e.g.*, Ex. 1161 ¶ 43).[23]

Petitioner relies on Schrum for teaching or suggesting all of the limitations of claim 1 except Petitioner turns to Geall's teaching that the encoded immunogen may be "a betacoronavirus (BetaCoV) S protein." *Id.* at 38–40. Petitioner cites Geall's teaching of administering to a mammal a dose of between 2–100 μg of immunogen-encoding RNA that encoded "[v]iral immunogens" including "those derived from SARS coronavirus,"

[23] As we noted at institution, Schrum teaches that its mRNA vaccines "may be formulated using methods described herein or known in the art" (Dec. Inst. 35 (quoting Ex. 1009 ¶ 346)), for which Schrum incorporates another Geall reference in its entirety ("Geall 2012" (Ex. 2021)). As we further noted, Geall 2012 formulates self-amplifying RNA vaccines in lipid nanoparticles. Inst. Dec. 84 n.38; *see also* Tr. 25:1–7 (stating Schrum's paragraph "346 basically provides another example of how we get to the LNP composition").

which may be a "spike polypeptide." Pet. 39 (quoting Ex. 1010, Abstr., 19:27–30 ("The coronavirus immunogen may be a spike polypeptide")).

We find that Geall teaches and renders obvious an encoded immunogen comprising the "BetaCoV S protein" of claim 1. Ex. 1002 ¶ 109 (testifying that a POSA would understand claim 1's "S protein" is met by Geall (citing, *e.g.*, Ex. 1010, 16:6–7, 19:26–30)); Ex. 1159 ¶¶ 41–46 (testifying that a POSA would have understood Geall's disclosure of a "spike polypeptide" as referring to a structural protein forming a spike, and would further interpret that disclosure as "refer[ring] to (or, at the very least, includ[ing]) the disclosure of a full-length S protein").[24]

We find, based on the evidence cited by Petitioner above, that the combination of Schrum and Geall teaches or suggests claim 1's limitation [1.b] reciting that the mRNA comprises "an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit."

With Dr. Griffin's testimony in support, Petitioner asserts that the POSA would have had reasons to combine Schrum and Geall because

[24] As discussed above, we disagree with Patent Owner's contentions that the claimed "S protein" reads only on a full-length spike protein. But, even accepting Patent Owner's narrower claim interpretation, we find that the full-length protein would have been obvious over Geall (especially when considered with numerous other prior art references, such as Yang, that undisputedly and expressly disclose the full-length protein as an immunogen). Ex. 1159 ¶ 46; Ex. 1011, 561; Ex. 1012 ¶ 111 (example in which "Spike protein was expressed as full-length protein"), ¶ 116 (example in which mice immunized with RNA encoding Spike protein "showed the presence of recombinant Spike-specific antibodies"); Ex. 1031, 229 (describing Yang (Ex. 1011) and other studies: "These reports suggest that the full-length S protein is highly immunogenic").

Schrum "identifies and incorporates Geall" and because "the two references are in the same field of endeavor." Pet. 40–42 (citing Ex. 1002 ¶¶ 112–114 (testimony of Dr. Griffin to this effect)). Moreover, according to Petitioner, the "spike" or S protein "was known to be the most promising antigen for development of a SARS-CoV vaccine." Pet. 40; *see also id.* at 6 (arguing "the 'spike protein' was well-established as the most promising antigen for vaccine development long before October 2015"); Ex. 1002 ¶¶ 45–47 (testifying, e.g., that "in 2005, scientists demonstrated that serum taken from mice immunized with spike RNA, followed by intraperitoneal injection of spike protein, showed the presence of recombinant spike-specific antibodies" (citing Ex. 1012 ¶ 116 (disclosing that spike protein "induces high titer anti-SARS antibodies in mice"))); Ex. 1031 ("Du"), 227 ("Because 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.").[25]

Petitioner argues that a skilled artisan would have had good reason to use Schrum's mRNA vaccine to encode a BetaCoV spike protein—an immunogen disclosed in Geall. Pet. 41–42; Ex. 1010, 15:32–16:7 ("The immunogen will typically be a surface polypeptide e.g. . . . a spike glycoprotein"), 19:26–29 ("immunogens include . . . those derived from a SARS coronavirus . . . [and] may be a spike polypeptide"). Petitioner also cites Yang's teaching that "a DNA vaccine encoding the spike

[25] Lanying Du et al., *The Spike Protein of SARS-CoV – A Target for Vaccine and Therapeutic Development,* 7 Nature Rev. Microbiology 226–236 (2009) (Ex. 1031 ("Du")).

(S) glycoprotein of the SARS-CoV induces T cell and neutralizing antibody responses, as well as protective immunity, in a mouse model." Ex. 1011, 561 (cited at Pet. 41–42). And Petitioner cites Du's teaching that "[a]mong all structural proteins of SARS-CoV, S protein is the main antigenic component that is responsible for inducing host immune responses, neutralizing antibodies and/or protective immunity against virus infection," and that "S protein has therefore been selected as an important target for vaccine and antiviral development." Ex. 1031, 229 (cited at Pet. 41); Pet. Reply 12–13 (arguing, *inter alia*, that the "spike protein is the only betacoronavirus vaccine immunogen pursued by each of Geall, Yang, and Altmeyer," and "echoed longstanding knowledge" about the S protein's importance and immunogenicity (citing, *e.g.*, Ex. 1132, 9804)).[26]

Petitioner contends that a skilled artisan would have had a reasonable expectation of success in combining Schrum and Geall to arrive at the composition of claim 1. Pet. 41–42. According to Petitioner, Schrum teaches that methods of synthesizing mRNA were known in the art, and Schrum provides examples where administration of protein-encoding mRNA formulated in lipid nanoparticles expressed the encoded protein in high volume. *Id.* (citing Ex. 1009 ¶¶ 291, 320, 942, 963, 995–1001 (Example 16, describing an mRNA dose-dependent effect on protein expression and that "the LNP formulations described above have about a 10,000-100,000-fold

[26] Ursula J. Buchholz et al., *Contributions of the structural proteins to severe acute respiratory syndrome coronavirus to protective immunity*, 101:26 Proceedings of the National Academy of Sciences 9804–9809 (2004) (Ex. 1132 ("Buchholz")).

increase in protein production" compared to delivery via a lipoplex or saline); Ex. 1002 ¶¶ 115); Ex. 1004 ¶¶ 72, 81. (testimony of Dr. Moon about Schrum's teachings on LNP formulations).

We find persuasive Petitioner's reasoning and evidence in support of the asserted motivation to combine Schrum and Geall, and a skilled artisan's reasonable expectation of success in making that combination to arrive at the subject matter of claim 1. We credit the cited evidence and reasons given by Petitioner above. We further address the issues of motivation to combine and expectation of success in more detail below when explaining our reasons for rejecting Patent Owner's counterarguments on those issues.

2. *Alleged Absence of All Claim 1's Limitations in Schrum and Geall*

Patent Owner argues that Ground 2 fails because the combination of Schrum and Geall does not "disclose or suggest the claimed S protein." PO Resp. 25–28; *see also* PO Sur-reply 9–11 (arguing alleged "Insurmountable Gaps" in the art's disclosures). According to Patent Owner, "Geall's sole relevant disclosure is mentioning coronavirus 'spike polypeptide' in a long list of immunogens," and Geall "does not teach a 'full-length' spike protein . . . or a spike protein that forms a spike." PO Resp. 27 (citing Ex. 1010, 19:26–30). Further, Patent Owner argues, because Geall includes no "data" or "working example" specific to the spike polypeptide, Geall does not suggest a BetaCoV S protein "that forms a spike as the claims require." *Id.* at 27–28 (citing, *e.g.*, Ex. 2111, 716–717 (describing possible "[t]ranslation errors" and "[f]olding errors" that can occur during protein formation generally); Ex. 2005, 2119–2121 (describing test where vaccination against

RSV did not result in detectable antibody titers for some vaccine types)); PO Sur-reply 18 (arguing the S protein is large and would have been considered difficult to translate, especially given stability issues with mRNA).

Patent Owner's rebuttal arguments are unavailing. *First*, Patent Owner's arguments are premised on a narrower claim construction than the one we adopt. As discussed above, we conclude that the claimed "S protein" is not limited to only the "full-length" protein. Given this determination, there is no reasonable dispute that a skilled artisan would understand "S protein" as reading on Geall's disclosure of a coronavirus "spike polypeptide"—the only coronavirus immunogen expressly identified in Geall. Ex. 1010, 19:26–30; *see also id.* at 16:6–7 (disclosing more generally that an RNA-encoded immunogen will "typically" be a surface polypeptide, such as an "envelope glycoprotein" or "spike glycoprotein").

Second, the Ground 2 challenge is for obviousness, not anticipation. Even if the claims were limited to a "full-length" S protein, we credit Dr. Griffin's unrebutted testimony that a POSA, in view of the totality of the relevant background art, would have understood Geall's disclosure as at least suggesting and rendering obvious the full-length protein. Ex. 1159 ¶¶ 26, 46 (testifying, *inter alia*, that "[a] 'full-length' betacoronavirus spike protein is simply the normal, 'default' version . . . as had already been described in the prior art—rather than an artificially shortened version of the protein" and that the POSA would "understand [Geall's] disclosure of a 'spike polypeptide' to refer to (or, at the very least, include) . . . a full-length S protein") (cited at Pet. Reply 7–8); *see, e.g.*, Ex. 1031, 229 ("Several vaccines that are based on the full-length S protein of SARS-CoV have been

reported."). And, to the extent Geall's "spike polypeptide" encompasses more than just full-length S protein, it would have been obvious to use the full-length S protein because, as Dr. Griffin credibly explains, "the prior art had already shown . . . that full-length S protein based vaccines were protective" and "it was known . . . that full-length betacoronavirus S protein vaccines induced stronger antibody responses . . . than truncated S protein-based vaccines." Ex. 1159 ¶¶ 238–239; *see also, id.* ¶¶ 236–243 (providing additional reasons why the POSA would have been motivated to use the full-length S protein).

Patent Owner's argument about Geall not disclosing that its "spike polypeptide" "forms a spike" fares no better. For the reasons discussed above, we do not construe "S protein" as requiring the protein actually form a spike in claim 1's composition. But even if that were a requirement of the claim (as suggested by Patent Owner's interpretation), there is no evidence of record cited that skilled artisans sought to express a BetaCoV S protein in any prior (or even later-developed) vaccine construct and were unable to do so. Tr. 105:19–23 (question inviting either party to identify any record evidence of S protein lack of expression or misfolding, and no such evidence was identified). Indeed, the evidence is to the contrary. *See, e.g.*, Ex. 1011, 561, Fig. 1 (describing expression of S proteins[27] using DNA vaccines as

[27] Patent Owner argues that Yang (Ex. 1011) only provides "data" for two truncated S proteins and not the full-length spike protein. *See, e.g.*, PO Sur-reply 10 ("Yang references a full-length S protein schematic, but discloses data only for naked DNA encoding truncated S-proteins"). Even so, the notion that a skilled artisan would doubt the ability to express the full-length S protein is not credible when Yang explicitly teaches successful expression

determined by western blot analysis); Ex. 1012 ¶¶ 111–113 (describing, in examples, preparation of an SFV RNA expression vector for the "full-length" spike protein, assay confirmation of expression and "correct folding and expected properties of the Spike protein"), 116 ("data indicate that the Spike protein expressed in the SFV vector could be successfully immunopurified in its native conformation"); Ex. 1159 ¶ 44 ("[B]y October 2015, it had already been shown that betacoronavirus spike proteins could be expressed using nucleic acid vaccines to induce a protective immune response.") (citing Ex. 1031, 226–36).

On this record, we find that the skilled artisan would have understood Geall's disclosure of a BetaCoV "spike polypeptide" as teaching (or at least suggesting) expression of this immunogen and that such expression would result in the formation of a "spike." Ex. 1010, 19:26–30. This is a result the POSA would have reasonably expected. Ex. 1159 ¶¶ 42–44 (testifying "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") (citing Ex. 1031, 227).

Moreover, as Dr. Griffin explains, the '600 patent "does not provide data" showing that any expressed S protein "actually" forms a spike.

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of, for example, a truncated S protein that is 1242 amino acids in length—only thirteen amino acids shorter in a portion of the cytoplasmic domain compared to full-length (1255 amino acid) protein. Ex. 1011, 561. Indeed, contemporary publications interpreted Yang's results as applying to full-length S protein. Ex. 1031, 229 ("Yang *et al.* showed that a DNA vaccine encoding the ***full-length*** S protein SARS-CoV Urbani strain could induce both T-cell and neutralizing antibody responses, as well as protective immunity.") (emphasis added).

Ex. 1159 ¶ 43 (testifying that Dr. Fuller "simply infers" that the expressed protein in the patent "formed a spike") (citing Ex. 2199 ¶ 246). And it is not altogether clear what specific "data" (e.g., X-ray crystallography) would actually meet Patent Owner's demands. Patent Owner gives no justification for requiring that Schrum or Geall provide detailed "data" of that sort when the patent itself does not. *Cf. In re Epstein*, 32 F.3d 1559, 1568 (Fed. Cir. 1994) (holding "the Board's observation that appellant did not provide the type of detail in his specification that he now argues is necessary in prior art references supports the Board's finding that one skilled in the art would have known how to implement the features of the references").

Schrum also teaches that its mRNA-LNP formulations—the construct Petitioner proposes would have been obvious to use in a vaccine—substantially increase protein expression. Schrum teaches that its mRNA-LNP formulations may be used to "increase the stability" of the delivered nucleic acids and "increase the translation of the encoded protein." Ex. 1009 ¶ 406. Although not exemplifying a BetaCoV S protein, Schrum's examples show that expressed protein production could be increased "100,000-fold" with mRNA-LNP formulations versus delivery of naked mRNA in saline. *Id.* ¶ 998. And, the '600 patent itself states that it "build[s] on the knowledge that RNA (e.g., messenger RNA (mRNA)) can safely direct the body's cellular machinery to produce ***nearly any protein of interes*t**." Ex. 1001, 3:24–28 (emphasis added); Ex. 1159 ¶ 44 (testifying "it was well-known by 2015 that 'any protein can be expressed from mRNA without the need to adjust the production process'" (quoting Ex. 1019, 1)); Ex. 1104, 78:5–79:2 (Dr. Fuller's testimony agreeing that "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").

Against this backdrop, Patent Owner's reference to hypothetical protein mistranslations and possible difficulties expressing large proteins does not undermine the POSA's reasonable expectation that an encoded S protein would be expressed via an mRNA-LNP vaccine and that it would fold as intended. PO Resp. 27–28; PO Sur-reply 7. Although Dr. Griffin acknowledged that it was possible that "some fraction" of a protein might fail to express or misfold, he testified "that would be quite the exception" and "if the mRNA sequence is correct and the protein is expressed, then the expressed S protein would fold." *See, e.g.*, Ex. 2253, 67:3–69:10 (testifying "it was well known by 2015 that the S protein, when expressed, would fold into figurative spikes"); Ex. 1159 ¶¶ 42–44 (disagreeing with proposition that "a POSA would have required a working example to conclude that Geall's disclosure of a 'spike polypeptide' would result in a structural protein forming a spike").

In short, Patent Owner's rebuttal arguments about the "S protein" are unpersuasive. We find, based on a preponderance of the evidence, that the combination of Schrum and Geall teaches or suggests the "S protein" of claim 1, and we would reach the same conclusion even under Patent Owner's proposed constructions requiring that "S protein" be limited to "full-length" and that the "S protein" actually "form a spike."

3. *Alleged Absence of Reasons to Combine Schrum and Geall*

Patent Owner argues that a POSA would not have been motivated to combine[28] Schrum and Geall for four reasons: 1) lack of relevant "data" in Schrum and Geall, 2) skepticism about mRNA vaccines, 3) availability of other, non-LNP, delivery methods, and 4) desire to avoid BetaCov S protein as the immunogen. PO Resp. 28–30, 39–43, 45–51. We address these arguments in turn below.

a) Lack of "Data" in Schrum and Geall

Patent Owner contends that there is "no data" in Schrum and Geall that would support Petitioner's proposed combination of the references. PO Resp. 28–29. According to Patent Owner, Petitioner is therefore left to cite inapplicable data regarding "***other*** technologies" to support the motivation to combine. *Id.* at 29.

