UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BIONTECH SE and PFIZER INC.
Petitioner

v.

MODERNATX, INC.
Patent Owner

U.S. Patent No. 10,933,127

PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 10,933,127

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I. INTRODUCTION

This *inter partes* review is about Patent Owner's attempt to coopt an entire field of mRNA technology. As the Board is no doubt aware, Petitioner BioNTech designed a vaccine against SARS-CoV-2, a virus which did not exist before 2019, and partnered with Petitioner Pfizer to bring the vaccine (Comirnaty®) to patients. Patent Owner obtained the patent at issue, during the pandemic, with unimaginably broad claims directed to a basic idea that was known long before the asserted priority date of 2015 – the use of mRNAs encoding any spike protein or spike protein subunit of any betacoronavirus, formulated in a broadly claimed lipid delivery system, to induce an immune response.

Scientists first demonstrated in 1990 that injecting mRNA encoding for a protein caused expression of that protein *in vivo*. (Ex. 1013 at 1465-66.) This discovery opened a world of possible medical applications, including using mRNA for vaccination to protect against disease. (*Id.* at 1468.) Within three years, scientists demonstrated that an mRNA vaccine encoding a protein as the "antigen" (a portion of a foreign pathogen, such as a protein on a virus) delivered via a lipid carrier (a delivery system of a combination of lipids that protects the mRNA payload during circulation in the body) induced a protective immune response *in vivo*. (Ex. 1014.)

Following the 1993 publication of using antigen-encoding mRNA, scientists in the field worked to optimize mRNA vaccines. Before 2015, the work led to mRNA vaccines that improved upon the 1993 iteration with respect to the (1) mRNA (including using naturally occurring uridine modifications, untranslated regions, and caps/tails); (2) encoded antigen used to induce an immune response; and (3) lipid-based carrier. The combination of these features claimed in the '127 patent had been disclosed in scientific and patent publications by 2015.

The challenged patent claims priority to nine provisional applications that Patent Owner filed in 2015, without data, directed to these same basic ideas. (*E.g.*, Ex. 1037, 1038.) In October 2016, Patent Owner filed a non-provisional application containing two examples of betacoronavirus (specifically, MERS-CoV) mRNA vaccines tested in mice and rabbits: PCT/US2016/058327. The mRNA structure of the specific vaccines was not disclosed. After numerous continuations, Patent Owner eventually obtained, in March 2021, the subject of this petition, U.S. Patent No. 10,933,127 ("the '127 patent").

The '127 patent has, by Patent Owner's own arguments, unimaginably broad claims reciting administering an mRNA vaccine encoding any spike protein or spike protein subunit of any betacoronavirus (whether in existence or arising at any later point in time), formulated in a lipid delivery system, to induce an immune response.

Its broad claims encompass subject matter disclosed in the art before October 22, 2015, the earliest date to which the '127 patent claims priority.

Petitioner therefore requests that this Petition be granted and that the challenged claims be found unpatentable and canceled.

II. MANDATORY NOTICES

Real Parties-in-Interest: Pursuant to 37 C.F.R. § 42.8(b)(1), Petitioner identifies the following as real parties-in-interest: BioNTech SE, BioNTech US Inc., BioNTech Manufacturing GmbH, and Pfizer Inc.

Related Matters: The '127 patent is asserted in the following civil action: *ModernaTX, Inc., et al. v. Pfizer Inc., BioNTech SE, et al.*, 1:22-cv-11378-RGS (D. Mass.).

The '127 patent issued in March 2021 from Application No. 16/880,829 ("the '829 application"). The '829 application was filed as a continuation of Application No. 16/805,587, which issued in 2020 as U.S. Patent No. 10,702,600 ("the '600 patent"). The '600 patent is the subject of a separate *inter partes* review petition concurrently filed by Petitioner.

Counsel and Service Information: Lead counsel is Naveen Modi (Reg. No. 46,224). Backup counsel are (1) Bruce Wexler (Reg. No. 35,409), (2) Eric Dittmann (Reg. No. 51,188), (3) David Krinsky (Reg. No. 72,339), (4) Stanley Fisher (Reg. No. 55,820), (5) Chetan Bansal (Reg. No. 81,590), (6) Rebecca Hilgar

(*pro hac vice* to be filed), and (7) Ryan Meuth (*pro hac vice* to be filed). Service information is Paul Hastings LLP, 2050 M Street NW, Washington, D.C. 20036, Tel.: 202.551.1700, Fax: 202.551.1705, email: BioNTech-Moderna-IPR@paulhastings.com and COVIDPatentPfizer@wc.com. Petitioner consents to electronic service.

III. PAYMENT OF FEES

The PTO is authorized to charge any fees due during this proceeding to Deposit Account No. 50-2613.

IV. STANDING

Petitioner certifies under 37 C.F.R. § 42.104(a) that the '127 patent is available for review and that Petitioner is not barred or estopped from requesting review on the grounds identified herein.

V. RELIEF REQUESTED AND GROUNDS RAISED

Petitioner respectfully requests review of claims 1-3, 6-9, 11-13, 17-18, and 20 of the '127 patent and cancellation of these claims as unpatentable based on the following grounds:

Ground 1: Claims 1-3, 6-9, 11-13, 17-18, and 20 are unpatentable under 35 U.S.C. § 102 as anticipated by US 2013/026640 ("Schrum") (Ex. 1009).

Ground 2: Claims 1-3, 6-9, 11-13, 17-18, and 20 are unpatentable under 35 U.S.C. § 103 as obvious based on Schrum in view of WO 2012/006369 ("Geall") (Ex. 1010).

Ground 3: Claims 1-3, 6-9, 11-13, 17-18, and 20 are unpatentable under 35 U.S.C. § 103 as obvious based on Schrum in view of Yang et. al., *A DNA Vaccine Induces SARS Coronavirus Neutralization and Protective Immunity in Mice*, 428 NATURE 561 (2004) ("Yang") (Ex. 1011).

Ground 4: Claims 1-3, 6-9, 11-13, 17-18, and 20 are unpatentable under 35 U.S.C. § 103 as obvious based on Schrum in view of WO 2005/118813 ("Altmeyer") (Ex. 1012).

VI. BACKGROUND

A. Technology Overview

1. Use of Vaccines to Induce an Immune Response

Vaccines are pharmaceutical compositions administered to stimulate (or "induce") the body's immune response against diseases. (Ex. 1002, ¶¶32-41.) Vaccines rely upon introduction of an "antigen," a portion of a disease-causing agent ("pathogen"). In the context of viruses, the antigen may be a single protein. Vaccine administration mobilizes the body's cells, which identify and neutralize the antigen, generating protective antibodies and T cells to fight infection. Upon subsequent

exposure to the live virus, the body recognizes the antigen and is able to fight infection more efficiently. (*Id.*, ¶36.)

Antigen selection can determine the protection achieved by vaccination. Certain portions of pathogens represent better targets for vaccine development. (*Id.*, ¶44.) Therefore, vaccine development is guided by scientific knowledge regarding the antigen that will induce the strongest immune response. (*Id.*)

Regarding betacoronaviruses,[1] the subject of the '127 patent claims, the "spike protein" was well-established as the most promising antigen for vaccine development long before October 2015. (*Id.*, ¶¶45-47; Ex. 1031 at 227.) Betacoronaviruses comprise four structural proteins: the spike, envelope, nucleocapsid, and membrane proteins. (Ex. 1002, ¶¶28-31; Ex. 1029 at 811-12.) By 2009, scientists recognized that the spike protein had "pivotal roles in viral infection and pathogenesis," including facilitating virus binding to cells and virus entry via "fusion between the viral envelope and the host cell membrane." (Ex. 1031 at 227.) "Because the S [*i.e.*, 'spike'] protein of SARS-CoV is involved in . . . virus

[1] Betacoronaviruses are a type of positive-sense, single-stranded RNA virus, which, as of October 2015, included, *inter alia*, SARS-CoV and MERS-CoV. (Ex. 1029 at 807; Ex. 1030 at 995.)

attachment and entry, it represents one of the most important targets for the development of SARS vaccines and therapeutics." (*Id.*; *see also id.* at 229.)

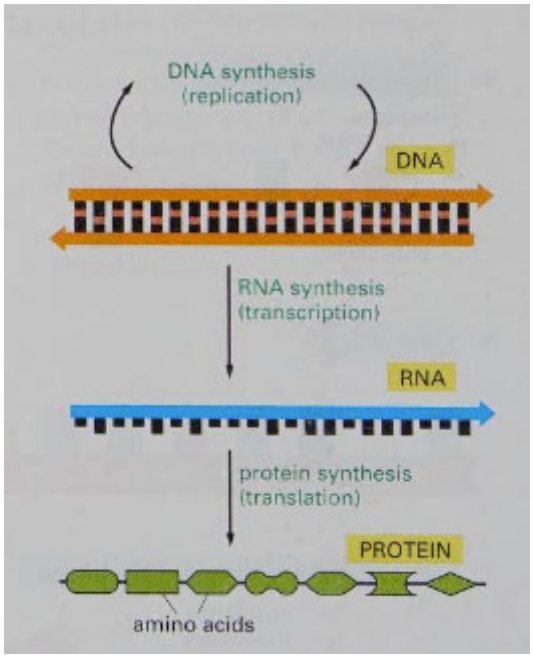
2. Nucleic Acid Vaccines

A traditional vaccine contains an antigen itself, such as a weakened or inactivated part of a virus. (Ex. 1002, ¶36.) But scientific advances pre-dating the claimed priority date of the '127 patent enabled a new vaccine modality: nucleic acid vaccines, such as mRNA and DNA vaccines, which *encode* the antigen.

Nucleic acid vaccines rely on the body's own cellular pathways to produce the encoded antigen (*e.g.*, a viral protein). (*Id.*, ¶¶37-41.) The immune system responds to this newly created antigen, training for subsequent pathogen exposure. Advantages of nucleic acid vaccines over "traditional" vaccines are well-documented, including: (1) improved safety by avoiding administration of live virus(es); (2) strong efficacy by "priming both [antibody ('B cell')] and T cell responses"; and (3) a focused immune response to the encoded antigen. (Ex. 1016 at 152.)

DNA and mRNA vaccines involve related cellular pathways. (Ex. 1002, ¶¶38-39.) DNA is "transcribed" into mRNA, which is then "translated" into the encoded protein:

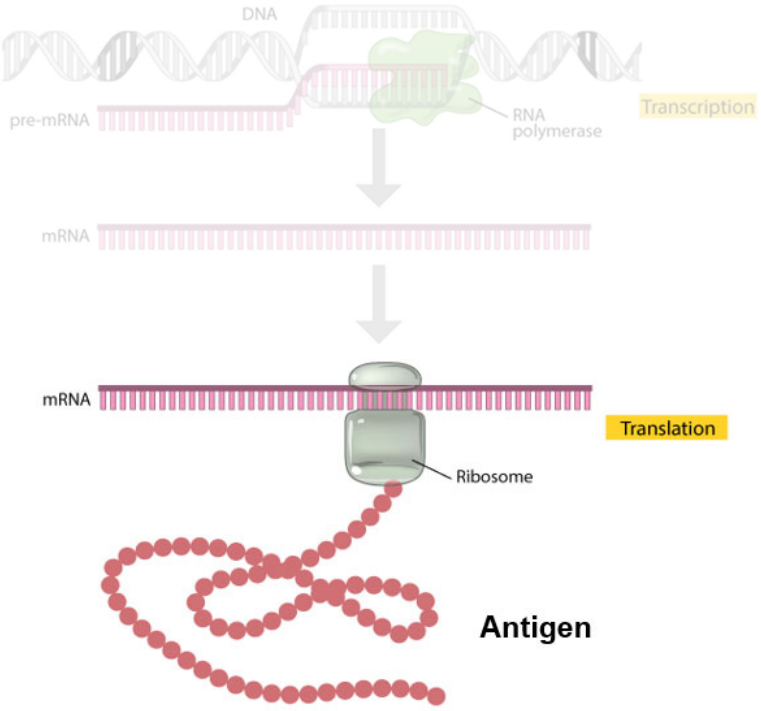
Flow of Genetic Information for Protein Synthesis



(Ex. 1043 at 6.) mRNA carries genetic information from the cell nucleus into the cytoplasm. (Ex. 1002, ¶¶21-27, 38.) There, mRNA binds to the ribosome, which converts the mRNA into proteins through translation.

For DNA vaccines, administered DNA enters the nucleus where the antigen-encoding DNA is transcribed (or converted) into mRNA encoding the same antigen. (*See* Ex. 1017 at Fig. 1.) The transcribed mRNA is translated into the antigen, which induces a protective immune response. (Ex. 1002, ¶38.)

mRNA vaccines rely on a more efficient pathway to achieve antigen synthesis. mRNA vaccines bypass the transcription step required of DNA vaccines and are directly translated into the encoded antigen:



(Ex. 1002, ¶¶21-27; Ex. 1018.)

3. Evolution of mRNA Therapeutics, Including mRNA Vaccines

After mRNA was first administered to induce protein production *in vivo* in 1990, "the concept of using mRNA as a basis for vaccines was pursued almost immediately." (Ex. 1019 at 1324.) Just three years later, scientists demonstrated that mRNA vaccines induced a protective immune response *in vivo*. (Ex. 1014.)

Despite early recognition of its utility and potential, widespread mRNA vaccine development slowed through the early 2000s. Delivering foreign ("exogenous") mRNA often activated too strong an "innate immune response"—a problem for vaccine development because it could destroy mRNA before achieving

sufficient antigen translation.[2] (Ex. 1002, ¶¶42-43; Ex. 1021 at 165.) In that timeframe, there was instead significant attention to DNA vaccines.

Thinking with respect to mRNA changed in 2005, thanks to innovation by Drs. Katalin Karikó and Drew Weissman—then at the University of Pennsylvania.[3] They published the first of their landmark papers that renewed focus on mRNA therapeutics. (*See* Ex. 1021.) Drs. Karikó and Weissman demonstrated that incorporating modified forms of the nucleoside uridine, found in nature, into exogenous mRNA reduced activation of the innate immune response and increased protein production. (*See id.* at 165; Ex. 1022 at 1833.)[4]

Patent Owner's co-founder characterized their discovery as "fundamental to th[e] entire field" of mRNA-based medicine and likely to "earn [Drs. Karikó and Weissman] a Nobel Prize because it really is what allows these mRNA vaccines and

[2] As Dr. Griffin explains, the "innate immune response" differs from the body's "adaptive immune response," which vaccines engage. (Ex. 1002, ¶¶32-35.)

[3] Dr. Karikó was later employed by Petitioner BioNTech SE from 2013-2022.