We disagree with Patent Owner that an alleged lack of "data" in Schrum and Geall undermines Petitioner's proffered reasons for combining the references.

[28] Many of Patent Owner's arguments on the issues of motivation to combine and reasonable expectation of success overlap to varying extents. *See generally* PO Resp. 28–51; *see, e.g.*, *id.* at 40–50 (arguing a POSA "would have had reasons not to combine the elements as claimed and not to expect success," citing, e.g., alleged skepticism with mRNA vaccines and alleged reasons to avoid the S protein). Although we address the motivation to combine and reasonable expectation of success issues in separate sections here, certain aspects of our discussions on one issue may apply to the other, particularly as we have sought to avoid redundancy where possible.

A reason for combining Schrum and Geall in the manner proposed comes directly from Schrum. In a section of Schrum's disclosure devoted to describing mRNA vaccines that may be used to induce an immune response in a subject, Schrum identifies and incorporates Geall's teachings in their entirety—including the teachings about dosing and the SARS spike polypeptide—the only coronavirus immunogen expressly identified in Geall. Ex. 1009 ¶ 342; Ex. 1010, 19:26–30.

Patent Owner argues that "Schrum incorporates Geall for dose, not everything." PO Resp. 16. This argument is not persuasive because Schrum expressly states that it incorporates Geall "in [its] entirety" (Ex. 1009 ¶ 342), distinguishing it from the patent at issue in *Cook Biotech Inc. v. Acell, Inc.,* 460 F.3d 1365, 1376 (Fed. Cir. 2006), which Patent Owner relies upon, but which did not include such "in [its] entirety" language. Moreover, although Schrum makes reference to "a dose amount large enough to be immunogenic" when incorporating Geall, that "dose amount" is expressly stated to be for an encoded immunogen. And, as Dr. Griffin explains, "the choice of immunogen influences the dosage level at which the vaccine will be given." Ex. 1159 ¶ 39; Ex. 1104, 119:15–120:8 (testimony of Dr. Fuller that "multiple things can influence a dose" including "the immunogen that you use"). Given the interrelationship between dose and immunogen, it would make little sense for Schrum to incorporate Geall for its teachings on dosing without also incorporating its teaching on immunogens.

The art also recognized that a vaccine against betacoronavirus (especially SARS and MERS) was desirable. *See, e.g.*, Ex. 1011, 561 (noting outbreaks of SARS-CoV, stating "concerns remain over the

possibility of future occurrences" and "[f]inding a vaccine for this virus therefore remains a high priority"); Pet. 6–7 (citing evidence (e.g., Ex. 1031, 229) about BetaCoV vaccine development before October 2015). Even the '600 patent cites a need for such vaccines as a known "background" fact. Ex. 1001, 2:67–3:8 ("The outbreaks of MERS-CoV have raised serious concerns worldwide, reinforcing the importance of developing effective and safe vaccine candidates against MERS-CoV" and "[b]ecause of a concern for reemergence or deliberate release of the SARS coronavirus, vaccine development was initiated"). Schrum's express incorporation of Geall's teachings and the preexisting knowledge about potential BetaCoV outbreaks provided the POSA with good reasons for targeting a coronavirus antigen, including Geall's BetaCoV "spike polypeptide," as the encoded immunogen in an mRNA vaccine like described in Schrum.

We also disagree with Patent Owner's suggestion that a POSA would not consider teachings or "data" related to other nucleic acid vaccine constructs when designing an mRNA vaccine. That suggestion is undermined by Schrum itself. Schrum is Patent Owner's own previously published patent application. Ex. 1009, code (71). Schrum's section on vaccines describes both mRNA and so-called self-amplifying RNA (saRNA) vaccines. Ex. 1009 ¶¶ 342, 345 ("In one embodiment, the self-replicating modified nucleic acid molecules or mmRNA of the invention may encode a protein which may raise an immune response."). Schrum thus suggests that its teachings related to saRNA vaccines are germane to mRNA vaccines. In addition, Schrum cites to and incorporates teachings from Geall (and other publications authored by Geall that tested saRNA vaccines), even when

describing mRNA vaccines more generally. *See, e.g.*, Ex. 1009 ¶¶ 342 (incorporating Geall), 346 (incorporating Geall 2012 (Ex. 2021) and its teaching related to LNP-delivery formulations); PO Resp. 10, 19, 21 (arguing that Geall is focused solely on saRNA).

Yang, which tested and provided "data" for DNA vaccines, similarly does not indicate that its teachings should be read so narrowly. Yang suggests that the viral genes it identifies may be useful in other delivery systems. Yang teaches that, "[f]or example, the SΔCD mutant [(i.e., nucleic acids encoding for S protein with a truncation in the cytoplasmic domain)] can be expressed in other vector delivery systems for analysis, alone or in various combinations." Ex. 1011, 563.

Whether DNA, saRNA, or mRNA, each of these vaccine types relies on a basic scientific principle—which Dr. Fuller characterized as "the central dogma of biology"—that, within cells, DNA is transcribed to create RNA and RNA is translated to form protein (i.e., an antigen or any protein of interest). Ex. 2199 ¶ 55. The mRNA vaccines do not rely on, and thus bypass, the DNA transcription step in the dogmatic protein processing pathway. Pet. Reply 21–22 (citing Ex. 1159 ¶¶ 208–213, 236–243, 357–367). While Patent Owner's declarant, Dr. Krause offers the truism that DNA and mRNA vaccines are "different," he agrees that "information about DNA vaccines . . . support the idea that one can exogenously give a nucleic acid vaccine (like mRNA or DNA) that may create an S protein that may induce an immune response, and that there were studies in which endogenously producing an S protein was not observed to pose a safety concern." Ex. 2200 ¶ 129.

b) Skepticism about mRNA Vaccines

Patent Owner contends that there was "significant skepticism" around mRNA vaccines and the "field had largely dismissed mRNA" as the basis for vaccines against infectious diseases. PO Resp. 40. According to Patent Owner, to the extent work was being done on "non-traditional vaccine technologies, it was primarily viral vector, DNA, and saRNA vaccines, not mRNA." *Id.* at 40–41 (citing, *e.g.*, Ex. 2109, 190; Ex. 2110, 10, Ex. 2021, 14604; 2132,780–781, Ex. 2199 ¶¶ 510–547). Patent Owner cites concerns that mRNA was "unstable and likely to trigger the body's innate immune response." *Id.* at 41 (citing Ex. 1016, 156; Ex. 2027, 261). Moreover, Patent Owner contends, Petsch[29] (in 2012) noted that mRNA had "exhibit[ed] promising immunogenicity" in "clinical testing in ***oncological indications***" yet remarked that "***whether mRNA vaccines*** induce protective antibody responses and ***are efficacious in infectious disease is not clear***." *Id.* (quoting (with Patent Owner's emphasis) Ex. 2025, 1210–11); *see also id.* (arguing that Petsch attributed success to "complexation [of the mRNA vaccines] with protamine") (citing Ex. 2025, 1215).

We do not agree that the alleged skepticism cited by Patent Owner would, on balance, have taught away from or otherwise discouraged Petitioner's proposed combination of Schrum and Geall. Schrum—again, Patent Owner's own prior published patent application—encourages use of mRNA-based vaccines to induce an immune response, and relays no

[29] Benjamin Petsch et al., *Protective Efficacy in in Vitro Synthesized, Specific mRNA Vaccines Against Influenza A Virus Infection,* 30 Nature Biotechnology No. 12, 1210–1216 (2012) (Ex. 2025, "Petsch").

skepticism. Ex. 1009 ¶¶ 340, 342 ("The mRNA molecules to be delivered may encode an immunogenic peptide or polypeptide" and "may be delivered to a vertebrate in a dose amount large enough to be immunogenic").

Patent Owner cites alleged concerns about mRNA's stability and/or its potential to trigger an innate immune response before the mRNA can encode the desired protein. But Schrum recognizes and addresses such concerns. *See*, *e.g.,* Ex. 1009 ¶¶ 3 ("Thus, there is a need to develop formulation compositions comprising a delivery agent that can effectively facilitate the in vivo delivery of nucleic acids to targeted cells without generating an innate immune response."), 50 ("The modified nucleic acid molecules of the present disclosure are capable of reducing the innate immune activity of a population of cells into which they are introduced, thus increasing the efficiency of protein production in that cell population."), 98 ("As described herein, the modified nucleic acids and mmRNA of the invention do not substantially induce an innate immune response of a cell into which the mRNA is introduced.");[30] Ex. 1002 ¶ 42 ("In order for

[30] Schrum teaches that nucleoside modifications address concerns about innate immune response and using LNPs addresses concerns about mRNA stability. *See* Ex. 1009 ¶¶ 53 (teaching that mRNA with nucleoside modifications "may have useful properties including . . . a significant decrease in or lack of substantial induction of the innate immune response" and "enhanced efficiency of protein production"), 406 (teaching LNPs "may . . . be used to increase the stability of the modified nucleic acid molecules or mmRNA"). *See* Pet. 10–11 (discussing "landmark" work of Karikó and Weissman (Ex. 1021, 165) showing that exogenous mRNA having modified forms of the nucleoside uridine "reduced activation of the innate immune response and increased protein production"), 12–13 (discussing, as background, known mRNA vaccine delivery systems (e.g., LNPs) to help

mRNA vaccines to work as planned, the exogenous mRNA has to successfully enter the patient's cells and remain present long enough to be translated into quantities of protein sufficient to trigger a response from the ***adaptive*** immune system. In this regard, scientists would want to avoid a response from the ***innate*** immune system to the mRNA therapeutic that could reduce protein production and cause cell death.") (footnotes omitted); *see* Pet. 26–27 (citing Schrum's teachings about the advantages of LNP delivery of mRNA), 30–32 (citing Schrum's teachings about replacing uracil with modified nucleosides in the mRNA molecules).

Patent Owner's contention that many (or perhaps most) researchers of non-traditional vaccines were focusing on DNA and saRNA vaccines, not mRNA, does not undermine Petitioner's challenge. A petitioner need not show a motivation to pursue only the best or most obvious solution. *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) ("[O]ur case law does not require that a particular combination must be the preferred, or the most desirable, combination described in the prior art in order to provide motivation for the current invention."); *Intel Corp. v. Qualcomm Inc.*, 21 F.4th 784, 800 (Fed. Cir. 2021).

Although DNA and other vaccine platforms may, in some respects, carry advantages, the prior art taught that mRNA had its own advantages. Ex. 1014, 1720–22 (teaching "mRNA . . . should be one of the best ways of introducing a foreign protein into the natural antigen processing pathways," and noting advantages of mRNA for vaccination versus DNA (e.g., avoids

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protect exogenous mRNA from degradation before being taken up by the cells and translated) (citing, *e.g.*, Ex. 1032, 231; Ex. 1062, 1:8–9, 34:3–5).

"potentially strict regulatory barriers related to gene therapy")); Ex. 1020, 11 (teaching that "[n]ucleotide vaccines based on mRNA offer the flexibility to encode virtually any protein as antigen in a very short time span . . ., which is of great importance in pandemic scenarios in infectious diseases," and noting "mRNA carries no risk of genomic integration . . . [which] gives mRNA an inherent safety advantage over DNA-based therapeutics"). Indeed, Kallen (2014)[31] reported that "[r]ecent advances strongly suggest that mRNA rather than DNA will be the nucleotide basis for a new class of vaccines and drugs." Ex. 1020, 10; Ex. 1019, 1326 ("mRNA-based vaccines promise to become a game-changing vaccine technology platform for therapeutic as well as prophylactic applications"). The prior art thus described the advantages and promise of mRNA vaccines, lending support to the position that a POSA would have been motivated to combine Schrum and Geall as proposed by Petitioner. Pet. Reply 17–18 ("Even [Patent Owner's] cited references . . . describe mRNA vaccines as 'effective' and 'promising.'") (citing Exs. 1016, 2024, 2025, 2027).

Patent Owner contends that Petsch reflects skepticism about mRNA vaccines, but, on the whole, Petsch's results are a ***success story*** with mRNA

[31] Karl-Josef Kallen et al., *A development that may evolve into a revolution in medicine: mRNA as the basis for novel, nucleotide-based vaccines and drugs*, 2:1 Therapeutic Advances in Vaccines 10–31 (2014). (Ex. 1020 ("Kallen (2014)")). Kallen (2014) discloses that "reports on nucleotide-based vaccines showed that vaccines produced on DNA or mRNA basis had similar activity" and that prior, perceived advantages of DNA over mRNA were "erroneous." Ex. 1020, 10–11 ("mRNA might be the ideal basis for the development of new vaccines against infectious pathogens" (citing Petsch (Ex. 2025)).

vaccines. PO Resp. 41–43. Petsch reports: "[h]ere we validated the mRNA vaccine approach for a B cell-dependent mode of protection against an infectious disease, influenza." Ex. 2025, 1211; *see also id.* at 1216 ("In summary, we introduce an mRNA vaccine platform that combines the simplicity, safety and focused immune response of subunit vaccines with the immunogenicity of live viral vaccines. Our findings open ***attractive perspectives for immunization against a broad range of pathogens***.") (emphasis added).

Petsch teaches that mRNA vaccines provide a protective antibody response in a variety of animals. *See, e.g.*, *id.* at Abstr. ("Here we show that mRNA vaccines induce balanced, long-lived and protective immunity to influenza A virus infection in even very young and very old mice."), 1212 ("[W]e conclude that the mRNA vaccine effectively induced long-lived (and even lifelong) protection in mice."), 1213 ("In summary, our findings suggest the feasibility of single-dose immunization against influenza with a multicomponent HA [hemagglutinin] and NA [neuraminidase] mRNA vaccine."), 1214–1215 ("To investigate whether mRNA vaccination was immunogenic in large animals approaching average human body weight (60 kg), we immunized 3-month-old female domestic pigs . . . . [T]he mRNA vaccine was clearly immunogenic in pigs."), 1215 ("[T]his experiment therefore established efficacy of mRNA vaccination in large animals."). And other researchers interpreted Petsch's results as demonstrating efficacy (i.e., success) with mRNA vaccines. *See, e.g.*,

Ex. 1016[32] (Geall 2013), 154 ("RNA vaccines (both mRNA and replicons [(i.e., saRNA)]) are effective at eliciting antigen-specific humoral and cellular immune responses in animal models of infectious and non-infectious diseases. . . . In many cases, functional, protective immunity was afforded by RNA vaccination." (citing, *inter alia*, reference 33 (Petsch)).

Patent Owner's contention that Petsch cited "complexation with protamine" as possibly important to Petsch's results is not wrong. PO Resp. 42 (citing Ex. 2024, 2265–66; Ex. 2025, 1215; Ex. 2198 ¶¶ 46–47, 181–183 (testimony of Dr. Chan related to Petsch's protamine complexed mRNA vaccines). Petsch, noting a prior report detecting "no humoral immune response" involving intradermal vaccination "with conventional mRNA," states that "we assume that the improved efficiency and duration of antigen expression *in vivo* . . . and complexation with protamine are necessary for the sustained immune response observed in this study." Ex. 2025, 1215. Importantly, however, Petitioner's proposed combination of Schrum and Geall does not simply involve "conventional" or "naked" mRNA. It involves LNP-delivered mRNA as described in Schrum; and, as recognized elsewhere in the prior art, "[f]rom all these published data [describing delivery of RNA vaccines], two strategies lead the field"—"protamine-complexed mRNA" and "lipid nanoparticles (LNPs)." Ex. 1016, 154.

For similar reasons, Patent Owner's argument about Kallen's observation that "naked mRNA 'achieved high antigen expression, but only

[32] Andrew J. Geall et al., *RNA: The New Revolution in Nucleic Acid Vaccines,* 25 Seminars in Immunology 152–159 (2013) (Ex. 1016, "Geall 2013").

weak immunostim[u]lation'" is unavailing. PO Resp. 42 (quoting Ex. 2024, 2265–66). Schrum's mRNA-LNP formulation is not naked mRNA. And immunostimulation—whether weak or strong—is still an immune response.

We also find unpersuasive Patent Owner's contention that Petsch found that some vaccine compositions encoding different flu proteins provided "only 40% protection" in mice while other compositions provided greater protection. *Id.* (citing Ex. 2025, 1210, 1213, Fig. 4a-b). The claims do not require an immune response or protection. Nor, given the breadth of the claims, is it necessary that the prior art have already proved that mRNA vaccines were "commercially viabl[e]" or ready for "approved" use in humans. PO Resp. 41–44 (arguing that various references suggested there was more research to be done and that, "by October 2015, there were ***no*** approved mRNA vaccines for infectious diseases, and just a handful being tested clinically").[33] As Petitioner notes, "[a]n 'approved' vaccine is not the barometer for a reasonable expectation of success—particularly here, where the claims do not require any level of efficacy." Pet. Reply 22. Indeed, making the claimed composition, even if simply for preclinical uses, such as testing on mice, would satisfy the claim.

[33] Even if Patent Owner's characterization about the status of clinical trials in October 2015 is correct, Geall 2013 reported that "[t]he RNA vaccine approach, based on mRNA and engineered RNA replicons derived from certain RNA viruses, is gaining increased attention and several vaccines are under investigation for infectious diseases, cancer, and allergy. Human clinical trials are underway and ***the prospects for success are bright***." Ex. 1016, Abstr. (emphasis added).

Altogether, and notwithstanding Patent Owner's arguments about alleged skepticism with mRNA vaccines, we find that the skilled artisan would have been motivated to use Schrum's mRNA-LNP formulations for a vaccine against BetaCoV S protein as proposed by Petitioner.

c) Non-LNP Delivery Methods

Patent Owner contends that there were multiple non-LNP delivery methods available in the prior art and "Petitioner has not provided sufficient reason why a POSA would have selected LNPs from those options." PO Resp. 38; Ex. 2198 ¶¶ 37–66. Patent Owner also contends that other mRNA-delivery technology, such as protamine complexation, were thought to be beneficial or necessary. *Id.* (citing Ex. 2024, 2264; Ex. 2025, 1210–16).

Patent Owner's argument does not undercut the skilled artisan's reasons for selecting LNPs as the delivery vehicle for Schrum's mRNA. In Schrum's own words, "a lipid nanoparticle may be formulated for use in a vaccine, such as, but not limited to, against a pathogen." Ex. 1009 ¶ 397. Patent Owner contends that "Schrum discloses data only on LNPs for use with therapeutics." PO Sur-reply 25. That "data" does not negate Schrum's other express teaching that LNPs may be used in a vaccine or otherwise suggest LNP delivery would be suitable for mRNAs encoding therapeutic proteins but somehow unsuitable for mRNA antigenic proteins (i.e., vaccines). *In re Mouttet*, 686 F.3d 1322, 1331 (Fed. Cir. 2012) ("A reference may be read for all that it teaches, including uses beyond its primary purpose."); *In re Lamberti*, 545 F.2d 747, 750 (CCPA 1976) ("[T]he fact that a specific symmetric dialkyl is taught to be preferred is not

controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered").

In any event, as Petitioner notes, "by 2015, a POSA would have known that formulating an RNA vaccine using lipid nanoparticles 'substantially' improved vaccine performance." Pet. Reply 18 (quoting Ex. 2021 (Geall 2012), 14604; citing Ex. 1161 ¶¶ 65–99; Ex. 1159 ¶¶ 244–62). Indeed, in addition to teaching that "lipid nanoparticle[s] may be formulated for use in a vaccine," Schrum's vaccine section cites and incorporates-by-reference Geall 2012, which tested LNP-encapsulated saRNA vaccines, as an example of suitable formulation methods "known in the art" that could be applied to Schrum's invention. Ex. 1009 ¶¶ 346, 397; Ex. 2021, 1064.[34]

That other delivery options (like protamine-complexation) existed does not demonstrate that use of LNPs would have been nonobvious, especially where the prior art described protamine and LNPs as the "two strategies [that] lead the field" for delivery of RNA vaccines. Ex. 1016, 154. LNPs were suggested as having broad utility, including for nucleic acid vaccines and therapeutics, and for small-molecule drug delivery. Pet. 11–12

[34] Geall 2012, which Schrum "incorporate[s] by reference in its entirety" (Ex. 1009 ¶ 346), provides additional relevant background for its experiments using LNP-delivered saRNA. For example, it teaches that "many of the obstacles to mRNA vaccine development have been surmounted," that "[i]njection of naked mRNA or self-amplifying RNA in vivo induces gene expression and generates immune responses, with self-amplifying RNA being more efficient" and, that because "naked RNA vaccines suffer from limited potency, in part due to RNA instability in vivo," "mRNA vaccines have been formulated with synthetic delivery vehicles such as liposomes to increase potency." Ex. 2021, 14604 (citations omitted).

(citing, *e.g.*, Ex. 1032, 221, 231 (explaining that it is "crucial to develop delivery systems that *in vivo* protect mRNAs from degradation and help internalization [in dendritic cells]" and that LNPs and other lipid systems "for mRNA deliver[y] are proposed and preclinical studies demonstrated their potentiality to induce antigen-specific immune response")); Ex. 1062, 1:8–9 ("Lipid nanoparticles (LNP) are the most clinically advanced drug delivery systems."), 34:3–4 ("[A]pplications include delivery of DNA or mRNA sequences that code for therapeutically useful polypeptides"). The preponderance of the evidence favors Petitioner's position that a POSA would have had sufficient reasons to choose LNPs as the delivery vehicle.

d) Reasons to Avoid the S Protein

Patent Owner argues that a POSA would not have been motivated to pursue an mRNA-LNP composition encoding full-length betacoronavirus spike protein. PO Resp. 44–51. According to Patent Owner, "S proteins . . . were not the only, or even most promising, proteins or protein pieces [being considered] for coronavirus vaccines." *Id.* at 45. Patent Owner contends, for example, that "M, N, HE, and E proteins were all being investigated." *Id.* (citing, *e.g.*, Ex. 2093, 4643–44; Ex. 2094, 16; Ex. 2095, 1175–76; Ex. 2096, 2591; Ex. 2029, 567; Ex. 2144, 121:19–122:4; Ex. 2199 ¶¶ 104–125, 607–620). Among the surface proteins, Patent Owner asserts that S protein is the largest and larger proteins are more difficult to translate. *Id.* at 45–46 (citing, *e.g.*, Ex. 2111, 716–17; Ex. 2199 ¶¶ 104–125, 571–576; Ex. 2200 ¶ 192).

Patent Owner argues that a POSA would have also been concerned about potential "disease enhancement" with use of the full-length S protein

as an immunogen. PO Resp. 46–51; PO Sur-reply 21–23. Patent Owner cites Du's disclosure that "[a]lthough full-length S protein-based SARS vaccines can induce neutralizing antibody responses against SARS-CoV infection, ***they may also induce harmful immune responses*** . . . ***or enhanced infection*** after challenge with homologous SARS-CoV ***raising concerns about the ultimate protective efficacy of vaccines that contain the full-length SARS-CoV S protein***." PO Resp. 46 (quoting Du, Ex. 1031, 229–230) (with Patent Owner's emphasis)). Patent Owner contends such risks were reported. *Id.* at 48 (citing, *e.g.*, Ex. 2136[35] (Lambert), 4785 as "summarizing evidence . . . of risks of enhanced disease with SARS-CoV-1 and MERS-CoV vaccines"). Patent Owner contends that BioNTech's CEO had concerns about disease enhancement when Petitioner developed its "Comirnaty®" vaccine for SARS-CoV-2. *Id.* at 47–48 (citing Ex. 2106, 68–69). And, Patent Owner contends, the FDA expressed concern and requested data about possible enhanced disease incident to the industry efforts to develop vaccines responsive to the COVID-19 public health emergency. *Id.* at 49–50 (citing, *e.g.*, Ex. 2104,[36] 6, 8; Ex. 2200 (Krause Decl.) ¶¶ 138–156 (discussing, *e.g.*, 2020 Guidance, and Th1/Th2 immune responses and the association with possible enhanced disease)).

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[35] Paul-Henri Lambert et al., *Consensus summary report for CEPI/BC March 12–13, 2020 meeting: Assessment of risk of disease enhancement with COVID-19 vaccines*, 38 Vaccine 4783–91 (2020) (Ex. 2136 ("Lambert")).

[36] Development and Licensure of Vaccines to Prevent COVID-19, Guidance for Industry, USHHS, FDA (June 2020). (Ex. 2104 ("2020 Guidance")).

We disagree with Patent Owner's contentions that a skilled artisan would have avoided use of a BetaCoV S protein.

The evidence overall indicates that the spike protein was the first immunogen that would have been considered for a BetaCoV vaccine. Each of Geall, Yang, and Altmeyer identified the S protein as a BetaCoV immunogen of choice. Ex. 1010, 19:26–30; Ex. 1011,[37] 561 (disclosing S, SΔTM, and SΔCD expression vectors); Ex. 1012, Abstr. (describing vaccines and "methods of making and using the nucleotides and encoded polypeptides associated with the Spike protein of SARS Corona Virus (SARS-CoV)"). Du describes the S protein as "the main antigenic component of SARS-CoV," discloses that the "S protein has therefore been selected as an important target for vaccine and anti-viral development," and states that the "full-length S protein is highly immunogenic and induces protection against SARS-CoV challenge . . . justifying the rationale that vaccines can be developed based on the S protein." Ex. 1031, 229. The potential for disease enhancement, which Du recognized (*id.* at 229–230), does not negate Du's other teachings. Indeed, despite recognizing the potential for disease enhancement, Du concludes: "It is likely . . . that S protein-based vaccines will bear fruit in the near future, as they have been proven to induce long-term and potent neutralizing antibodies and/or protective immunity against SARS-CoV." *Id.* at 234.

[37] Yang noted reports of possible disease enhancement ("immune potentiation of disease") in vaccines against feline infectious peritonitis virus, but Yang reported that its "results suggest that antibodies against SARS-CoV S glycoprotein protein protect against SARS-CoV challenge and do not enhance infection in this animal model." Ex. 1011, 563.

Even Dr. Fuller admits that, before 2015, while there were some "other vaccine candidates testing other immunogens . . . there were quite a few of them focused on S protein." Ex. 1104, 62:11–17. And she further testified that the S protein was used in several types of vaccines:

> Q. Are you aware of any SARS-CoV vaccines using spike proteins that induced an immune response?
> A. Yes.
> Q. Which ones are you aware of?
> A. ***Pretty much every vaccine type out there***. There was primarily inactivated recombinant protein, there was DNA vaccine. There were others, various ones using different antigens formulated with different vaccines.

Ex. 1104, 65:15–66:2 (emphasis added); Pet. Reply 14.

A possible use of other BetaCoV proteins as antigens for a vaccine does not demonstrate that use of the S protein would have been nonobvious. Buchholz, for example, tested several BetaCoV proteins for immunogenicity in a hamster model and reported that "N, M, E, and ME vectors did not induce detectable resistance to SARS-CoV challenge, and thus these proteins were not significant protective antigens." Ex. 1132, 9808 (noting, however, that those antigens remained potential antigens for antiviral cytotoxic T cells). In contrast, Buchholz found that "SARS-CoV spike protein (S) induced a high titer of SARS-CoV-neutralizing serum antibodies, only 2-fold less than that induced by SARS-CoV infection." *Id.* at 9804. "These results," Buchholz reported, "identify ***S*** among the structural proteins as ***the only significant SARS-CoV neutralization antigen and protective antigen***." *Id.* (emphasis added). Thus, like other prior art references of record, Buchholz taught towards, not away from, the S protein. And,

Buchholz found no evidence of disease enhancement. *Id.* at 9809 ("[T]here 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."); Ex. 1159 ¶ 229 (explaining how Buchholz expressly distinguished its results from the ADE (antibody-dependent [disease] enhancement) seen in Vennema's 1990 study (Ex. 2029, 1407) related to a feline virus).

Further to Patent Owner's arguments about disease enhancement, Dr. Griffin testifies persuasively that enhancement is a *potential* risk with all vaccines. *See, e.g.*, Ex. 1159 ¶¶ 215–216 (testifying that "[d]isease enhancement is a potential complication inherent to vaccines as a category of medical treatment" and "would have remained a theoretical concern for a betacoronavirus vaccine using an immunogen or any surface protein, surface protein fragment, or mixture of proteins and fragments") (citing, *e.g.*, Ex. 1140, 2369–72 (reporting that N protein vaccines led to ADE while S proteins did not); Ex. 2057, 2); *see* Ex. 1105 (Dr. Krause), 22:17–23:10 (characterizing enhanced disease as a "potential or theoretical risk").[38]

[38] The "phenomenon" of ADE "has been well-known in the field for many decades" and "occurs when—instead of protecting an individual from infection and disease—the prior vaccination makes a subsequent infection with the virus more severe that it would have been if the subject had never gotten the vaccine." Ex. 2200 ¶ 138. Further, Dr. Krause explains, ADE is more likely to arise when the body produces an overabundance of total antibodies versus neutralizing antibodies (i.e., when the response to vaccination is skewed towards a Th2/IgG1 response compared to the Th1/IgG2 response). *Id.* ¶¶ 142–145 (testifying that, relative to this balance, "when non-neutralizing antibodies predominate, further exposure to the antigen can result in stimulation of an unproductive immune response.").

Patent Owner itself acknowledges that "[v]accines have been known since the 1960s to risk enhanced disease." PO Resp. 47 (citing Ex. 2136, 4784).

As Dr. Griffin explains, "[i]f a POSA were dissuaded from designing vaccines because of the possibility of disease enhancement, then vaccine development would fully halt." *Id.* ¶ 215. Also, Dr. Griffin explains, if enhanced disease is more likely when the neutralizing antibody response is low, that would tend to steer a POSA toward a vaccine immunogen known to produce high levels of neutralizing antibodies, such as the S protein. Ex. 1159 ¶¶ 217–218 (citing Ex. 1132, 9808; Ex. 2199 ¶ 126).

The evidence here also shows that, notwithstanding the risks or reports of potential disease enhancement, skilled artisans continued to develop and successfully test vaccines based on the S protein—including in the period leading up to October 2015. Wang,[39] for example, "show[ed] 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." Ex. 1101, 1–2 ("The full-length S DNA regimen induced a significantly higher antibody response than the truncated

[39] Lingshu Wang et al., *Evaluation of candidate vaccine approaches for MERS-CoV*, 6 Nature Communications 7712 (2015) (Ex. 1101 "Wang"). Wang which includes several of the same authors/researchers as Yang (Ex. 1011) tested eight vaccine regimens and, based on favorable results, moved three candidates forward in testing (S DNA, S DNA-S1 protein, and S1 protein alone). Ex. 1101, 2–3. Although, among those three, Wang showed that S DNA prime with S protein boost was the most effective, Wang showed robust neutralization titers with S DNA (prime and boost) without separate protein administration. *See id.* 2–3 (Figs. 1b, 1c); Ex. 1159 ¶¶ 207, 239–240 (discussing Wang).

S-ΔTM or S1 DNA regimens"). Likewise, Song,[40] also aware of possible ADE, described in 2013 a vaccine expressing "full-length MERS-CoV spike (S) protein" as "a suitable candidate vaccine for clinical testing." Ex. 1109, 11950, 11953 (citing Jaume (Ex. 2030) and Vennema (Ex. 2029)); Ex. 1159 ¶¶ 234–230 (discussing Song, Jaume, and Vennema's disclosures).