[4] In 2006, Drs. Karikó and Weissman filed a patent application disclosing and claiming uridine-modified mRNA, including 1-methylpseudouridine-modified mRNA, which has since been licensed by Patent Owner. (*See* Ex. 1023 at claim 1; Ex. 1026, § 3.)

any mRNA therapeutics down the road." (Ex. 1024; *see* Ex. 1025.)

Following Drs. Karikó and Weissman's publications, and before the priority date of the '127 patent, mRNA vaccines were recognized as more promising than DNA vaccines. (*See* Ex. 1020 at Abstract ("Recent advances strongly suggest that mRNA rather than DNA will be the nucleotide basis for a new class of vaccines and drugs."); *see also* Ex. 1019 at 1319; Ex. 1028 at 948; Ex. 1016 at 153.)

4. Formulation of mRNA Therapeutics in Lipid Carriers

Well before 2015, lipid-based formulations, specifically lipid nanoparticles, had emerged as the principal formulation vehicle for delivery of mRNA. (Ex. 1032 at 231; Ex. 1004, ¶¶19-34.) To be effective, mRNA must get into cells, but exogenous mRNA is vulnerable to degradation before being taken up by cells and translated. (*See* Ex. 1019 at 1322.) It was therefore "crucial to develop delivery systems that protect mRNAs *in vivo* from degradation and help internalization in [the cells]." (Ex. 1032 at 221.) Lipid nanoparticles met that need as "the most clinically advanced drug delivery system[]." (Ex. 1062 at 1:8-9, 34:3-5 (*inter alia* disclosing using lipid nanoparticles for mRNA delivery).)

Before 2015, using certain lipid components in lipid nanoparticle formulations had been well-established. (Ex. 1004, ¶¶33-44.) Lipid nanoparticles were known to be made up of (1) a cationic lipid, (2) a phospholipid, (3) a PEG-lipid,

and (4) a sterol. (*Id.*)[5] Each component serves a purpose. For example, the cationic lipid facilitates encapsulation of nucleic acids and can aid in cellular uptake of the lipid nanoparticle; the phospholipid can further contribute to encapsulation efficiency of the lipid nanoparticle; cholesterol aids in stability of the lipid nanoparticle; and the PEG-lipid helps to stabilize and control the size of the lipid nanoparticle, increase storage stability, and prolong systemic circulation. (*See* Ex. 1004, ¶¶35-44.)

B. '127 Patent Overview

The '127 patent issued on March 2, 2021, from the '829 application, filed May 21, 2020. The '127 patent claims priority to nine U.S. provisional applications, four filed on October 28, 2015 and five filed on October 22, 2015.

[5] Patent Owner represented to the Board that these lipid components "were known to be basic building blocks" of lipid nanoparticles by 2008. (Ex. 1072 at 7) ("[U.S. Patent No. 8,058,069, claiming priority to April 2008,] discloses four lipid components: a cationic lipid, two non-cationic lipids (a phospholipid and cholesterol), and a conjugated lipid (e.g., a polyethylene glycol ("PEG") lipid). These lipid components were known to be basic building blocks of nucleic acid-lipid particles long before the '069 patent.").)

The ’127 patent claims a combination of disclosed technologies. Claim 1 is directed to a method comprising three broad features: (1) administration of an mRNA composition (*i.e.*, an mRNA vaccine) to induce an immune response; (2) using a betacoronavirus spike protein or subunit thereof as an antigen (*i.e.*, including known targets for a vaccine); and (3) formulation of the mRNA in lipid particles made of four know lipid components according to broad lipid ranges. (Ex. 1002, ¶¶14-19; Ex. 1004, ¶¶45-47.)

The claims that depend from claim 1 recite various attributes that add nothing to patentability—*i.e.*, that the mRNA vaccine induces an antibody response (claim 3), is administered intramuscularly (claim 6), includes known structural components (claims 7-9), and/or uridine modifications previously disclosed in the art (claims 11-13). The second independent claim (claim 17) and the claims that depend therefrom (claims 18 and 20) recite the same features. (Ex. 1001 at 741:11-742:44.)

VII. LEVEL OF ORDINARY SKILL

With respect to the ’127 patent, a POSA would include 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. (Ex. 1002, ¶11.)

Patent Owner advanced the following definition of a POSA in litigation: a POSA with respect to the '127 patent would have had an M.D. and/or a 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.

The challenged claims are unpatentable under either definition. (Ex. 1002, ¶¶11-13, 229; Ex. 1004, ¶18.)

VIII. OVERVIEW OF THE PRIOR ART

A. Schrum

Patent Owner filed US 2013/0266640 ("Schrum"), titled "Modified Nucleoside, Nucleotide, and Nucleic Acid Compositions" on June 14, 2013, published on October 10, 2013. Schrum is prior art under 35 U.S.C. §§ 102(a)(1)

and 102(a)(2).[6] During prosecution, Schrum was included only in an information disclosure statement with more than three hundred other documents.

Schrum provides "formulation compositions comprising modified nucleic acid molecules which may encode a protein. . . . [that] further include a modified nucleic acid molecule and a delivery agent." (Ex. 1009, ¶4; Ex. 1002, ¶¶51-57; Ex. 1004, ¶¶50-53.) The nucleic acids were "modified mRNA." (Ex. 1009, ¶53.) Schrum discloses administering mRNA formulated in lipid nanoparticles comprising a (1) cationic lipid, (2) neutral lipid (phospholipid), (3) cholesterol, and (4) PEG-lipid. (*E.g.*, *id.*, ¶¶8, 35, 38, 995-999.)

Schrum discloses using mRNA as a vaccine to induce an immune response. Under the heading, "Activation of the Immune Response: Vaccines," Schrum states that "[i]n one embodiment of the present invention, mRNA molecules may be used to elicit or provoke an immune response in an organism. The mRNA molecules to be delivered may encode an immunogenic peptide or polypeptide." (Ex. 1009, ¶340;

[6] After Schrum published in 2013, and had been deemed abandoned on August 12, 2015, Patent Owner then began filing the multiplicity of provisional applications leading, years later, to the '127 patent. (Ex. 1039.)

see also id., ¶397.) The mRNA in such a vaccine "may be delivered to a vertebrate in a dose amount large enough to be immunogenic." (*Id.*, ¶342.)

In its discussion of suitable immunogens (*i.e.*, antigen[7]) and amount of such immunogen-encoding mRNA to be delivered, Schrum "incorporates by reference in [its] entirety" Geall (Ex. 1010), which discloses that the immunogen in an RNA vaccine may be the spike protein of SARS-CoV. (*See* Ex. 1009, ¶342; Ex. 1010 at 19:26-29, 15:35-16:7.) Geall is discussed further below.

Schrum discloses various well-known (and naturally occurring) structural mRNA components, such as: a poly-A tail (*e.g.*, Ex. 1009, ¶¶89-95), a 5′ cap analog (*id.*, ¶80), and 5′ and 3′ untranslated regions ("UTR's") (*e.g.*, *id.*, ¶¶61-64.) Schrum also discloses that the "modified mRNA" may comprise chemical nucleoside modifications, including 1-methylpseudouridine. (*See id.*, ¶¶25, 58.)

B. Geall

Geall, titled "Immunisation of Large Mammals with Low Doses of RNA," was filed on July 6, 2011 by Novartis AG (claiming priority to July 2010), and published on January 12, 2012. Geall is prior art under 35 U.S.C. § 102(a)(1). Like Schrum, Geall was listed only on an information disclosure statement among hundreds of references.

[7] The terms "antigen" and "immunogen" may be used interchangeably.