Inasmuch as the S protein was known to produce high levels of neutralizing antibody titers, a POSA would have had good reasons to develop and administer vaccines encoding for the S protein antigen. Pet. Reply 16 (citing Ex. 1159 ¶¶ 236–247). Dr. Fuller conceded that Wang's teaching that the full-length spike protein induced higher antibody titers was "not surprising because . . . the full-length S protein will have more epitopes, neutralizing antibody epitopes to target." Ex. 1104, 260:9–15. Although Dr. Fuller testified that a POSA may still have been concerned because "those additional antibodies may be bad antibodies and contribute to enhanced disease" (*id.* at 260:16–18), Wang reflects no such concerns.

Patent Owner also argues that, after Yang's earlier testing in 2004 (described in Exhibit 1011), Yang's research group[41] later "found DNA vaccines encoding ***full-length*** spike protein resulted in enhanced disease . . . whereas a ***truncated*** spike protein did not." PO Resp. 32–33 (citing

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[40] Fei Song et al., *Middle East Respiratory Syndrome Coronavirus Spike Protein Delivered by Modified Vaccinia Virus Ankara Efficiently Induces Virus-Neutralizing Antibodies*, 87:21 Journal of Virology 11950–54 (2013) (Ex. 1109, "Song").

[41] Zhi-yong Yang et al., Evasion of antibody neutralization in emerging severe acute respiratory coronaviruses, 102:3 PNAS 797–801 (2005) (Ex. 2137 ("Yang 2005")).

Ex. 2137 ("Yang 2005"), 797–800); PO Sur-reply 17 n.14, 21, 23–24; Ex. 2137, 797–800 (finding enhancement with a DNA vaccine encoding full-length S protein against a viral strain found in the palm civet but S protein "truncated at amino acid 1153, induced neutralizing Abs to human isolates that failed to cause Ab enhancement of entry"). Patent Owner suggests such a result could explain why the group then initiated a Phase 1 human clinical trial using a truncated- rather than the full-length S protein. PO Resp. 32–33 (citing Ex. 2138 ("Martin 2008")[42]); Ex. 2138, 6338–6339 (disclosing "single-plasmid DNA vaccine encoding the Spike (S) glycoprotein ([specifically SΔCD]) was evaluated in 10 healthy adults," "[t]he vaccine was well tolerated" and "SARS-CoV-specific antibody was detected by ELISA in 8 of 10 subjects and neutralizing antibody was detected in all subjects who received 3 doses of vaccine").

We disagree that Yang 2005 or Martin 2008 would have discouraged a POSA's use of the S protein in an mRNA-LNP vaccine of Schrum. *First*, Patent Owner's argument presumes a construction of S protein that excludes immunogenic S protein fragments (like SΔCD described in Martin 2008). We do not adopt that construction. *See supra* § II.C.2.a. *Second*, Yang 2005 showed an enhancement of entry of a specific pseudovirus strain (from a specific animal, the palm civet), but stated, "[t]o date, Ab-dependent enhancement has not been observed with any human SARS-CoV strain, which may allay concerns that such vaccines might enhance infection."

[42] Julie E. Martin et al., *A SARS vaccine induces neutralizing antibody and cellular immune responses in healthy adults in a Phase 1 clinical trial*, 26 Vaccine 6338–43 (2008) (Ex. 2138 ("Martin 2008")).

Ex. 2137, 800; Ex. 1159 ¶ 233 (testifying that Yang 2005 continued to report that the S protein is "***the major target for vaccine and immune therapy***" (quoting Ex. 2137, 797), and that Yang does not teach away but only reflects some uncertainty whether the full-length S caused the noted enhancement). *Third*, as evidenced by Wang, researchers from within this same group continued to design and conduct preclinical animal testing using vaccines encoding full-length BetaCoV S proteins even several years after the results reported in Yang 2005 and Martin 2008. Ex. 1101, 1.[43] That suggests skilled artisans would not have been—and, indeed, were not—dissuaded from using full-length S proteins as the antigen for BetaCoV vaccines.

Patent Owner's reliance on the Miller book, chronicling Petitioner's development of "Comirnaty®," is unavailing. PO Resp. 47–48 (citing Ex. 2106, 68–69). That book was published in 2022 and retrospectively highlights some of the perceived risks and challenges with developing a SARS-CoV2 vaccine in response to the COVID-19 pandemic, yet the book explained that "[t]here was little doubt" that "the best way to build a coronavirus vaccine that was both effective and safe" was "to engineer an authentic copy of the spike protein." Ex. 2106, 69 (citing a study from 2009); *but see* PO Sur-reply 22–23 (arguing Petitioner's concerns with full-S protein expression were assuaged only after studying Moderna's data (citing Ex. 2107, 198)). Regardless, even if Petitioner had, at some point, noted concerns about vaccines expressing a full-length spike protein (which

[43] For example, at least Zhi-yong Yang, Kwanyee Leung, and Wing-Pui Kong (authors of Wang) were also co-authors on Yang 2005. *Compare* Ex. 1101, *with* Ex. 2137.

claim 1 encompasses, but is not limited to), the balance of the evidence of record supports that the potential for disease enhancement would not have discouraged a POSA from using a BetaCoV S protein as an antigen of choice prior to October 2015.

Patent Owner's reliance on the FDA's 2020 Guidance noting the theoretical risk of disease enhancement and requesting safety studies to better understand those potential risks with newly-developed COVID-19 vaccines does not weigh significantly against Petitioner's challenge. PO Resp. 50–51 (citing, *e.g.*, Ex. 2104, 6, 8). *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013) (explaining that the FDA's request for clinical safety and efficacy data "reflects attention to the FDA's normal duties," not skepticism). We address the FDA-related evidence further below (when discussing reasonable expectation of success), including Patent Owner's own exchanges with the FDA concerning ***pre-2015*** prior art studies, which Patent Owner represented demonstrated "Proof-of-Concept with mRNA-Based Vaccines" in "various animal models." *See, e.g.*, Ex. 2050, 12–13. Patent Owner's arguments about the FDA evidence do not, however, indicate that a POSA would have lacked motivation to pursue a vaccine based on the S protein prior to October 2015.

e) Conclusion Regarding Motivation to Combine

Considering the full trial record, and for the reasons explained above, we find that the skilled artisan would, on balance, have been motivated to combine Schrum's and Geall's teachings as proposed by Petitioner.

4. *Alleged Absence of a Reasonable Expectation of Success*

Patent Owner argues that a POSA would not have combined Schrum and Geall with a reasonable expectation of success in arriving at claim 1. Patent Owner contends that development of nucleic acid vaccines and extrapolating results between different vaccine platforms was fraught with unpredictability. PO Resp. 28–40. Patent Owner contends there was skepticism about mRNA infectious disease vaccines. *Id.* at 40–44. And Patent Owner contends that concerns about potential disease enhancement undermine any expectation of success. *Id.* at 46–51; *see also* PO Sur-reply 11–19. We address these arguments below.

Before turning to Patent Owner's arguments, however, we are mindful that the correct inquiry centers on whether a skilled artisan would have combined the art with a reasonable expectation of success in arriving at *what is actually claimed*. *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2014). One need not show a reasonable expectation of success concerning features or results that the claims do not require. *Id.*

With the proper inquiry in mind, we reiterate that claim 1 is quite broad. It recites a composition with three key features: 1) mRNA, 2) encoding an S protein, 3) formulated in a LNP. Many of Patent Owner's arguments that the POSA would not reasonably have expected success suggest that claim 1 requires more than what the claim actually recites and requires. There is no requirement, for example, for administration of the claimed composition. Nor is there any requirement that the composition produce an immune response, much less a clinically effective immune

response, if it were so administered. Further, to the extent Petitioner's position that it would have been obvious to make the claimed composition presumes some basis for doing so—i.e., a desire to make an efficacious composition—claim 1 encompasses making such composition in settings falling far short of a successful clinical trial. For example, claim 1 encompasses formulating the composition for testing in mice to see whether it induces an immune response. Thus, whether other mRNA infectious disease vaccines had, by October 2015, been "approved" or commercialized is not determinative here of whether the POSA would have had a reasonable expectation of success.

a) Lack of Data and Vaccine Unpredictability

Patent Owner argues that the combination of Schrum and Geall lacks "data" for an mRNA-LNP vaccine encoding a BetaCoV S protein. PO Resp. 28–29. According to Patent Owner, Petitioner's expert agreed that such data would be necessary to form a reasonable expectation of success. *Id.* (citing Ex. 2114, 124:19–125:7); *see also id.* (arguing that Geall's "data" is for saRNA vaccines against RSV, and Schrum's "data" is for mRNA therapeutics, not vaccines).

This argument is unpersuasive. We have already addressed the alleged absence of "data" in Schrum and Geall. As discussed above, the combination of those references suggests making an mRNA-LNP vaccine encoding a BetaCoV S protein. For the reasons discussed below, upon administration, the POSA would reasonably expect the mRNA-LNP vaccine to express the protein and provoke an immune response. Even Dr. Fuller agreed that, "[o]nce you know that the spike protein is expressing, you

would expect that vaccine candidate to induce an immune response." Ex. 1104, 50:21–51:6; *see also id.* at 51:7–52:9 (testifying that "it's just basic fundamental nucleic acid vaccine biology that when you have a DNA or an RNA vaccine and can validate that it expresses a protein in vitro, . . . [y]ou can give that antigen to express in animal, and the hypothesis is that it will elicit an immune response"). As we explained above, there is no evidence of record cited here, in any vaccine construct, where an S protein failed to express the immunogen as intended. The evidence is to the contrary. *See, e.g.*, Ex. 1011, 561, Fig. 1; Ex. 1012 ¶¶ 111–113, 116; Ex. 1159 ¶ 44; Ex. 1031, 226–36; Ex. 1132, 9804–9809; Ex. 1101, 1–3, 7–8.

Also, the notion that a skilled artisan would regard Geall's teachings as relevant to only saRNA or RSV is at odds with both Geall and Schrum. Notwithstanding that it is focused on saRNA and that its data is limited to saRNA, Geall discloses that its invention has broader applications related to RNA-based vaccines. Ex. 1010, 1:5 ("This invention is in the field of non-viral delivery of RNA for immunization."), claim 9 (dependent claim narrowing broader claim to RNA vaccine by further reciting saRNA); *see also id.* at 12:1–2 ("The invention involves *in vivo* delivery of RNA which encodes an immunogen. The RNA can trigger innate immunity pathways and is also translated, leading to expression of the immunogen."), 15:32–16:7 (stating broadly that the RNA may encode a polypeptide immunogen and "can elicit an immune response in the recipient," and introducing categories of immunogens), 18:16–19 (listing immunogens derived from RSV and other viruses), 19:26–30 (listing coronavirus spike polypeptide as immunogen). Schrum also teaches that its inventions have broad application

to RNA-based vaccines. Ex. 1009 ¶¶ 340–346 (describing mRNA vaccines broadly and incorporating teachings of references authored by Geall (one of which Patent Owner argues is limited to saRNA vaccines exemplifying an RSV immunogen)). In short, we disagree that a POSA would read Schrum's and Geall's teachings or "data" as narrowly as Patent Owner urges.[44]

We have also considered the testimony of Dr. Griffin cited by Patent Owner. Contrary to Patent Owner's suggestion, Dr. Griffin did not demand "data" to form a reasonable expectation of success in combining Schrum and Geall to arrive at claim 1's method. Instead, Dr. Griffin testified that a POSA "would need to see the data to be able to evaluate" whether a vaccine that encoded the N or M surface protein "caused enhanced disease or early death." Ex. 2114, 124:21–125:7; *see* Pet. Reply 20 n.9 (noting that "enhanced disease" is a risk for all vaccines and that eliminating it is an unclaimed element).

Patent Owner contends that vaccine development was unpredictable and, among nucleic acid vaccines, different vaccine platforms could produce different results—even when encoding the same protein. PO Resp. 30–36. Patent Owner cites a study by Brito[45] (involving Dr. Geall and other

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[44] Patent Owner asserts that any finding that Geall describes mRNA vaccines is "incorrect." PO Resp. 34 (citing the Board's discussion to the contrary in the Institution Decision (Paper 19, 61); *see also id.* at 34–35 (asserting that all of Geall's working examples relate to saRNA (i.e., "replicons")). For purposes of our analysis, we accept Patent Owner's position that Geall does not provide any specific examples or data for mRNA vaccines.

[45] Luis A. Brito et al., *A Cationic Nanoemulsion for the Delivery of Next-generation RNA Vaccines*, 22 Molecular Therapy 2118–2129 (2014) (Ex. 2005, "Brito"). Brito is somewhat related to a declaration of Dr. Geall (from

Novartis researchers). *Id.* at 31–32 (citing, *e.g.*, Ex. 2005), 33–36 (arguing saRNA and mRNA are different platforms that can produce different results). Patent Owner argues that Brito tested saRNA, mRNA, and DNA vaccines encoding the RSV F protein and found that "***mRNA produc[ed] the worst results***." *Id.* at 30 (citing Ex. 2005, 2121, 2129; Ex. 2199 ¶¶ 548–62); *see also id.* (arguing Brito also tested an HIV protein at the same doses and with the same formulation across the three platforms "but found saRNA generated neutralizing titers, whereas mRNA and plasmid DNA did not"). Further, Patent Owner argues, different delivery methods can generate different outcomes. *Id.* at 31–32 (citing, e.g., the protamine used in Petsch and cationic nanoemulsions (CNE) like described in Brito); Ex. 2025 (protamine complexation); Ex. 2005, 2118, 2121–22 (CNE-delivered nucleic acids).

We agree with Patent Owner that, in Brito's testing, saRNA, mRNA, and DNA vaccines produced different results. Brito administered saRNA (called "SAM" in Brito), mRNA, and DNA vaccines encoding RSV-F protein to mice; in one experiment each vaccine was unformulated (i.e., in saline), and in another experiment the vaccines were delivered as part of a CNE-formulation. Ex. 2005, 2118–2121. Brito found unformulated saRNA and DNA vaccines produced measurable F-specific antibody titers, whereas unformulated mRNA did not. Ex. 2005, 2119, 2121 (Fig. 2a (showing titer results for each of the SAM, mRNA, and pDNA in PBS (saline)). Brito also

October 2014) submitted during prosecution of a counterpart application to the Geall reference describing similar testing and results with mRNA, DNA, and saRNA vaccines. Ex. 2026, 406–409.

detected neutralizing titers in CNE-formulated SAM RNA at 15 μg, but not in CNE-formulated mRNA or DNA at that same dose. *Id.* (2121 (Fig. 2b)). This evidence, and Dr. Fuller's related testimony about it (e.g., Ex. 2199 ¶¶ 550–562), does indicate that specific results can vary and, thus, are not interchangeable across nucleic acid vaccine platforms.

Whatever unpredictability this lack of interchangeability may be suggest is, however, tempered by the promise and successes elsewhere described in the prior art with mRNA vaccines. *See, e.g.*, Ex. 1016, Abstr. (noting clinical trials with mRNA vaccines are underway and "the prospects for success are bright"); Ex. 1014, 1721 ("according to our results, such translation [of mRNA] certainly occurs *in vivo*, [and] it should be one of the best ways of introducing a foreign protein into the natural antigen processing pathways"); Ex. 1020, 10 ("Recent advances strongly suggest that mRNA . . . will be the nucleotide basis for a new class of vaccines" and "prophylactic vaccines against viral pathogens and allergens have demonstrated their activity in animal models"); Ex. 2025, 1210 ("In ferrets and pigs, mRNA vaccines induce immunological correlates of protection and protective effects similar to those of a licensed influenza vaccine in pigs."). Even Brito reports that "mRNA has emerged as an alternative to pDNA with a number of high profile reports using mRNA for vaccine and gene therapy applications." Ex. 2005, 2118 (noting that DNA's need to cross the nuclear membrane and be transcribed is "a process known to be inefficient" compared to processing of mRNA).

Brito also offers a plausible (even if somewhat speculative) explanation for why mRNA did not yield detectable antibodies or a

neutralizing titer in its testing. Brito discloses: "mRNA was unable to induce responses in our hands, perhaps due to the low dose being tested here. Previous reports with mRNA have shown that much higher doses (80 μg) of mRNA have been used to generate immune responses in mice.[6]" Ex. 2005, 2124 (citing reference 6 (i.e., Petsch (Ex. 2025)). Dr. Fuller testifies that 15 μg mRNA is above the upper limit for which a response would be expected in mice, and, therefore, low dosing does not explain the differences observed in Brito between saRNA and mRNA. Ex. 2199 ¶ 554. However, Dr. Fuller provides no independent support for that opinion. Plainly, as Brito recognized, Petsch disclosed the use of higher mRNA dosing. Ex. 2025, 1215 ("When given twice at an 80-μg dose, mRNA vaccines induced protective immunity in mice of all ages."); Ex. 1159 ¶ 262 (testifying "[a] POSA would have understood [e.g., from Brito] that mRNA would need to be administered at higher doses as compared to saRNA, not that it would fail to work all together").[46]

We also find that Patent Owner's FDA submissions weaken Patent Owner's arguments about the state of the art and the extent to which skilled artisans would have considered prior art, preclinical studies about mRNA, DNA, and saRNA relevant and reasonably predictive of safety and efficacy across platforms. For example, in a 2016 Investigator Brochure, Patent Owner expressly cited numerous ***pre-2015*** preclinical studies, including

[46] As we discussed above, Petitioner's combination also involves an mRNA-LNP formulation, which Schrum teaches can increase cell transfection and increase *in vivo* protein production 10,000–100,000-fold versus lipoplex or saline delivery. Ex. 1009 ¶¶ 995–998.

Petsch (2012), Geall (2012), and Brito (2014) as supporting "Proof-of-Concept with mRNA-Based Vaccines" in "various animal models." Ex. 2050, 10–12; *see* Ex. 2025 (testing protamine-complexed mRNA encoding flu-A protein); Ex. 2021 (testing LNP-encapsulated saRNA); Ex. 2005 (testing, e.g., naked and CNE-delivered saRNA, mRNA, and pDNA encoding RSV-F). Thus, much like Patent Owner's own prior art Schrum reference, which, when describing mRNA vaccines, directed the skilled artisan to Geall's teachings about saRNA vaccines, Patent Owner's FDA submissions do likewise. Pet. Reply 23–24 n.11 (arguing that Patent Owner's statements to the FDA were undisputedly expected to be truthful (citing Ex. 1164 ¶¶ 2, 23; Ex. 1105 (Krause tr.), 20:8–11)) and "are, most importantly, consistent with the disclosures of the respective references").

Patent Owner's FDA submissions specific to the development of its COVID-19 mRNA vaccine also cite prior art successes *with DNA vaccines* in support. In a Division of Microbiology and Infectious Disease ("DMID") Protocol dated February 14, 2020, Patent Owner represented:

> Prior preclinical studies have demonstrated that coronavirus spike (S) proteins are immunogenic and S protein-based vaccines, including deoxyribonucleic acid (DNA) and mRNA delivery platforms, are protective in animals. Prior clinical trials of vaccines targeting related coronaviruses and other viruses have demonstrated that DNA and mRNA-based vaccines are safe and immunogenic. *It is therefore anticipated that mRNA-1273* [i.e., Spikevax] *will generate robust immune responses to the 2019-nCoV S protein*.

Ex. 2054, MOD_000477497 (emphasis added). This document cites, for example, prior art Wang (2015) and Martin (2008), which described, respectively, administering *DNA vaccines* encoding a full-length S protein

and truncated SΔCD protein as discussed above. *Id.* at MOD_000477505; Ex. 1101; Ex. 2138; *see also* Ex. 2055, MOD_000471992 (citing Martin 2008 as disclosing that a DNA vaccine expressing SARS S protein was "safe and well tolerated" as well as "immunogenic").[47]

Further to these FDA materials, we have also considered the cited testimony of the parties' respective FDA experts (Drs. Krause and Pierce). Patent Owner cites Dr. Krause as supporting that statements to the FDA about "proof of concept" do not support a reasonable expectation of success, but he did not review the prior art asserted here, so his testimony on that issue carries less weight. *See* PO Resp. 36–38 (citing, *e.g.*, Ex. 2200 ¶¶ 41, 47–137; Ex. 2199 ¶¶ 622–653); Ex. 1105, 11:3–14:13.[48] Dr. Krause also testifies that scientists would not read those submissions (or portions of them) in isolation, but would understand, as further context, that Patent

[47] Consistent with this evidence, Dr. Fuller admitted that she looked at data about other vaccine types in selecting the SARS-CoV-2 spike protein as the antigen of choice to be encoded by an saRNA vaccine she was developing. Ex. 1104, 43:15–44:4 ("We looked at all vaccine literature" not just saRNA in selecting the spike protein); *but see id.* at 269:17–271:9 (testifying, on redirect, that "a potentially entirely different immune response" may still arise when using DNA, mRNA, and saRNA even if "you are using all of the same components"); Ex. 1099 (publication describing Dr. Fuller's co-development of saRNA vaccine).

[48] As noted *supra* n. 8, in reaching this decision, we consider only arguments and evidence properly raised in the parties' briefing. To the extent Patent Owner's citation to 90 paragraphs of Dr. Krause's testimony here raises argument or evidence not presented in the briefing, we do not consider it. 37 C.F.R. § 42.6(a)(3). Patent Owner does include narrower citations to support its argument about its argument about FDA submissions. PO Resp. 38 (citing Ex. 2200 ¶¶ 90–115). We have considered this testimony.

Owner had also submitted its own non-prior-art data about generating its mRNA-LNP vaccines. *Id.* We do not disagree that post-priority data, including Moderna's own, provides additional context for those submissions. The fact remains, however, that "[Patent Owner's] reference to the cited preclinical DNA-based vaccine studies reflects that these DNA-based studies were relevant to FDA's evaluation of an mRNA vaccine encoding a similar antigen." Ex. 1164 ¶¶ 44–47, 73–74 (testimony of Dr. Pierce explaining that, "by [Patent Owner] including these statements [about prior DNA vaccines expressing S proteins], showed that the sponsor viewed the clinical trial with DNA-based vaccines as having relevance to the expected safety and/or efficacy of [Patent Owner's] vaccine under investigation").

Altogether the evidence supports a finding that skilled artisans would not have limited their consideration to only data and results about the particular nucleic acid vaccine platform (mRNA, DNA, saRNA) under development when forecasting a reasonable likelihood of success.[49]

[49] In its Sur-Reply and in furtherance of its argument that vaccines are unpredictable, Patent Owner again references alleged stability concerns with mRNA and criticizes Petitioner as suggesting S protein expression and immune response "is inherent." PO Sur-reply 15–16, 18. Schrum, as we explained, discloses means of addressing stability issues (e.g., uracil modifications and LNP-delivery). Petitioner's proposed combination incorporates these aspects of Schrum's disclosure. And the issue is not inherency, but obviousness—whether, from the combined teachings of Schrum and Geall (and against the backdrop of art like Yang, Wang, Du, and others), the skilled artisan would have reasonably expected to arrive at the claimed composition. To the extent that requires an expectation that the encoded S protein would express and induce an immune response, based on

b) Skepticism and Alleged Clinical Failures

Patent Owner argues that the "literature was replete with reasons for skepticism" related to mRNA vaccines, and most vaccine work still centered on traditional vaccines, viral vector, DNA, and saRNA. PO Resp. 40–42. For example, Patent Owner cites Geall 2013 and contends that "mRNA required 'much more research and development' for commercial viability." *Id.* at 41 (quoting Ex. 1016, 156)); *see also id.* at 41–42 citing Pardi[50] (Ex. 2027, 261), and DeFrancesco[51] (Ex. 2028, 193).

We addressed many of Patent Owner's skepticism arguments above, and Patent Owner's contentions of skepticism remain unpersuasive here in rebutting the skilled artisan's reasonable expectation of success. On balance, we find that the pre-priority technical literature supports a finding of substantial promise and reported successes with mRNA vaccines. *See, e.g.*, Ex. 1019, 1319, 1324, 1326 (teaching that in vivo administration of mRNA was "proven to be feasible," "offers strong safety advantages," and "mRNA offers a promising vaccine vector in light of being flexible, effective, and safe"); Ex. 2025, 1210 (reporting successes in animal models where mRNA produced "long-lived and protective" immunity to flu

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the preponderance of the evidence herein, we find that the answer is "yes" (e.g., as we explained above, there is no evidence in this case of any instance in any vaccine modality in which an S protein did not express or provoke some type of immune response).

[50] Norbert Pardi et al., *mRNA Vaccine – A New Era in Vaccinology*, 17 Nature Reviews 261–279 (2018) (Ex. 2027, "Pardi").

[51] Laura DeFrancesco, *The 'Anti-hype' Vaccine*, 35 Nature Biotechnology 193–197 (2017) (Ex. 2028, "DeFrancesco").

infection, and, "[t]hus, mRNA vaccines could address substantial medical need in the area of influenza prophylaxis and the broader realm of anti-infective vaccinology"). That is not to suggest that researchers in the field did not note the opportunity for further developments and improvements—many did, as Patent Owner suggests. *See, e.g.*, Ex. 2021; *see also* Ex. 1019, 1326. But the relevant measure of success here is not, as Patent Owner urges, established clinical efficacy or proven commercial viability.

Even the references cited by Patent Owner suggest promise and note successes with mRNA. Geall 2012 (which Schrum cites and incorporate-by-reference approvingly when describing its mRNA vaccines) teaches "[i]njection of naked mRNA or self-amplifying RNA in vivo induces gene expression and generates immune responses." Ex. 2021, 14604. That Geall 2012 may have reported saRNA as being the "more efficient" option or cited a need to formulate mRNA vaccines in synthetic delivery vehicles to improve potency, does not materially detract from the POSA's reasonable expectation of success on this record—particularly given that Schrum teaches LNP-encapsulation of the mRNA-encoding payload. Ex. 1009 ¶¶ 346, 397. Pardi (which is a post-priority 2018 publication) discloses that "[v]arious mRNA vaccine platforms have been developed in recent years and validated in studies of immunogenicity and efficacy" and cites Petsch's 2012 study in support. Ex. 2027, 262 (footnote omitted), 276 n.18 (describing Petsch as "demonstrat[ing] that directly injected, non-replicating mRNA can induce protective immune responses against an infectious pathogen"). And DeFrancesco (a post-priority 2017 publication), although indicating that mRNA may, at one time, have been a less favored nucleic-

acid vaccine option ("few in the research community considered RNA a good starting point" with "DNA reigning supreme"), explained that funding by the U.S. government[52] had, since 2011, provided "crucial impetus for advances" in mRNA technology. Ex. 2028, 193; *see also id.* at 196 (Table 1, listing funding from the Defense Advanced Research Projects Agency (DARPA) and other entities for various RNA vaccines in development (many pre-dating October 2015)).

Patent Owner also argues that, by October 2015, mRNA vaccines had not yet been proven in the clinic. PO Resp. 44. At that time, according to Patent Owner, "there were ***no*** approved mRNA vaccines for infectious diseases, and just a handful being tested clinically." *Id.* (citing Ex. 2027, 268). Among the "seven clinical trials for three mRNA vaccines" ("one rabies, two HIV", and "***none*** for BetaCoV"), Patent Owner argues that "all three ultimately ***failed*** in clinical trials." *Id.* (citing, *e.g.*, Ex. 2084, 187; Ex. 2027, 267–268; Ex. 2043, 2; Ex. 2046, 7–8; 2044, 7; 2085, 250–252).

This argument is unpersuasive for three reasons. *First*, Patent Owner provides no sufficient explanation why these clinical trials evidence *failures*. Patent Owner cites, for example, Exhibit 2046, which relates to a human clinical trial with an mRNA rabies vaccine. No further explanation is provided in Patent Owner's papers. But even considering the exhibit and

[52] We have considered Patent Owner's argument that the funding in question came from DARPA, which focuses on "early breakthrough, high-risk, things that would not normally be funded." Ex. 2028, 193; PO Resp. 42 n.9. Regardless, even crediting Patent Owner's argument that DeFrancesco evidences some historical skepticism related to mRNA vaccines, its significance is outweighed by the balance of other evidence on this record.

Dr. Fuller's testimony about it (Ex. 2199 ¶ 522), the results are more nuanced than Patent Owner's argument suggests. Although "needle-syringe injection was ineffective," the trial reports *success* with a needle-free delivery: "This first-ever demonstration in human beings shows that a prophylactic mRNA-based candidate vaccine can induce boostable functional antibodies against a viral antigen when administered with a needle-free device." Ex. 2046, 1, 9 ("Our study provides the first proof-of-concept that an mRNA-based prophylactic vaccine is reasonably safe and capable of inducing rabies antibodies in humans.").

Second, Patent Owner does not point us to any alleged clinical trial failures *before* the putative October 2015 priority date. Tr. 74:7–75:23 (identifying no failures before October 2015). That several researchers were moving forward with human clinical trials using mRNA vaccines for infectious diseases in the period leading up to the critical date (even if those trials provided mixed or even negative results after the critical date) is more suggestive of an expectation of success, not failure, prior to October 2015.

Third, efficacy in human clinical trials and immunity results that would support regulatory approval and commercialization are not the appropriate "reasonable expectation" benchmarks for the claimed composition. As we noted previously, claim 1 is broad and recites a composition in which mRNA encoding betacoronavirus S protein is formulated in a LNP. Petitioner need only show a reasonable expectation of success in arriving at that claimed subject matter.

c) Potential Antibody-Dependent Disease Enhancement (ADE)

Patent Owner cites reports of potential disease enhancement with vaccine delivery, including prior reports related to the S protein. PO Resp. 46–51 (citing, *e.g.*, Ex. 1031 (Du), 229–230). Patent Owner contends this known risk undermines any expectation of success. *Id.* (citing, *e.g.*, Ex. 2199 ¶¶ 126–138, 571–606, 654–667).

We addressed disease enhancement (i.e., ADE) above. *See supra* § II.E.3.d. And, as we explained, we find that the evidence shows that skilled artisans would not have been (and, indeed, were not) dissuaded from developing vaccines encoding the S protein due to fears of ADE. Moreover, although there were some reports of potential ADE with vaccines encoding the full-length S protein (e.g., Yang 2005 (Ex. 2037)), other studies reported no ADE with either the full-length or truncated S proteins (e.g., Yang 2004 (Ex. 1011), Martin 2008 (Ex. 2138), and Wang 2015 (Ex. 1101).; *see also* Ex. 1132, 9809 ("[T]here was ***no evidence*** that immunization with any of the SARS-CoV antigens . . . led to antibody-mediated enhancement of infection.") (emphasis added). On balance, we find the skilled artisan would have reasonably expected success notwithstanding the potential for ADE as seen in some studies. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) (holding that "the expectation of success need only be reasonable, not absolute").

d) Conclusion on Reasonable Expectation of Success

Considering the record developed through trial, and for the reasons explained above, we find that the skilled artisan would have reasonably

expected success in arriving at claim 1's subject matter through Petitioner's proposed combination of Schrum and Geall.

5. *Alleged Hindsight*

Patent Owner argues that Petitioner invokes hindsight to reach the subject matter of claim 1. PO Resp. 51.

We disagree. Schrum teaches or suggests that the skilled artisan may use LNPs to deliver an mRNA vaccine encoding an immunogen to elicit an immune response. Ex. 1009 ¶¶ 340–346, 397. Geall, which Schrum incorporates, identifies the immunogen—a betacoronavirus spike protein. Ex. 1010, 19:26–30. And the prior art recognized the potential for a betacoronavirus (SARS, MERS) outbreak and the "high priority" need for a vaccine against such viruses. Ex. 1011, 561; Ex. 1001, 2:67–3:8 (recognizing same as background in the '600 patent). Patent Owner simply took the next logical step (a step suggested by its own prior art patent application and related art) of using an mRNA-LNP vaccine targeting the BetaCoV S protein. No hindsight bias is involved. Pet. Reply 17–19.