Geall discloses using RNA vaccines encoding the spike protein of a betacoronavirus, SARS-CoV. (*See* Ex. 1002, ¶¶58-59.) It "provides a method of raising an immune response in a large mammal, comprising administering to the mammal a dose of between 2 μg and 100 μg of immunogen-encoding RNA." (Ex. 1010 at Abstract.) Geall instructs that the "immunogen will typically be a surface polypeptide, *e.g.* . . . a spike glycoprotein" (*id.* at 16:6-7), and discloses that "[v]iral immunogens include, but are not limited to, those derived from a SARS coronavirus . . . The coronavirus immunogen may be a spike polypeptide" (*id.* at 19:26-30.).

Geall confirms that lipid-based delivery vehicles are preferred for RNA administration "to enhance both entry to immune and non-immune cells." (Ex. 1010 at 3:25-26; Ex. 1004, ¶¶54-57.) Specifically, "[l]iposomes[8] are a preferred delivery system." (Ex. 1010 at 3:30-31.) Geall discloses that the lipid delivery system comprises a cationic lipid, neutral lipid (*i.e.*, neutral phospholipid), cholesterol, and PEG. (Ex. 1010 at 31:4-6.)

[8] Geall's reference to lipid particles of nanometer size, matching the components and molar ratios discussed in the '127 patent, are lipid nanoparticles, as explained by Dr. Moon. (Ex. 1004, ¶¶22, 95-98.)

C. Yang

Titled "A DNA vaccine induces SARS coronavirus neutralization and protective immunity in mice," Yang was published in the journal *Nature* on April 1, 2004. Yang is prior art under 35 U.S.C. § 102(a)(1). Yang was not before the Examiner.

In Yang, the authors analyzed DNA vaccines encoding the SARS-CoV spike protein "for their ability to elicit antiviral immunity" and to "elicit a neutralizing antibody response." (Ex. 1011 at 562-63.) Administration of the DNA vaccine elicited a strong immune response, as Yang reported "induc[ing] cellular and humoral immunity to the SARS-CoV S glycoprotein." (Ex. 1011 at 563; *see also id.* at 561 ("Here we show that a DNA vaccine encoding the spike (S) glycoprotein of the SARS-CoV induces T cell and neutralizing antibody responses, as well as protective immunity, in a mouse model.").) Testing showed that "[v]iral replication was reduced by more than six orders of magnitude in the lungs of mice vaccinated with these S plasmid DNA expression vectors." (*Id.*; *see* Ex. 1002, ¶¶60-63.)

D. Altmeyer

WO2005/118813 is a patent application published on December 15, 2005. Altmeyer is prior art under 35 U.S.C. § 102(a)(1). Altmeyer was not before the Examiner.

Titled "Nucleic Acids, Polypeptides, Methods of Expression, and Immunogenic Compositions Associated with SARS Corona Virus Spike Protein," Altmeyer "provides a method of RNA and/or DNA vaccination" against SARS-CoV that "includes administering any combination of the nucleic acids encoding Spike polypeptides." (Ex. 1012, ¶97.) Such methods "allow[] the administration of nucleic acids encoding [s]pike polypeptides, naked or encapsulated, directly to tissues and cells without the need for production of encoded proteins prior to administration." (*Id.*, ¶98) Altmeyer demonstrates that RNA vaccines, encoding the spike protein of SARS-CoV induced "induce[d] high titer anti-SARS antibodies in mice." (*Id.*, ¶116; Ex. 1002, ¶¶64-66.)

IX. CLAIM CONSTRUCTION

Petitioner adopts, for purposes of this petition only, the following claim constructions advanced by Patent Owner and adopted by the district court in parallel litigation (Ex. 1035):

- **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."[9]

The Board need not construe any other claim terms, as the claims are unpatentable under any reasonable construction. *Toyota Motor Corp. v. Cellport Systems, Inc.*, IPR2015-00633, Paper No. 11 at 16 (P.T.A.B. Aug. 14, 2015).

X. DETAILED EXPLANATION OF GROUNDS

Each challenged claim is unpatentable. In Schrum, Patent Owner disclosed the same standard mRNA and lipid nanoparticle components later claimed in the '127 patent. Schrum also discloses, including through its incorporation of Geall, encoding the spike (S) protein of a betacoronavirus, SARS-CoV, in an mRNA vaccine to induce an immune response thereto (Ground 1). But, even if Schrum did not incorporate Geall, numerous other references, such as Geall, Yang, and Altmeyer, identified the S protein of a betacoronavirus, SARS-CoV, as a key antigen to be encoded in nucleic acid vaccines, including mRNA vaccines (Grounds 2, 3, and 4, respectively). Accordingly, the challenged claims of the '127 patent are unpatentable as both anticipated by and obvious in view of the prior art.

[9] Petitioner and Patent Owner agreed to this construction during litigation.

A. Ground 1: Schrum Anticipates Claims 1-3, 6-9, 11-13, 17-18, and 20 of the '127 Patent

1. Claim 1

i) [1.pre] "A method comprising administering to a subject"

Schrum discloses this limitation. (Ex. 1002, ¶¶67-68.) Schrum discloses delivering nucleic acids encoding a protein by contacting the "mammalian cell or tissue with a formulation comprising a modified mRNA encoding a polypeptide of interest." (Ex. 1009, ¶¶3-5, claim 1.) The "formulation" includes a "delivery agent." (*Id*., ¶¶4-5, 22.) Schrum discloses administering such an mRNA formulation "to elicit or provoke an immune response in an organism," such as a mammal (an exemplary "subject," Ex. 1001 at 67:65-68:3). (Ex. 1009, ¶¶340, 342, 355.)

ii) [1.a] "a messenger ribonucleic acid (mRNA)"

Schrum discloses this limitation. (Ex. 1002, ¶69.) It provides "formulation compositions comprising modified nucleic acid molecules which may encode a protein," which include "mRNA molecules [that] may be used to elicit or provoke an immune response in an organism." (Ex. 1009, ¶¶4, 340, claim 1.)

iii) [1.b] "comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit"

Schrum discloses this limitation. (Ex. 1002, ¶¶70-73.) Schrum discloses that "the modified nucleic acid molecules and/or mmRNA of the invention may encode an immunogen . . .[, which] may be delivered to a vertebrate in a dose amount large

enough to be immunogenic to the vertebrate (see WO2012006472 and WO2012006369 [Geall]; each of which is herein incorporated by reference in their entirety)." (*Id.*, ¶342.) Schrum incorporates these references for their teaching of disclosed immunogens and dose amounts necessary to achieve an immunogenic effect—*i.e.*, to induce an immune response to the encoded immunogen.

One reference incorporated "in [its] entirety," Geall ("WO2012006369"), describes RNA vaccines against various viral illnesses, including SARS-CoV. (Ex. 1010 at 18:11, 19:26-29.) Geall discloses that the immunogen in the case of SARS-CoV is a "spike polypeptide," *i.e.*, an S protein. (*Id.* at 19:26-29.) Because SARS-CoV is a "betacoronavirus" (Ex. 1002, ¶¶49, 111), Schrum discloses that the encoded immunogen of the disclosed RNA vaccine is a betacoronavirus spike polypeptide (*i.e.*, a BetaCov S protein, as claimed). *See Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000); *Paice LLC v. Ford Motor Co.*, 881 F.3d 895, 906-07 (Fed. Cir. 2018).[10] Indeed, Schrum later recognizes that

[10] As Patent Owner successfully argued before the Board in connection with patents covering mRNA-related technology, the disclosures of incorporated references "are 'effectively part of the host document as if it were explicitly contained therein.'" *Moderna Therapeutics, Inc. v. Protiva Biotherapeutics, Inc.*, IPR2018-00680, Paper

"the modified nucleic acid molecules and mmRNA may encode all or a part of a positive-sense or a negative-sense stranded RNA virus genome." (Ex. 1009, ¶349.)