6. *Objective Indicia of Nonobviousness*

Factual inquiries for an obviousness determination include an evaluation and crediting of objective evidence of nonobviousness. *See Graham*, 383 U.S. at 17. Objective evidence of nonobviousness "may often be the most probative and cogent evidence in the record" and "may often establish that an invention appearing to have been obvious in light of the prior art was not." *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012). Thus, notwithstanding what the teachings of the prior art would have suggested to

one skilled in the art, secondary considerations (objective evidence of nonobviousness) may lead to a conclusion that the challenged claims would not have been obvious. *In re Piasecki*, 745 F.2d 1468, 1471–72 (Fed. Cir. 1984). Objective indicia of nonobviousness can include any of the following: long-felt but unsolved needs, failure of others, unexpected results, commercial success, copying, licensing, and praise. *See Graham*, 383 U.S. at 17; *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007).

In order to accord substantial weight to objective evidence of nonobviousness, "the evidence of secondary considerations must have a 'nexus' to the claims, i.e., there must be 'a legally and factually sufficient connection' between the evidence and the patented invention." *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019) (quoting *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988)). Patent Owner bears the initial burden of proving a nexus. *WMS Gaming Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1359 (Fed. Cir. 1999). "A showing of nexus can be made in two ways: (1) via a presumption of nexus, or (2) via a showing that the evidence is a direct result of the unique characteristics of the claimed invention." *Volvo Penta of the Americas, LLC v. Brunswick Corp.* 81 F.4th 1202, 1210 (Fed. Cir. 2023). Whether a patentee has established nexus is a question of fact. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1331–32 (Fed. Cir. 2016).

Here, Patent Owner argues that long-felt but unmet need, skepticism and failure of others, unexpected results, industry praise, and commercial success provide objective indicia that the challenged claims would not have

been obvious. PO Resp. 63–69. We begin by considering whether Patent Owner has established a nexus between the evidence Patent Owner relies on as objective indicia of nonobviousness and the patented invention. We then consider each of the alleged objective indica in turn.

a) Nexus

Although Patent Owner's Response included argument that Patent Owner was entitled to a presumption of nexus (PO Resp. 59–62), at the hearing, Patent Owner made clear that it was relying only on the connection between the evidence its submitted and the unique characteristics of the clamed invention to establish a nexus (Tr. 90 ("[Counsel]: And to simplify the issues for the Board, [Patent Owner] is relying now only on reasonable commensurateness and the unique characteristics of the claimed invention, neither of which are rebutted. [The Board]: So just to be clear, you're not relying on presumption? [Counsel]: That's right."). Accordingly, we do not consider whether Patent Owner is entitled to a presumption of nexus. Instead, we focus our analysis on whether Patent Owner has shown sufficient connection between its objective indicia and the unique characteristics of the claimed invention.

Much of the objective evidence Patent Owner identifies as supporting the non-obviousness of the challenged claims relates to the parties' commercial products, Spikevax and Comirnaty. Accordingly, we begin by considering whether Patent Owner has established that these products, embody the challenged claims. PO Resp. 61. Patent Owner contends that both products embody the challenged claims. *Id.* More specifically, Patent Owner contends that both products: "encode an S protein that forms a

spike," "have mRNA comprising 5' and 3' untranslated regions, poly(A) tail, [and a] 5' cap analog," "have mRNA comprising a 1-methylpseudouridine modification where at least 80% of the uracil is modified," and "are formulated in a lipid nanoparticle comprising 20–60% ionizable cationic lipid, 5–25% neutral lipid, 25–55% cholesterol, and 0.5–15% PEG-modified lipid." *Id.* (citing claim charts appended to the Declaration of Dr. Krause (Ex. 2200)).

Petitioner does not meaningfully contest that Spikevax and Comirnaty meet the limitations of the challenged claims. At the hearing, counsel for Petitioner asserted that it contested infringement in the related district court litigation and that there was a dispute in this proceeding as to whether these commercial products embody the challenged claims. Tr. 40:10–41:13. However, the briefing and testimony Petitioner called out as reflecting the dispute in this proceeding does not identify any limitation of the challenged claims as missing from the commercial products. Tr. 42:12–16 (citing Pet. Reply 26, Ex. 1159 ¶¶ 457–64). The cited portion of Dr. Griffin's declaration does include the heading "Spikevax® and Comirnaty® Do Not Embody the Challenged Claims." Ex. 1159 ¶ 457. But the testimony under the heading asserts only that Spikevax and Comirnaty have important unclaimed attributes—i.e., that they are not coextensive with the challenged claims. *Id.* ¶¶ 457–464. Moreover, in his deposition, when asked, Dr. Griffin did not identify any limitations of the challenged claims that are not present in the commercial products. Ex. 2253, 103:18–106–6. Accordingly, Dr. Krause's testimony that Spikevax and Comirnaty meet all of the

limitations of the challenged claims stands unrebutted. Ex. 2020 ¶¶ 225–226, Appendices C and E.

Having considered the arguments and evidence before us, we find that Patent Owner has established, by a preponderance of the evidence, that Spikevax and Comirnaty meet all of the limitations of the challenged claims. We next consider whether Patent Owner has established that the objective evidence Patent Owner identifies as supporting the nonobviousness of the challenged claims is a "direct result of the unique characteristics of the claimed invention." *Fox Factory, Inc. v. SRAM, LLC,* 944 F.3d 1366, 1373–74 (Fed. Cir. 2019).

Patent Owner contends that the safety and efficacy of Spikevax and Comirnaty are "due to the unique claimed combination, including protective features of the LNP, translation of the mRNA into an S protein/subunit, and recruitment of adaptive immune cells to make antibodies." PO Resp. 62. According to Patent Owner, "[n]exus is even stronger for claims 9 and 21, which recite the 1-methylpseudouridine modification," as evidenced by the fact that Spikevax and Comirnaty, which use that modification, were more successful that several vaccines that lacked the 1-methylpseudouridine modification. *Id.*

Petitioner does not dispute that the combination of mRNA, LNP, and S protein contributed to the safety and efficacy of the claimed vaccines. Instead, Petitioner argues that Spikevax and Comirnaty are not coextensive with the scope of the challenged claims, that they encode sequences that were not known at the time of the invention, and that unclaimed features contributed to their success. Pet. Reply. 25–26. For the reasons discussed

below, we find that Patent Owner has carried its burden to establish the safety and efficacy of Spikevax and Comirnaty are directly attributable to the challenged claims. Petitioner's arguments do not persuade us otherwise.

The evidence supports that the combination of mRNA, LNP, and the betacoronavirus S protein contributed directly to the safety and efficacy of Spikevax and Comirnaty. Dr. Krause testifies that the claimed "lipid nanoparticle protects the mRNA from degradation and delivers the mRNA to the cell," that the "mRNA is then translated into the betacoronavirus S protein," and that the combined "mRNA-LNP platform . . . serves to recruit adaptive immune cells that learn to make antibodies against the S protein." Ex. 2200 ¶ 227. This testimony is unrebutted and consistent with the record evidence as to how the claimed vaccine works. Dr. Krause further testifies the vaccines are "remarkably safe" and that the efficacy of the claimed vaccine "stems from the endogenous production of the S protein or S protein subunit in a way that stimulates the adaptive immune system to induce strong, protective immune responses." *Id.* ¶ 228. Again, this testimony is unrebutted and credible.

Petitioner argues that Spikevax and Comirnaty are not coextensive with the challenged claims, pointing to the fact that the claims encompass any betacoronavirus S protein, not just SARS-CoV-2 S protein. Pet. Reply. 25. This argument is not persuasive because, as Patent Owner explains (PO Sur-reply 27), coextensiveness is relevant only to the presumption of nexus, which Patent Owner no longer relies upon.

Petitioner argues that "Comirnaty® and Spikevax® encode antigens not in existence as of the priority date." Pet. Reply 25–26 (citing Ex. 1159

¶¶ 457–464). In the cited testimony, Dr. Griffin testifies that both Comirnaty and Spikevax use "a modified version of the spike protein that introduces two proline residues [2P modification]," that is "not described or claimed in the '600 patent," and that "improv[es] vaccine performance." Ex. 1159 ¶¶ 458–459; *see also id.* ¶¶ 260–264 (discussing evidence regarding the importance of this modification). Dr. Krause concedes that the "2P mutation may help improve the immunogenicity of the vaccines" but contends that "it is not required." Ex. 2200 ¶ 232. The evidence supports Dr. Krause's testimony that the 2P modification is not required. *see also id.* ¶ 232–238 (citing data from the '600 patent showing immune response even without the 2P modification, also citing comparative testing between 2P modified and unmodified S protein). But even if we were to find, contrary to the evidence of record, that the 2P modification was not only an improvement but a necessity, it would not change that the efficacy and safety of Comirnaty and Spikevax are a direct result of the unique characteristics of the claimed invention. As discussed above, the claimed mRNA-LNP platform allows for betacoronavirus S protein, including 2P modified S protein, to be expressed in a way that recruits adaptive immune cells that learn to make antibodies against the S protein.

The fact that the 2P modified sequence did not exist as of the priority date is of no moment. Indeed, the adaptability of the claimed vaccine platform—the fact that it can be modified to account for changes in antigens—is one of the reasons for its success. As Dr. Krause persuasively explains, "one of the great benefits of the invention is that it can be used to make a vaccine for any betacoronavirus by changing the mRNA sequence"

which has allowed Spikevax and Comirnaty to be "updated to include mRNA encoding the S protein of new variants of SARS-CoV-2 that emerged over time to ensure that recipients were protected against the then-most-common strain." Ex. 2200 ¶ 228. Accordingly, there was no need for the specific sequence used in the Spikevax and Comirnaty vaccines to be in existence for the claimed features to be directly responsible for the success of those vaccines.

Finally, Petitioner argues that, "in addition to different LNP formulations, [the Spikevax and Comirnaty vaccines] have 'different [mRNA] sequences, 5' caps, 5' and 3' untranslated regions, [and] codon optimizations'—each of which impact vaccine performance." Pet. Reply 26 This argument is not persuasive because, as Patent Owner explains, "Spikevax® and Comirnaty® have ***nearly identical*** efficacy ***despite*** differences in these features." PO Sur-reply 28 (citing Ex. 2169, Table 2; Ex. 2168, Fig. 2; Ex. 2200, ¶¶230-231, 239).

To summarize, Patent Owner has established by a preponderance of the evidence that the safety and efficacy of the Spikevax and Comirnaty vaccines is a direct result of the unique characteristics of the challenged claims. We thus find a nexus between the alleged objective evidence of nonobviousness pertaining to Spikevax and Comirnaty and the challenged claims.

b) Long-Felt Unmet Need

Patent Owner contends that, beginning with the 2002 SARS outbreak, there existed a need for vaccines that would be safe and effective against betacoronaviruses. PO Resp. 63–64 (noting that, roughly a decade later,

MERS also showed pandemic potential). According to Patent Owner, the '600 patent's claimed invention met this long-standing need, as most directly shown when Patent Owner's Spikevax and Petitioner's Comirnaty vaccines, which are alleged to practice the claimed invention, were promptly developed and made available to the public in late 2020 in response to the SARS-CoV-2 outbreak and consequent COVID-19 pandemic. *Id.* (citing, *e.g.*, Ex. 2200 ¶¶ 173–177; Ex. 2160).

We find that Patent Owner's evidence of long-felt need constitutes objective indicia of nonobviousness that is entitled to weight. The need for a safe and therapeutically-effective human vaccine against BetaCoV existed since at least 2002—as the '600 patent itself describes. Ex. 1001, 2:67–3:8 (describing the need for SARS and MERS vaccines arising from outbreaks in 2002 and 2012); Ex. 1002 ¶¶ 112–116 (testimony of Dr. Griffin regarding preexisting need for BetaCoV vaccines that he opines would have motivated the prior-art combinations in question); Ex. 1011, 561 (disclosing, in 2004, that "[f]inding a vaccine for this virus ([SARS-CoV]) remains a high priority"); Pet. Reply 13 (citing Dr. Griffin's testimony and describing SARS-CoV's identification as a "top-ten pathogen with pandemic potential by October 2015"). That need manifested worldwide in early 2020 when SARS-CoV-2 gained a foothold and began spreading, kicking off the COVID-19 global pandemic. And, based on the evidence here, we find that Petitioner's and Patent Owner's respective products (Comirnaty and Spikevax) met the need, gaining emergency approvals in December 2020. *See, e.g.*, Ex. 2160 (press release dated December 19, 2020, announcing FDA authorization of Moderna's COVID-19 vaccine); Ex. 2200 ¶¶ 173–177

(testimony of Dr. Krause about the "speedy development" of Moderna's and Petitioner's vaccines, and the emergency authorization "to combat widespread severe disease and death").

Petitioner provides no persuasive evidence to the contrary on the alleged long-felt need. Instead, Petitioner suggests Patent Owner's argument and evidence is inapt because the SARS-CoV-2 virus did not exist in October 2015 and, thus, there was no preexisting and longstanding need for a vaccine against it. Pet. Reply 26–27 (citing *Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 989, 997 (Fed. Cir. 2009)).

We disagree with Petitioner's position. The need was for a safe and therapeutically-effective vaccine that could be used against existing, reemergent, or future BetaCoV outbreaks. On this record, we find that need existed before the putative October 2015 priority date. *Proctor & Gamble*, 566 F.3d at 998 (suggesting the need must exist at the patent's applicable filing date, not that it is necessarily met (e.g., produced and available in commerce) at that date).[53] The parties' vaccines that practice the claimed invention (for which there is no persuasive evidence to the contrary) met such need as explained above. For the above reasons, we find that Patent Owner's contentions support that there was a long-felt and unmet need and are entitled to significant weight as objective indicia of nonobviousness.

[53] Petitioner did not argue in this proceeding that any preexisting vaccine could have or did meet the need at issue.

c) Skepticism and Failure of Others

Patent Owner argues that skepticism and failure of others support a determination that the claims would not have been obvious. PO Resp. 64–66.

First, Patent Owner contends, there was "deep skepticism" about mRNA vaccines and research mostly focused on other vaccine technologies like DNA, saRNA, and traditional vaccines. *Id.* at 64–65 (citing, *e.g.*, Ex. 2025 (Petsch); Ex. 2027 (Pardi); Ex. 2028 (DeFrancesco)). We addressed substantially the same contention above when addressing alleged skepticism with mRNA vaccines. For the same reasons the alleged skepticism of mRNA vaccines would not have detracted from the skilled artisan's reasons for selecting an mRNA vaccine encoding the S protein or from the artisan's reasonable expectation of success in doing so, skepticism of mRNA vaccines does not support the nonobviousness of the claimed method.

Second, Patent Owner argues, the field was skeptical about using the S protein as an antigen based on its size and risk of disease enhancement. PO Resp. 65 (citing, *e.g.*, Ex. 1031(Du), 229–230). Here too, we addressed this argument above. As explained above, notwithstanding the known potential for disease enhancement, many researchers designed vaccines based on a BetaCoV S protein, successfully expressed that protein with those vaccine products, and found no evidence of enhancement. *See, e.g.*, Ex. 1011; Ex. 1101; Ex. 1132; Ex. 2138.

Third, Patent Owner argues, by October 2015, only three mRNA vaccines (two for HIV, one for rabies) were in clinical trials and all "ultimately failed." PO Resp. 65 (citing e.g., Ex. 2200 ¶¶ 193–197). This

does not demonstrate any failure relative to any attempt to design or administer an mRNA vaccine encoding the S protein. Human clinical efficacy is a much higher benchmark than is required by the broad claims here. And, as we explained above, at least the rabies vaccine that was undergoing a phase 1 human clinical trial was ultimately reported as being "reasonably safe" and producing "functional antibodies." Ex. 2046, 1, 9; *see also* Ex. 2027, 268 (discussing clinical trial results for HIV-1 mRNA vaccine, noting the vaccine "proved to be safe and elicited antigen-specific $CD4^+$ and $CD8^+$ T cell responses, but no clinical benefit was observed").