Encoding a BetaCoV S protein, as Schrum discloses, necessarily involves an open reading frame of the mRNA encoding for such protein. The open reading frame is the part of the mRNA encoding the protein produced. (Ex. 1002, ¶¶26, 72.) As the POSA would have appreciated, an mRNA encoding a betacoronavirus spike protein necessarily contains a start codon, followed by the coding sequence for the betacoronavirus spike protein, followed by a stop codon, constituting an open reading frame encoding for the same. (*Id.*)

Any argument from Patent Owner that Schrum's incorporated disclosure of the SARS-CoV spike protein as an encoded antigen is not anticipatory because it lists the spike protein among other potential antigens is legally insufficient. The Federal Circuit has long since "reject[ed] the notion that one of [a number of alternatives] cannot anticipate because it appears without special emphasis in a longer list." *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1376 (Fed. Cir. 2005). Equally, "anticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabling

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26 at 17 (quoting *Advanced Display*, 212 F.3d at 1282), *aff'd*, 65 F.4th 656 (Fed. Cir. 2023).

to one of skill in the art." *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1379 (Fed. Cir. 2001); *see also Arbutus Biopharma Corp. v. ModernaTX, Inc.*, 65 F.4th 656, 662 (Fed. Cir. 2023). This is indisputably the case here.

iv) [1.c] "formulated in a lipid nanoparticle"

Schrum discloses this limitation. (Ex. 1004, ¶¶58, 62-66; Ex. 1002, ¶¶74-75.) Schrum discloses that "the formulation comprising the modified mRNA is a nanoparticle which may comprise at least one lipid." (Ex. 1009, ¶6.) Schrum provides that formulations of the invention may include "a modified nucleic acid molecule and a delivery agent," wherein "the delivery agent comprises at least one method to improve delivery selected from the group consisting of . . . lipid nanoparticles."[11] (Ex. 1009 at Abstract, ¶34.) Such "lipid nanoparticles may be used to improve the efficacy of modified nucleic acid molecules or mmRNA [modified mRNA] directed protein production." (*Id*., ¶406.) Schrum expressly contemplates using mRNA encoding an immunogen encapsulated in a lipid nanoparticle "for use in a vaccine such as . . . against a pathogen." (*Id.*, ¶397.) And, Schrum reports successfully administering modified mRNA encapsulated in a lipid nanoparticle. (*E.g.*, *id*., ¶¶995-1000, 1002-20, 1022-36, 1046-51.)

[11] Schrum discloses that the lipid nanoparticles are "nanosized." (Ex. 1004, ¶65; Ex. 1009, ¶7, 405, 995-99, 1028.)

v) [1.d] "in an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit,"

Schrum discloses this limitation. (Ex. 1002, ¶¶76-78.) With respect to the vaccine discussed in Section X.A.1.iii, Schrum discloses that the "mRNA molecules to be delivered may encode an immunogenic peptide or polypeptide" and "may be used to elicit or provoke an immune response in an organism." (Ex. 1009, ¶340.) A POSA would have understood that disclosure of mRNA used to elicit an immune response to the encoded immunogen (here, the BetaCov S protein), refers to administering mRNA in an effective amount to induce such an immune response. (Ex. 1002, ¶77.)[12]

Moreover, Schrum expressly discloses delivering an effective amount of the mRNA composition, teaching that the immunogen-encoding mRNA "may be delivered to the vertebrate in *a dose large enough to be immunogenic* to the vertebrate," *i.e.*, an effective amount. (Ex. 1009, ¶342 (emphasis added).) Furthermore, Schrum expressly incorporates Geall, which teaches dosages for the immunogen-encoding RNA that are immunogenic. (*Id.*, at 1:24-4:8.)

[12] The '127 patent claims do not require administration of specific amounts of mRNA or quantified levels of immune response induction.

vi) [1.e] "wherein the lipid nanoparticle comprises 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid."

Schrum discloses this limitation. (Ex. 1004, ¶¶68-76; Ex. 1002, ¶¶79-81.) Schrum discloses a "lipid nanoparticle" as the delivery agent for the mRNA vaccines disclosed therein. (*Supra*, Section X.A.1.iv.) Schrum further provides that the lipid nanoparticles have molar lipid ratios directly within the ranges recited for the four lipid components in this limitation. Specifically, Schrum discloses that "the lipid nanoparticle composition may comprise 50 mol % cationic lipid, 10 mol % DSPC, 1.5-3.0 mol % PEG and 37-38.5 mol. % cholesterol." (Ex. 1009, ¶38.) Example 16 in Schrum describes the lipid nanoparticles used in *in vivo* studies, and explains that "[t]he LNPs were formulated at a 20:1 weight ratio of total lipid to modified mRNA with a final lipid molar ratio of 50:10:38.5:1.5 (***DLin-KC2-DMA:DSPC:Cholesterol:PEG-c-DOMG***)." (*Id*. at ¶995) (emphases added). These are the same specific lipids and molar ratios that the '127 patent discloses and claims, foreclosing any attempt by Patent Owner to argue that subtle differences in wording somehow distinguish between the lipid categories disclosed in Schrum and those claimed in the '127 patent. (Ex. 1004, ¶¶70-73.)

DSPC is disclosed and claimed in the '127 patent as "neutral." (*See* Ex. 1001 at 73:26-27, claim 16 (742:20-21.) Similarly, Schrum refers to "PEG" lipids and provides that "the PEG lipid is PEG-DMG." (Ex. 1009, ¶¶16, 37, claim 13.) PEG-

DMG is a "PEG-modified lipid" per the '127 patent specification and claims. (Ex. 1001 at 75:3-4, claim 16.) Finally, Schrum discloses that "the cationic lipid may be . . . DLin-MC3-DMA . . . and DLin-KC2-DMA" (Ex. 1009, ¶¶34, 395), which are the same lipids identified in the '127 patent as exemplary "ionizable" cationic[13] lipids. (Ex. 1001 at 72:62-66 ("Lipid nanoparticle formulations typically comprise a lipid, in particular, an ionizable cationic lipid, for example . . . (DLin-KC2-DMA) . . . [and] (DLin-MC3-DMA)".)

Indeed, Schrum discloses precisely the same lipid formulations as the '127 patent. The '127 patent states, "[i]n some embodiments, the molar lipid ratio is 50/10/38.5/1.5 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG, PEG-DSG or PEG-DPG." (Ex. 1001 at 74:51-62.) Schrum discloses the same, providing that "the formulation may have a molar ratio of 50:10:38.5:1.5-3.0 (cationic lipid:fusogenic lipid:cholesterol:PEG-lipid). The PEG lipid may be selected from, but is not limited to PEG-c-DOMG, PEG-DMG. The fusogenic lipid may be DSPC." (Ex. 1009, ¶8.) While Schrum uses the word "fusogenic" rather than "neutral" for the standard phospholipid component, Schrum

[13] Schrum provides that the "cationic lipid" can be an ionizable cationic lipid, such as, DLinDMA, DLin-KC2-DMA, or DLin-MC30DMA. (*E.g.*, Ex. 1009, ¶¶6, 37, 47, 385, 395.)

explains that "the fusogenic lipid is disteroylphophatidyl choline (DSPC)," which is a neutral lipid. (Ex. 1009, ¶37.)

Schrum further claims mRNA-encapsulating lipid nanoparticles with molar ratios falling within the ranges claimed in the '127 patent: 50% (within 20-60 mol %) cationic lipid, 10% neutral lipid (within 5-25 mol %), 38.5% (within 25-55 mol %) cholesterol, and 1.5-3% (within 0.5-15 mol %) PEG-modified lipid. (*Id.*, ¶8, claims 1, 3, 11-12.) As the Federal Circuit held in affirming Patent Owner's own challenge to patent claims directed to lipid nanoparticles with nearly identical lipid components, "[w]hen a patent claims a chemical composition in terms of ranges and a single prior art discloses a composition that falls within each of the ranges, the range is anticipated." *Arbutus Biopharma Corp. v. ModernaTX, Inc.*, 65 F.4th 656, 666 (Fed. Cir. 2023).

* * *

Schrum discloses combining the components of claim 1, as arranged in the claim. Schrum discloses that "the modified nucleic acid molecules and/or mmRNA of the invention may encode an immunogen," incorporating the disclosure of mRNA encoding a specific immunogen—the SARS-CoV spike protein. (Ex. 1009, ¶342.) Schrum further instructs that "the modified nucleic acid molecules or the mmRNA may be encapsulated into a lipid nanoparticle." (*Id.*, ¶409; Ex. 1004, ¶¶62-66, 68-76.) This is more than sufficient to be anticipatory. *Blue Calypso, LLC v. Groupon,*

Inc., 815 F.3d 1331, 1344 (Fed. Cir. 2016) (anticipation found where reference "teaches that the disclosed components or functionalities may be combined and one of skill in the art would be able to implement the combination"). A POSA would readily envisage delivering the mRNA vaccines of Schrum—including those encoding the betacoronavirus S protein—using the disclosed lipid nanoparticles. (Ex. 1009, ¶¶342, 378, 397 ("the lipid nanoparticle may be formulated for use in a vaccine."); *see Blue Calypso*, 815 F.3d at 1344.)

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

Schrum discloses this limitation. (Ex. 1002, ¶82.) As discussed in Section X.A.1.iii, Schrum describes administering mRNA comprising an open reading frame encoding a betacoronavirus spike protein.

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

Schrum discloses this limitation. (Ex. 1002, ¶¶83-87.) As discussed in Section X.A.1.v, Schrum describes administering mRNA comprising an open reading frame encoding a betacoronavirus spike protein to induce an immune response. Schrum incorporates Geall's teaching that "RNA delivery according to the invention is for eliciting an immune response *in vivo* against an immunogen of interest. The immune response is preferably protective and preferably involves antibodies and/or cell-mediated immunity." (Ex. 1009, ¶342 (incorporating Geall);

Ex. 1010 at 24:15-17.) Specifically, it "may comprise an antibody response (usually including IgG) and/or a cell-mediated immune response." (Ex. 1010 at 14:33-15:3 As a result, "the mammal can be protected against . . . [*e.g.*,] viral diseases." (Ex. 1010 at 24:15-17.)

Well before 2015, a POSA would have recognized that an antibody response included "neutralizing" antibodies specific to the immunogen that was administered. (Ex. 1002, ¶86; Ex. 1011 at 561 ("a DNA vaccine encoding the spike (S) glycoprotein of the SARS-CoV induces T cell and neutralizing antibody responses . . . ."); Ex. 1031 at 227.).) A POSA would recognize that Geall's disclosure—incorporated by Schrum—involves a neutralizing antibody response specific to the BetaCoV S protein. (Ex. 1002, ¶¶85-87.)

Additionally, Schrum incorporates Geall's disclosure of using RNA vaccines to induce a neutralizing antibody response. Administration of a RNA vaccine encoding the full-length fusion protein of RSV—like the spike protein of a betacoronavirus, responsible for viral fusion and cell entry—resulted in induction of neutralizing antibodies. (Ex. 1010 at Fig. 9, 34:11-18; *see* Ex. 1002, ¶86; Ex. 1081 at 2.)

Moreover, claim 3 is merely directed to the body's reaction to the mRNA vaccine of claims 1 and 2, which is an intended effect or result entitled to no patentable weight. *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1296 (Fed. Cir.

2013) ("a newly-discovered *result or property* of an existing (or obvious) *method of use* is not patentable") (emphasis in original). Regardless, a POSA would have understood that the body's response to the BetaCov S protein includes a neutralizing antibody response.

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

Schrum discloses this limitation. (Ex. 1002, ¶88.) Schrum discloses that "[t]he mammalian cells or tissues may be contacted by a route of administration such as, but not limited to . . . ***intramuscular***" administration and exemplifies intramuscular administration of modified mRNA encapsulated in lipid nanoparticles. (Ex. 1009, ¶¶13, 995-99, claim 25; *see also id.*, ¶535.)

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

Schrum discloses this limitation. (Ex. 1002, ¶89.) Schrum discloses a formulation including (1) a modified mRNA, (2) encoding a polypeptide of interest, and (3) a delivery agent. (Ex. 1009, ¶¶4-5, claim 1.) Describing the mRNA, Schrum discloses that untranslated regions (UTRs) "can be incorporated into the modified mRNA molecules of the present invention to enhance the stability of the molecules." (*Id.*, ¶61.) Schrum describes 5′ UTRs and 3′ UTRs (*id.*, ¶¶62-66) and teaches that the modified mRNA molecule can include both a 5′ and 3′ untranslated region.

(Ex. 1009, ¶309 ("a 5′ untranslated region (UTR) and/or a 3′ UTR are provided.").[14]) Schrum exemplifies administration of modified mRNA comprising a 5′ untranslated region and a 3′ untranslated region. (*Id*., ¶¶995-99.) The optional inclusion of both a 5′ and 3′ UTR sequence discloses the inclusion of both elements. *See Upsher-Smith Labs., Inc. v. Pamlab L.L.C.*, 412 F.3d 1319, 1322 (Fed. Cir. 2005).

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

Schrum discloses this limitation. (Ex. 1002, ¶90.) As discussed in Section X.A.5, Schrum describes the structure of the modified mRNA molecule including various parts thereof. In addition to UTRs, Schrum discloses that the modified mRNA molecule includes a "(poly-A tail) [that] may be added to a modified nucleic acid molecule . . . in order to increase stability." (Ex. 1009, ¶89.)[15]) Schrum exemplifies administration of modified mRNA comprising a polyA tail. (*Id*., ¶¶995-99.)

[14] The '127 patent admits that a 5′ UTR and a 3′ UTR are "basic components of an mRNA molecule." (Ex. 1001, 41:65-66.)

[15] The '127 patent admits that a poly(A) tail is a "basic component[] of an mRNA molecule." (Ex. 1001, 41:65-66.)