None of the above arguments about alleged failure of others and skepticism persuasively supports a determination of nonobviousness. The argument is generic as to mRNA and disconnected from Patent Owner's proffered evidence about Spikevax and Comirnaty and our discussion above regarding nexus. Moreover, it is unpersuasive on the merits for reasons already explained, including because the record evidence, on balance, does not reflect significant or overriding skepticism about mRNA vaccines. *See, e.g.*, Ex. 1016, Abstr. (teaching that mRNA vaccine trials are underway and "prospects for success are bright"); Ex. 2025, 1210 (after noting successful induction of protective immunity in mice using mRNA vaccine, remarking "mRNA vaccines could address substantial medical need in the area of influenza prophylaxis and the broader realm of anti-infective vaccinology").

Patent Owner offers one final argument related to alleged failure of others. PO Resp. 65–66. That is, Patent Owner contends that hundreds of other manufacturers tried to make vaccines responsive to the COVID-19 pandemic. *Id.* (citing Ex. 2171, 5). According to Patent Owner, "vaccines

that did not use [Patent Owner's] invention failed or were abandoned" with Spikevax and Comirnaty ultimately dominating the market. *Id.* (citing Ex. 2200 ¶¶ 198–199 (testifying "[t]he vast majority of these [other candidate] programs used technology platforms other than mRNA" and "[o]ther technologies were either too slow to meet the urgent need for a vaccine or far less effective"); Ex. 2197 ¶¶ 13–17 (testifying, *inter alia*, that "of the many vaccine candidates for COVID-19, only 11 have been authorized for use" by FDA and/or WHO); Figure 1 (identifying authorized vaccines, with Spikevax and Comirnaty reporting the highest efficacy).

This final argument is substantively unrebutted by Petitioner and, we find, has merit. We treat the evidence that Spikevax and Comirnaty succeeded (technologically and in the market) whereas many other vaccine candidates failed to produce acceptable alternative COVID-19 vaccines as objective indicia of nonobviousness entitled to weight (both as evidence of failure of others, and related to commercial success, which we discuss separately below).

d) Unexpected Results

Patent Owner argues that unexpected results constitute objective indicia that favor a finding of nonobviousness. PO Resp. 66–67; *see also* PO Sur-reply 27.

Patent Owner contends that many in the field thought that protamine or saRNA would be necessary to generate a sufficient immune response, yet the patent describes an mRNA-LNP formulation that generated strong immune responses. PO Resp. 66 (citing Ex. 1001, 40:13–41:30; Ex. 2200 ¶¶ 200–201).

This argument does not weigh in favor of a conclusion of nonobviousness. Schrum discloses the mRNA-LNP platform, including for vaccines, and suggests that platform can express the desired protein in high volume and trigger an immune response in the subject receiving it. *See, e.g.*, Ex. 1009 ¶¶ 340, 342–346, 397, 995–999. And Geall, which Schrum expressly incorporates-by-reference in Schrum's section devoted to mRNA vaccines when describing dosing and immunogens, identifies the BetaCoV S protein as a known-target immunogen. *Id.* ¶ 342; Ex. 1010, 19:26–30. Moreover, while some discussed the use of protamine for mRNA vaccine delivery, the art taught that LNPs were the other leading delivery strategy, as we discussed above. Ex. 1016 (Geall 2013), 154; *see also* Ex. 2021, 14604 (teaching LNP delivery "substantially-increased immunogenicity" versus unformulated RNA). From the art's teachings, we find that an immune response would have been expected. *In re Skoner*, 517 F.2d 947, 950 (CCPA 1975) ("Expected beneficial results are evidence of obviousness of a claimed invention.").

Patent Owner contends that it was unexpected that full-length S protein expressed well and produced higher antibody titers than the S2 subunit. *Id.* at 67 (citing e.g., Ex. 1001, 213:56–214:9, Figs. 17–18; Ex. 2200 ¶ 208). We disagree. As we discussed above, numerous vaccine modalities used and expressed the S protein (both full-length and truncated forms)—and, in none of those studies, is there any allusion to concerns about the ability to do so. *See, e.g.*, Ex. 1011, 561–562 (data showing expression of SΔCD (only thirteen amino acids shorter than the 1,255 amino acid full-length S protein)); Ex. 1101, 1–3, 7 (expressing full-length

BetaCoV S protein and describing neutralization assays in mice and primates). Moreover, the skilled artisan would not have been surprised that full-length S protein produced higher antibody titers than the much smaller S2 subunit. Ex. 1101, 260:9–15 (Dr. Fuller testifying "they ended up showing the full-length spike protein ***not surprisingly*** actually induced higher antibody titers than the truncated version" because "the full-length S protein will have more epitopes, neutralizing antibody epitopes to target") (emphasis added).[54]

Patent Owner contends it was surprising that the claimed inventions did not result in vaccine-dependent enhanced disease. PO Resp. 67 (citing Ex. 2200 ¶¶ 206–207 (Dr. Krause testimony that "[t]he lack of disease enhancement was borne out by the successful human clinical trials of Spikevax® and Comirnaty®"); *see also id.* (arguing "the parties' COVID-19 vaccines have not caused enhanced disease").

The alleged absence of disease enhancement does not constitute persuasive objective indicia of nonobviousness on this record. As we explained above, vaccine- or antibody-dependent disease enhancement (ADE) is an inherent risk with any and all vaccines. Although ADE was a known potential risk, we are not persuaded that it was expected with the claimed mRNA-LNP vaccine encoding the S-protein (or that its absence, unexpected). Some research had reported evidence of potential ADE

[54] The S2 subunit includes about 600 amino acids as seen, for example, in Wang. Ex. 1101, 7 (Fig. 1a); *see also* Ex. 1001, Table 11 (amino acid sequences for full-S protein and S2 subunit of MERS-CoV); Ex. 2199 ¶ 122.

connected to use of a spike protein (*see* Ex. 2030, 10590[55]). However, numerous other researchers found no such evidence. *See, e.g.*, Ex. 1011, 563 (results suggest antibodies against SARS-CoV S glycoprotein "do not enhance infection in this animal model"); Ex. 1132, 9809 ("no evidence that immunization with any of the SARS-CoV antigens . . . led to antibody-mediated enhancement of infection"); *see also* Ex. 2137, 800 (disclosing "Ab-dependent enhancement has not been observed with any human SARS-CoV strain."). The '600 patent suggests, and results from administration of Spikevax and Comirnaty substantiated, that potential ADE would did not arise, but that result has not been shown to be *surprising* on this record. The absence of ADE in Spikevax and Comirnaty, while a beneficial and welcome feature with these vaccines, is entitled to no, or at best only minimal, weight as an alleged unexpected result.

Patent Owner also argues that the "degree" of immunogenic success shown by experimental results with the claimed invention was surprising. PO Resp. 66–67. Those results, according to Patent Owner, include: (i) the '600 patent's example where rabbits receiving two doses of mRNA MERS-CoV vaccine showed reduced viral load in the nose and lungs, and "complete protection" in the throat against viral challenge; and (ii) the

[55] Martial Jaume et al., *Anti-Severe Acute Respiratory Syndrome Coronavirus Spike Antibodies Trigger Infection of Human Immune Cells via a pH- and Cysteine Protease-Independent FcyR Pathway*, 85 Journal of Virology 10582–10597 (2011) (Ex. 2030, "Jaume"). Dr. Griffin explains that Jaume's *in vitro* assay is of limited relevance to predicting ADE because enhanced disease can only be evaluated after the subject has been vaccinated and later infected with the virus. Ex. 1159 ¶ 224 n. 376 (citing, e.g. testimony of Dr. Krause in further support (Ex. 1105, 68:19–21)).

reported "efficacy of Spikevax® and Comirnaty®" in the face of health officials' hopes for a vaccine with at least 75% efficacy and acceptable efficacy thresholds around 50–60%. *Id.* at 66–67 (citing, *e.g.*, Ex. 1001, 214:34–53 (MERS-CoV study in rabbits), Figs. 19A-C, 20A, 20B, 21; Ex. 2175; Ex. 2200 ¶¶ 202–205).

This evidence is entitled to some weight as objective indicia of nonobviousness. As discussed herein, we find that the skilled artisan would have expected an immune response, including production of neutralizing antibodies, in the proposed method resulting from the combination of Schrum and Geall (or Schrum and Yang). *See supra* § II.E.1–4. However, Petitioner does not provide persuasive rebuttal argument or evidence addressing the cited objective indicia that explains why the degree of efficacy shown in the '600 patent's cited examples or in the reported clinical efficacy data about Spikevax and Comirnaty would have been expected. *See* Pet. Reply 27 (arguing that the generic concept of mRNA-LNP vaccine encoding S protein was "squarely in the prior art" and cannot show unexpected results); Ex. 2200 ¶¶ 202–205 (testimony of Dr. Krause reviewing testing results and opining that "the degree of success shown by Moderna's inventions was surprising and unexpected").

e) Industry Praise

Patent Owner contends that Spikevax and Comirnaty have received "significant praise." PO Resp. 67. The evidence of record supports this. It includes: several news articles lauding the efficacy of the claimed vaccines after the results of clinical trials were announced (Exs. 2176, 2177, and 2178); the publication of Moderna's clinical trial results in prestigious

journals like the New England Journal of Medicine and Nature Medicine (Ex. 2200 ¶ 212 (testimony of Dr. Krause citing Exs. 2035, 2179, 2036, and 2181); and Spikevax's receipt of several prestigious industry awards (Ex. 2041 (Prix Galien UK Award for best biotechnology product)), Ex. 2040 (American Chemical Society Heroes of Chemistry Award), and Ex. 2043 (CPHI Pharma Award for Excellence in Pharma)).

Petitioner does not challenge that Spikevax and Comirnaty received significant industry praise. Petitioner does, however, assert that "any industry praise . . . is not due to the claimed features." Pet. Reply 27. This assertion is not further explained, and is supported by citation to 166 paragraphs of witness testimony. *Id.* (citing Ex. 1163, ¶¶1-154; Ex. 1159, ¶¶478-90). We do not consider the cited witness testimony because it violates our rules against incorporation by reference. 37 C.F.R. § 42.6(a)(3). And, Petitioner's bald assertion that industry praise is not attributable to the claimed features is insufficient to preserve that argument. *SmithKline Beecham*, 439 F.3d at 1320. Moreover, we have already considered, and rejected, Petitioner's nexus-related arguments that the safety and efficacy of Spikevax and Comirnaty are not the direct result of the claimed features.

We credit Patent Owner's evidence that Spikevax and Comirnaty have received praise in the industry. We find the awards Patent Owner received for Spikevax particularly persuasive and accord this praise, and the other praise of record, significant weight as an objective indicator of the non-obviousness of the claimed composition.

f) Commercial Success

Patent Owner argues that the "tremendous market success" of Spikevax and Comirnaty supports a determination that the claims would not have been obvious. PO Resp. 69. As support, Patent Owner cites the testimony of Mr. Malackowski, who provides sales data for both vaccines. Ex. 2197 ¶¶ 19–20. Mr. Malackowski opines that "the market success of Spikevax® and Comirnaty® is remarkable" particularly "when considered against the competitive landscape." *Id.* ¶¶ 21–22. According to Mr. Malackowski, "there were over 200 vaccines for COVID-19 under development by late 2020" but "[o]ut of that highly competitive field, Spikevax® and Comirnaty® are the only two vaccines that have achieved any meaningful level of market success in the U.S." *Id.* ¶ 22; *see also id.* ¶¶ 24–29 (discussing lack of market success for other vaccines).

Petitioner does not challenge that Spikevax and Comirnaty were commercially successful. *See* Ex. 2255, 72:5–17 (testimony of Mr. Bakewell that his declaration does not offer the opinion that Spikevax and Comirnaty were not commercially successful). Petitioner does, however, assert that "any . . . commercial success is not due to the claimed features." Pet. Reply 27. This assertion is supported by the same evidence cited in connection with industry praise and, like the industry praise assertion, is not further explained in the briefing. For the reasons discussed in connection with industry praise, Petitioner's bald assertion is insufficient to support its argument and Petitioner's citation to 166 paragraphs of witness testimony violates our rules. *SmithKline Beecham*, 439 F.3d at 1320; 37 C.F.R. §42.6(a)(3). And, as also discussed above, Petitioner's argument that the

safety and efficacy of Spikevax and Comirnaty are not the direct result of the claimed features is unpersuasive.

We credit Mr. Malackowski's unrebutted testimony that Spikevax and Comirnaty achieved "tremendous market success" and that this market success was particularly impressive "when considered against the competitive landscape." Ex. 2197 ¶¶ 10, 22. We find that this market success is entitled to significant weight as an objective indicator of the nonobviousness of the claimed composition.

7. *Conclusion on Claim 1*

Based on the totality of the argument and evidence of record, we conclude that claim 1 would have been obvious over the combination of Schrum and Geall.

We find that Petitioner made a very strong showing that Schrum and Geall teach or suggest the subject matter of claim 1, and that the skilled artisan would have been motivated to combine their teachings as proposed with a reasonable expectation of success. For example, Schrum teaches the mRNA-LNP vaccine platform, teaches the same can be used to deliver an encoded immunogen and induce an immune response in a subject, and expressly points the skilled artisan to Geall's teachings, which identify a betacoronavirus spike protein—a well-known and prevalent target for vaccine development in the art that was repeatedly shown to be highly immunogenic across a variety of vaccine platforms.

We find Patent Owner's rebuttal evidence on whether Schrum and Geall teach or suggest the claimed subject matter and the motivation issue comparatively weak. Patent Owner's argument and evidence marginally

diminishes our estimation of whether the POSA would have reasonably expected success but, we find, the record still strongly supports Petitioner's position—especially when we consider the breadth of the challenged claim.

On the other hand, we find that Patent Owner has presented strong (and, in some cases, substantively unrebutted) evidence on objective indicia of nonobviousness on this record. We place significant weight on the asserted commercial success, industry praise, and long-felt need met by the parties' COVID-19 vaccines, especially paired with the asserted failure of others in the industry to develop and commercialize viable alternatives. We give some weight to the asserted unexpected degree of efficacy obtained by vaccines that use the claimed method. We give the asserted skepticism and the remaining unexpected results minimal or no weight for the reasons discussed above. Collectively, we give Patent Owner's objective indicia evidence substantial weight.

Ultimately, the Board is tasked with weighing the evidence—both for and against a determination of obviousness. Here, we find that the preponderance of the evidence favors Petitioner and a determination of obviousness. Key factors favoring Petitioner include, as already discussed, the broad claims, the closeness of the prior art to the claimed subject matter, compelling reasons the skilled artisan had for selecting the S protein as the target antigen/immunogen, and the consistent (if not universal) recognition that delivering the S protein provoked an immune response in the vaccine recipient. Patent Owner's objective indicia, while given substantial weight, are outweighed by the very strong evidence of obviousness. *Pfizer*, 480 F.3d at 1372 ("Although secondary considerations must be taken into account,

they do not necessarily control the obviousness conclusion."); *Purdue Pharma L.P. v. Accord Healthcare, Inc.*, No. 2023-1953, 2024 WL 5244764, at *9 (Fed. Cir. Dec. 30, 2024) ("[A] strong showing of obviousness may stand even in the face of considerable evidence of [secondary considerations]."); *Leapfrog Enters.,* 485 F.3d at 1162 (finding no basis to disagree with the district court's conclusion that the patent owner "provided substantial evidence of commercial success, praise, and long felt need, but that, given the strength of the prima facie obviousness showing, the evidence on secondary considerations was inadequate to overcome a final conclusion" of obviousness); *Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1472 (Fed. Cir. 1997) ("In reaching an obviousness determination, a trial court may conclude that a patent claim [would have been] obvious, even in the light of strong objective evidence tending to show nonobviousness.").[56]

8. *Claims 2, 4–6, 8–12, 16, 17, 20, 21, and 26*

Claims 2, 4–6, and 8–12 depend from, and further limit, claim 1 by reciting additional requirements on: the protein encoded (claims 2 and 3), the mRNA (claims 4–6 and 8–10), and the lipid nanoparticle (claims 11 and 12). Claim 16 is an independent claim that recites the components of claim 1 and further limits the mRNA and the lipid nanoparticle. Claims 17, 20 and 21 depend from claim 16 and further limit the protein encoded (claim 17)

[56] For avoidance of doubt, we also considered and weighed the cited objective indicia of nonobviousness before making any determination that the dependent claims (addressed below) would have been obvious and before making a determination on Ground 3.

and the mRNA (claims 20 and 21). Claim 26 is an independent claim that recites the components of claim 1 and further limits the lipid nanoparticle.