7. Claim 9: "The method of claim 1, wherein the mRNA further comprises a 5′ cap analog."

Schrum discloses this limitation. (Ex. 1002, ¶91.) As discussed in Sections X.A.5 and X.A.6, Schrum describes the structure of the modified mRNA molecule including various parts. Schrum explains that "the nucleic acid molecule, [*i.e.*, mRNA] may comprise at least one 5′ terminal cap." (Ex. 1009, ¶29, claim 42.) "According to the present invention, 5′ terminal caps may include endogenous caps or cap analogs." (*Id.*, ¶86.) Exemplary disclosed 5′ cap analog "structures include, but are not limited to, 7mG(5′)ppp(5′)N,pN2p(cap 0), 7mG(5′) ppp(5′)NlmpNp (cap 1)." (*Id.*, ¶84.) Delivery of modified mRNA comprising "cap 1" is exemplified in, *e.g.*, Example 16 (*Id.*, ¶¶995-999), while "cap 0" is the cap analog disclosed and claimed in the '127 patent. (Ex. 1001 at 11:47-48, claim 10.)[16]

8. Claim 11: "The method of claim 1, wherein the mRNA comprises a chemical modification."

Schrum discloses this limitation. (Ex. 1002, ¶92.) Schrum discloses a formulation including (1) a ***modified*** mRNA (2) encoding a polypeptide of interest and (3) a delivery agent for delivering the mRNA to the mammalian cell. (Ex. 1009, ¶¶4-5, 22, claim 1.) Schrum explains that "modified mRNA" "contain[s] one or

[16] The '127 patent admits that a 5′ cap is a "basic component[] of an mRNA molecule." (Ex. 1001, 41:65-66.)

more modified nucleosides or nucleotides." (*Id.*, ¶53.) Schrum further discloses that the "modified nucleic acid molecules may be chemically modified." (*Id.*, ¶57.) The chemical modification "may include a compound selected from the group consisting of . . . 1-methyl-pseudouridine." (*Id.*, ¶26; *see also id.,* claim 45.) Schrum contains numerous examples demonstrating successful delivery of mRNA comprising a chemical modification to express a protein. (*E.g.*, *id.*, ¶¶995-99.)

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

Schrum discloses this limitation. (Ex. 1002, ¶93.) Schrum identifies 1-methylpseudouridine as a chemical modification included in the disclosed mRNA compositions. (Ex. 1009, ¶26.) Schrum's examples demonstrate protein production in mice using mRNA compositions in which all uracil residues have been replaced with a 1-methylpseudouridine modification. (*See, e.g.*, *id.*, ¶¶1065-80, ¶¶1186-98, ¶¶1300-02, ¶¶1306-1308, ¶¶1319-20, ¶¶1323-26.)

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

Schrum discloses this limitation. (Ex. 1002, ¶94.) Schrum discloses that, in the disclosed mRNA compositions, "at least 80%, at least 90%, or 100% of the uracil in the nucleic acid may be replaced with a modified uracil." (Ex. 1009, ¶326; *see also id.*, ¶300.) Schrum discusses mRNA sequences "fully modified" at each

cytosine and uridine replacement site, *i.e.*, chemically modifying 100% of the uracils in the mRNA sequence, including the open reading frame. (Ex. 1009, ¶936; *see, e.g.*, *id.*, ¶¶940, 942. 963, 979, 981, 989, 995, 1178.) Schrum asserts that full (*i.e.*, "100% modification") results in increased protein expression. (*See id.*, ¶1183-85.)

11. Claim 17

Schrum discloses every limitation of claim 17, as arranged in the claim, for the reasons discussed below and in Section X.A.1.

i) [17.pre] "A method comprising administering to a subject"

Schrum discloses this limitation, as discussed in Section X.A.1.i. (Ex. 1002, ¶95.)

ii) [17.a] "an mRNA"

Schrum discloses this limitation, as discussed in Section X.A.1.ii. (Ex. 1002, ¶96.)

iii) [17.b] "comprising a 5′ cap analog,"

Schrum discloses this limitation, as discussed in Section X.A.7. (Ex. 1002, ¶97.)

iv) [17.c] "a 5′ untranslated region,"

Schrum discloses this limitation, as discussed in Section X.A.5. (Ex. 1002, ¶98.)

v) [17.d] "an open reading frame encoding a BetaCoV S protein or S protein subunit,"

Schrum discloses this limitation, as discussed in Section X.A.1.iii. (Ex. 1002, ¶99.)

vi) [17.e] "a 3′ untranslated region,"

Schrum discloses this limitation, as discussed in Section X.A.5. (Ex. 1002, ¶100.)

vii) [17.f] "and a poly(A) tail"

Schrum discloses this limitation, as discussed in Section X.A.6. (Ex. 1002, ¶101.)

viii) [17.g] "formulated in a lipid nanoparticle"

Schrum discloses this limitation, as discussed in Section X.A.1.iv. (Ex. 1004, ¶84; Ex. 1002, ¶102.)

ix) [17.h] "in an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit,"

Schrum discloses this limitation, as discussed in Section X.A.1.v. (Ex. 1002, ¶103.)

x) [17.i] "wherein the lipid nanoparticle comprises 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid."

Schrum discloses this limitation, as discussed in Section X.A.1.vi. (Ex. 1004, ¶86; Ex. 1002, ¶104.)

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

Schrum discloses this limitation, as discussed in Section X.A.1.iii. (Ex. 1002, ¶105.)

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

Schrum discloses this limitation. (Ex. 1002, ¶106.) As discussed, Schrum discloses that, in the disclosed mRNA compositions, "at least 80%, at least 90%, or 100% of the uracil in the nucleic acid may be replaced with a modified uracil." (Ex. 1009, ¶326; see also id., ¶300.) Additionally, Schrum's examples disclose protein production in mice using mRNA compositions in which all uracil residues, *i.e.*, 100% of the uracil in the mRNA sequence, have been replaced with a 1-methylpseudouridine modification. (*See e.g., id*., ¶¶1065-80 (Example 32), ¶¶1186-98 (Examples 58-60), ¶¶1300-02 (Example 87-88), ¶¶1306-1308 (Example 90-91), ¶¶1319-20 (Example 92), ¶¶1323-26 (Examples 94-95).) (Ex. 1002, ¶¶91-93, 105.)

B. Ground 2: Schrum in View of Geall Renders Claims 1-3, 6-9, 11-13, 17-18, and 20 Obvious

1. Claim 1

i) [1.pre] "A method comprising administering to a subject"

Schrum discloses this limitation, as discussed in Section X.A.1.i. (Ex. 1002, ¶¶107-08.)

ii) [1.a] "a messenger ribonucleic acid (mRNA)"

Schrum discloses this limitation, as discussed in Section X.A.1.ii. (Ex. 1002, ¶109.)

iii) [1.b] "comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit"

Schrum discloses this limitation, as discussed in Section X.A.1.iii. Any argument that Schrum does not incorporate Geall's disclosure is legally incorrect. But even if accepted, Schrum in view of Geall discloses or suggests the limitation. (Ex. 1002, ¶¶110-13.)

Schrum discloses modified mRNA molecules encoding an immunogen used "to elicit or provoke an immune response in an organism." (Ex. 1009, ¶340.) Schrum provides that "the modified nucleic acid molecules and/or mmRNA of the invention may encode an immunogen . . .[, which] may be delivered to a vertebrate in a dose amount large enough to be immunogenic to the vertebrate." (*Id.*, ¶342.)

Geall teaches using RNA encoding a betacoronavirus spike protein to induce an immune response thereto. It "provides a method of raising an immune response in a large mammal, comprising administering to the mammal a dose of between 2 μg and 100[μg] of immunogen-encoding RNA." (Ex. 1010 at Abstract.) Geall discloses that "[v]iral immunogens" to be encoded include "those derived from a SARS coronavirus," which is a betacoronavirus. (*Id.* at 19:27-30; Ex. 1002, ¶72.)