Petitioner argues the combination of Schrum and Geall teach or suggest the subject matter of claims 2, 4–6, 8–12, 16, 17, 20, 21, and 26 and that a POSA would have combined and modified the prior art with a reasonable expectation of success to arrive at that subject matter. Pet. 42–48; *see also, id.* at 28–37 (Petitioner's showing for anticipation, much of which is incorporated in its obviousness showing). Petitioner's argument is supported by citation to the prior art and persuasive expert testimony that we credit. *See*, *e.g.,* Ex. 1002 ¶¶ 117–139; Ex. 1004 ¶¶ 101–122; *see also,* Ex. 1002 ¶¶ 117–139 (anticipation testimony relevant to obviousness) Ex. 1004 ¶¶ 67–93 (anticipation testimony relevant to obviousness). Except as discussed below, Patent Owner does not differentiate its arguments by claim or present any unique counterargument to the above-challenged claims.

Patent Owner asserts: "As Dr. Fuller explains, the Petition also fails to show each dependent claim is unpatentable. Ex. 2199, §§XI.B-XI.J, XI.L-XI.M." PO Resp. 26. This threadbare assertion does not preserve argument specific to each of the challenged dependent claims. *SmithKline Beecham*, 439 F.3d at 1320. Moreover, the attempt to support this assertion with citation to myriad sections of Dr. Fuller's declaration (which cited sections liberally incorporate analysis from many more sections of the declaration) is an improper incorporation-by-reference, contrary to the Board's rules. 37 C.F.R. §42.6(a)(3).[57]

[57] Although we do not consider arguments raised in Dr. Fuller's testimony that are not explained in Patent Owner's response, we recognize that

The only dependent claims for which Patent Owner provided in its papers anything resembling separate argument are claims 8, 9, 10, 20, and 21. *See* PO Resp. 21 (arguing, in the section of its response addressing anticipation, that Geall's testing of "chemical modifications of saRNA, including uridine modifications, which did not work as well as unmodified saRNA, giv[e] a POSA further reason not to use chemical modifications (as required in challenged claims 8, 9, 10, 20 and 21)"). We address claims 8–10, 20, and 21 below.

Petitioner argues that claims 8–10, 20, and 21 would have been obvious over Schrum and Geall. Pet. 43–44, 46–47; *see also, id.* at 30–32, 36–37 (incorporated anticipation testimony). More specifically, Petitioner argues a POSA would have had reason to make the uracil chemical modifications as claimed because "Schrum discloses, consistent with the foundational knowledge of Karikó and Weissman, that incorporation of a naturally-occurring pseudouridine analog, which includes 1-methylpseudouridine, functions to reduce the innate immune response caused by exogenous mRNA administration, as compared to unmodified mRNA." *Id.* at 43 (citing, *e.g.*, Ex. 1009 ¶¶ 26, 50, 1191–1198, 1306–1309; Ex. 1023, 8:26–30, 26:22–29, 22:38–45; Ex. 1002 ¶¶ 118).[58] Indeed,

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Petitioner retains the burden of proof in this proceeding. 35 U.S.C. § 312(a)(3); *Harmonic Inc.*, 815 F.3d at 1363. We have reviewed Petitioner's contentions and determine that Petitioner has shown, by a preponderance of the evidence, that 2, 4–6, 8–12, 16, 17, 20, 21, and 26 would have been obvious over the combination of Schrum and Geall.

[58] Petitioner's citation of Ex. 1002 ¶ 118 appears to be a typographical error. The testimony relating to the subject matter for which it is cited appears at Ex. 1002 ¶ 122. We regard this as a harmless error.

Petitioner contends, "Schrum's examples confirm" the proposed modifications "promote protein expression." *Id.* Further, Petitioner cites evidence and testimony supporting that replacement of 100% of the uracils in the mRNA sequence results in increased expression. Pet. 31, 44; Ex. 1009 ¶¶ 26, 1183; Ex. 1002 ¶¶ 83, 123.

Petitioner persuades us that the subject matter of claims 8–10, 20 and 21 would have been obvious over Schrum and Geall. We credit the evidence cited by Petitioner above, including Dr. Griffin's testimony about the express teachings of Schrum and the obviousness of modifying mRNA uracils as proposed, which Schrum exemplifies and encourages. *See, e.g.*, Ex. 1009 ¶¶ 26, 1065–80, 1191–98, 1204–1210, 1300–1302, 1306–1309; Ex. 1002 ¶¶ 83, 118, 123, 135 (testifying Schrum's examples "reflect the use of mRNA in which every uracil has been replaced with 1-methylpseudouridine to promote protein expression"). Patent Owner's barebones contention that, in one test from Geall, a chemically-modified saRNA "did not work as well" as an unmodified analog does not materially undermine Petitioner's evidence or its challenge to claims 8–10, 20 and 21. PO Resp. 21 (citing Ex. 1010, 38:7–39:15).

For the reasons above, we determine that Petitioner has proved by a preponderance of the evidence that claims 2, 4–6, 8–12, 16, 17, 20, 21, and 26 would have been obvious over Schrum and Geall.

F. Ground 3: Obviousness over Schrum and Yang

Petitioner argues that claims 1, 2, 4–6, 8–12, 16, 17, 20, 21, and 26 would have been obvious over Schrum in combination with Yang. Pet. 48–57; Ex. 1002 ¶¶ 140–173; Ex. 1004 ¶¶ 123–140.

We find that Petitioner has proved by a preponderance of the evidence that the challenged claims would have been obvious over Schrum and Yang for the reasons given in the Petition. The only material difference between Grounds 2 and 3 is that, for Ground 3, Petitioner relies expressly on Yang's BetaCoV (SARS-CoV) S protein as the immunogen to be encoded by the mRNA-LNP vaccine suggested by Schrum. In other words, Yang takes Geall's place in the proposed combination relative to the identification of the S protein in the claims. Pet. 48–49 (citing Yang's S protein and results); 50–52 (arguing reasons to combine Schrum and Yang, and reasonable expectation of success).

If there was any question about whether Geall's disclosure of a "spike polypeptide" met claim 1's "S protein," there is no question that Yang teaches or suggests both the full-length and truncated S protein as an immunogen. Ex. 1011, 561. Patent Owner argues that Yang lacks immune response data for the full-length S protein, and only provides such data for truncated S protein. PO Resp. 52–53. We addressed substantially the same argument under Ground 2, and that analysis applies here. *See supra* §§ II.E.2, II.E.3.a, II.E.4.a. Among other things, the claimed S protein does not exclude truncations like Yang's SΔCD, about which Yang undisputedly provides detailed data, including that expression of that immunogen induced robust neutralizing antibodies. Ex. 1011, 561–563; *see also* Ex. 1031 (Du), 229 (interpreting Yang as showing that vaccine encoding "full-length S protein [for] SARS-CoV Urbani strain could induce T-cell and neutralizing antibody responses").

The remainder of the parties' arguments about Ground 3 are substantively the same as Ground 2. *See, e.g.*, PO Resp. 52–554; Pet. Reply 10–27 (arguing Grounds 2–4 as a group); PO Sur-reply 9–28 (same). We addressed those arguments above for Ground 2 and that analysis applies equally here.

III. OTHER GROUNDS (GROUNDS 1 AND 4)

Petitioner argues that all of the challenged claims are anticipated by Schrum (Ground 1), and further that those claims would have been obvious over Schrum and Altmeyer (Ground 4). Pet. 22–38 (Ground 1), 57–66 (Ground 4).

Because Petitioner carried its burden to show unpatentability of all challenged claims under Grounds 2 and 3 (as discussed above), we exercise our discretion and do not reach Grounds 1 and 4. *SAS*, 138 S. Ct. at 1359 (holding petitioner is entitled to a final written decision that covers all challenged claims); *Bos. Sci. Scimed, Inc. v. Cook Grp. Inc.*, 809 F. App'x 984, 990 (Fed. Cir. 2020) (nonprecedential) (explaining that "the Board has discretion to decline to decide additional instituted grounds once petitioner has prevailed on all its challenged claims.").

IV. OBJECTIONS

The parties filed respective objections to their opponents' demonstratives. Paper 84 (Petitioner's Objections); Paper 83 (Patent Owner's Objections). Petitioner objects to a single slide (slide 55) of Patent Owner's demonstratives (Paper 78). Paper 83, 1. Patent Owner objects to over thirty slides in Petitioner's demonstratives (slides 15, 50, 54–56, 76–78,

87, 89, 90, 99–104, 108–111, 116, 120–122, 126, 128, 129, and 135–137) (Exhibit 1320). Paper 83, 2–10.

Petitioner objects to Patent Owner's slide 55 on the basis that it allegedly includes citation to "new evidence" that is not "introduced into the record" and "new argument" about the same. Paper 84, 1. Patent Owner's objections generally relate to whether Petitioner is raising new argument or citing new evidence that was not discussed in Petitioner's papers. *See, e.g.*, Paper 83, 2–3 (objecting to Petitioner's slide 55 concerning an alleged use of a portion of Dr. Moon's Reply Declaration as "improper use of expert testimony for improper new argument").

We have considered the parties' objections, but they are overruled. Demonstratives are not evidence. Paper 76, 3–4. Demonstratives are also not a vehicle for the parties to advance untimely new argument or new evidence for which no argument is developed in the record. *Id.* In any event, this Decision is not based on the demonstratives.

V. MOTIONS TO SEAL

Patent Owner and Petitioner have each filed motions to seal. Papers 42, 71, 78 (Patent Owner's Motions to Seal); Paper 58 (Petitioner's Motion to Seal).

Patent Owner moves to seal Exhibits 2141, 2146, and 2147 (Investigator Brochures), 2143 (Pre-Investigational New Drug Meeting Request), 2194–2196 (Biologics License Application excerpts), and portions of the Declarations of Drs. Fuller (Ex. 2199) and Krause (Ex. 2200), insofar as those declarations contain excerpts or detailed descriptions of the aforementioned exhibits (e.g., Exs. 2141, 2146, and 2147). Paper 42, 1–5.

Patent Owner also moves to seal portions of Exhibit 2256 (Pierce transcript) and portions of Patent Owner's Sur-Reply (Paper 72). Paper 71, 1–4. Lastly, Patent Owner moves to seal portions of Patent Owner's demonstratives (Paper 78). None of Patent Owner's motions is opposed. Paper 78, 1–3.

Petitioner moves to seal Exhibits 1105, 1159, 1161, and 1164, and portions of Petitioner's Reply (Paper 58) that rely on those exhibits. Paper 58, 1–2. Petitioner's motion is unopposed.

The Board recognizes "a strong public policy for making all information filed in a quasi-judicial administrative proceeding open to the public, especially in an inter partes review which determines the patentability of claims in an issued patent and therefore affects the rights of the public." *Garmin Int'l v. Cuozzo Speed Techs., LLC*, IPR2012-00001, Paper 34 (PTAB Mar. 14, 2013), 1–2. Except as otherwise ordered by the Board, the record of an *inter partes* review shall be made available to the public. 35 U.S.C. § 316(a)(1); 37 C.F.R. § 42.14.

The moving party bears the burden of showing that the relief requested should be granted. 37 C.F.R. § 42.20(c). The standard for granting a motion to seal is "for good cause." 37 C.F.R. § 42.54(a).

Patent Owner contends that good cause exists to seal the exhibits, paper, and demonstratives that are the subjects of its three motions. *See generally* Papers 42, 71, 78. Patent Owner contends, for example, that Exhibits 2141, 2146, and 2147 are confidential "Moderna Investigator Brochures regarding Moderna mRNA vaccine candidates" that have been marked as confidential in this proceeding and a related district court

proceeding, that those documents are part of regulatory submissions containing proprietary research data, and that the Board has already sealed other exhibits (e.g., Exs. 2050–2052) containing excerpts of same confidential information appearing in the longer documents. *See, e.g.*, Paper 42, 2. Patent Owner contends that its Sur-Reply contains excerpts and detailed discussions of those same exhibits. *See, e.g.*, Paper 71, 2–3. And, Patent Owner contends that certain of its demonstratives contain excerpts of documents that are sealed (Ex. 2050) or for which motions to seal remain pending. *See, e.g.*, Paper 78, 2.

Having considered the unopposed argument in Patent Owner's motions, Patent Owner has shown good cause to seal the materials in question. The exhibits appear to include Patent Owner's research data and information related to some of its vaccine products that Patent Owner maintains is highly confidential and, in which, Patent Owner represents it has an interest in keeping private at this time. We observe further that Patent Owner has filed redacted versions of the exhibits and papers for which it seeks only partial sealing (e.g., Ex. 2257 (redacted Pierce transcript); Ex. 2201 (redacted Fuller declaration); Paper 73 (redacted Sur-Reply)). Exhibits 2141, 2143, 2146, 2147, 2194–2196, 2199, 2200, 2256, and Papers 72 and 78 are, therefore, sealed.

Petitioner's motion to seal is also granted. Petitioner establishes good cause to seal portions of Exhibits 1105, 1159, 1161, and 1164, as well portions of Petitioner's Reply, for the same reasons explained above on Patent Owner's motion. Paper 58, 1–2. Petitioner has also provided

redacted and publicly-available versions of the exhibits and Reply in question. *See, e.g.*, Paper 60 (Reply (redacted)).

Insofar as this Final Written Decision may include portions of the record that are presently sealed, the parties are instructed to meet and confer concerning whether any portions of this Decision should be redacted before it is made available to the public. If any party maintains that redactions to the Final Written Decision should be made, they will, within seven (7) days of entry, submit a proposed redacted and publicly-available version of the Final Written Decision along with a motion to seal explaining why the redactions are necessary and outweigh any public interest in the redacted information. Any opposition to such motion must be filed within ten (10) days after the motion is filed. In resolving any such motion, we remind the parties that the Board has a strong policy favoring a record that is open and understandable for the public. Accordingly, as it concerns the Final Written Decision, it is unlikely that the Board will allow redactions unless they are specific, minimal, and supported by a persuasive justification from the movant. If no motion is filed within the timeline set forth above or if the parties otherwise inform the Board (via email to trials@uspto.gov) that no redactions are necessary, the Final Written Decision will be made available to the public in unredacted form.

VI. CONCLUSION

Petitioner has shown by a preponderance of the evidence that the challenged claims are unpatentable as summarized below.

Claims	35 U.S.C. §	Reference(s)/Basis	Claims Shown Unpatentable	Claims Not shown Unpatentable
1, 2, 4–6, 8–12, 16, 17, 20, 21, 26	102(a)	Schrum[59]		
1, 2, 4–6, 8–12, 16, 17, 20, 21, 26	103	Schrum, Geall	1, 2, 4–6, 8–12, 16, 17, 20, 21, 26	
1, 2, 4–6, 8–12, 16, 17, 20, 21, 26	103	Schrum, Yang	1, 2, 4–6, 8–12, 16, 17, 20, 21, 26	
1, 2, 4–6, 8–12, 16, 17, 20, 21, 26	103	Schrum, Altmeyer[60]		
Overall Outcome			1, 2, 4–6, 8–12, 16, 17, 20, 21, 26	

[59] Because all challenged claims are determined to be unpatentable based on other asserted grounds, we decline to further address this additional ground.
[60] Because all challenged claims are determined to be unpatentable based on other asserted grounds, we decline to further address this additional ground.

VII. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner has proved by a preponderance of the evidence that claims 1, 2, 4–6, 8–12, 16, 17, 20, 21, and 26 are unpatentable;

FURTHER ORDERED that the Parties' Motions to Seal (Papers 41, 58, 71, and 78) are *granted* as provided above (Section V);

FURTHER ORDERED that, within seven (7) days of this Final Written Decision, the parties will meet and confer regarding any redactions to Final Written Decision and, as appropriate, file a motion to seal as provided above (Section V); and

FURTHER ORDERED that, because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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