And, the "coronavirus immunogen" is taught to be a "spike polypeptide," or "spike protein" as claimed in the '127 patent. (*Id.*) Because Geall discloses an RNA encoding a coronavirus S protein, Geall discloses "an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit," as claimed. (Ex. 1002, ¶111.) The knowledge that the SARS-CoV spike protein had "been selected as an important target for vaccine and anti-viral development" (Ex. 1031 at 227) and successfully used as the encoded antigen in a DNA vaccine provided good reason to incorporate the same as the encoded immunogen in Schrum. (Ex. 1002, ¶112.)

iv) [1.c] "formulated in a lipid nanoparticle"

Schrum discloses this limitation, as discussed in X.A.1.iv. Additionally, Geall discloses this limitation, providing an identical lipid nanoparticle formulation to that disclosed and claimed in the '127 patent. (Ex. 1004, ¶¶95-98.; Ex. 1002, ¶¶114-15.)

v) [1.d] "in an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit,"

Schrum discloses this limitation, as discussed in Section X.A.1.v. Additionally, Schrum in view of Geall discloses or suggests the limitation. (Ex. 1002, ¶¶116-18.)

Schrum states that the "mRNA molecules to be delivered may encode an immunogenic peptide or polypeptide" "in a dose amount large enough to be immunogenic." (Ex. 1009, ¶340-42.)

Geall teaches using RNA to induce an immune response to the encoded immunogen. "RNA delivery according to [Geall's] invention is for eliciting an immune response *in vivo* against an immunogen of interest. The immune response is preferably protective and preferably involves antibodies and/or cell-mediated immunity." (Ex. 1010 at 24:15-19; *see also id.* at 15:33-16:3.)

Geall discloses administration of RNA encoding the SARS-CoV spike to induce an immune response thereto. "Viral immunogens" that may be encoded by the disclosed RNA vaccine include those "derived from a SARS coronavirus." (*Id.* at 19:27.) In such case, the "coronavirus immunogen may be a spike polypeptide." (*Id.* at 19:29-30.) Accordingly, "[d]elivery according to the invention" of the SARS-CoV-encoding RNA "elicit[s] an immune response *in vivo* against [the] immunogen of interest": the SARS-CoV spike protein. (Ex. 1010 at 24:15-19.)

vi) [1.e] "wherein the lipid nanoparticle comprises 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid."

Schrum discloses this limitation, as discussed in Section X.A.1.vi. (Ex. 1002, ¶¶119-20.) Additionally, Geall discloses this limitation, providing an identical lipid nanoparticle formulation to that disclosed and claimed in the '127 patent. (Ex. 1004, ¶¶95-98.)

* * *

It would have been obvious for a POSA to combine the teachings of Schrum and Geall to arrive at the method of claim 1. Schrum discloses using an mRNA vaccine—having identical mRNA and lipid nanoparticle components to that claimed in the '127 patent—encoding an immunogen to induce an immune response thereto. Geall discloses the immunogenic use of an RNA vaccine encoding the S protein of SARS-CoV, which was known to be the most promising antigen for development of a SARS-CoV vaccine. As discussed above, the immunogen (SARS-CoV S protein) would be encoded by the ORF of the mRNA. (*Supra* Section X.A.1.iii.) Combining these known elements to achieve a method of claim 1 involves only a "combination of familiar elements" to "yield predictable results," and would have been obvious to a POSA. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 401 (2007).

A POSA would have had good reason to combine Schrum's disclosure of an mRNA vaccine encoding an "immunogenic peptide or polypeptide"—*i.e.*, "mmRNA encoding an immunogen"—with Geall's disclosure of an RNA vaccine encoding the SARS-CoV spike protein. (Ex. 1009, ¶¶340, 342.) Schrum identifies and incorporates Geall, providing a motivation to combine the references (to the extent Patent Owner asserts Geall is not actually incorporated). In addition, the two references are in the same field of endeavor. (Ex. 1002, ¶¶121-23.) A POSA would have recognized that nucleic acid vaccines encoding the spike protein of SARS-CoV "induc[e] T cell and neutralizing antibody responses, as well as protective

immunity" *in vivo*. (Ex. 1011, Yang at 861.) These known results would have been consistent with a POSA's knowledge that "S protein is the main antigenic component that is responsible for inducing host immune responses, neutralizing antibodies and/or protective immunity against virus infection. S protein has therefore been selected as an important target for vaccine and anti-viral development." (Ex. 1031 at 229.)

A POSA would have reasonably expected success in combining the disclosures of Schrum and Geall to arrive at the method of claim 1.

First, a POSA would have reasonably expected success in making an mRNA composition encoding a SARS-CoV S protein following well-known methods. (Ex. 1002, ¶124.) Schrum discloses that "[t]he modified nucleic acid and mmRNA molecules for use in accordance with the invention may be prepared according to any useful technique" and that "[m]ethods of synthesizing RNA are known in the art." (Ex. 1009, ¶¶291, 320.) Schrum provides examples of the administration of protein-encoding mRNA formulated in lipid nanoparticles to express the encoded protein. (*E.g.*, *id.*, ¶942, 963, 995-1001)

Second, a POSA would have reasonably expected success in inducing an immune response to the SARS-CoV spike protein using such a vaccine. (Ex. 1002, ¶¶125-26.) A POSA would have known that nucleic acid vaccines encoding a betacoronavirus spike protein vaccine induced both "T cell and neutralizing antibody

responses, as well as protective immunity, in a mouse model." (Ex. 1011 at 561.) Administration of such vaccines achieved a "$>10^6$-fold reduction in viral load in the lungs compared with a control group" and a "60- to 300-fold reduction of virus titre in the nasal turbinates." (*Id.* at 562.) Those results were consistent with the knowledge of a POSA that the SARS-CoV S protein "represents one of the most important targets for the development of SARS vaccines and therapeutics." (Ex. 1031 at 227.)

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

Schrum in view of Geall discloses or suggests this limitation, as discussed in Section X.A.1.iii. (Ex. 1002, ¶127.)

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

Schrum in view of Geall discloses or suggests this limitation. (Ex. 1002, ¶¶128-31.) Geall discloses that "RNA delivery according to the invention is for eliciting an immune response *in vivo* against an immunogen of interest. The immune response is preferably protective and preferably involves antibodies and/or cell-mediated immunity." (Ex. 1010 at 24:15-17.) A POSA would have recognized that Geall's teaching that the induced immune response may comprise "an antibody response (usually including IgG) and/or a cell-mediated immune response" necessarily encompasses a neutralizing antibody response specific to the BetaCoV

S protein. A POSA understood an antibody response to include "neutralizing antibodies" specific to the immunogen that was administered. (Ex. 1002, ¶¶83-87; (Ex. 1011 at 561 ("a DNA vaccine encoding the spike (S) glycoprotein of the SARS-CoV induces T cell and neutralizing antibody responses . . . ."); Ex. 1031 at 227.).)

Additionally, Geall discloses using RNA vaccines to induce a neutralizing antibody response. Administration of a RNA vaccine encoding the full-length fusion protein of RSV—which, like the spike protein of a betacoronavirus, sits on the external portion of the virus and is responsible for viral fusion and cell entry—resulted in induction of neutralizing antibodies thereto *in vivo*. (Ex. 1010 at Fig. 9, 34:11-18.)

Even if, *quod non*, Schrum in view of Geall did not disclose or suggest inducing a neutralizing antibody response, claim 3 is merely directed to the body's reaction to the mRNA vaccine of claims 1 and 2, which is an intended effect or result entitled to no patentable weight. *Allergan*, 726 F.3d at 1296.

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

Schrum discloses this limitation, as discussed in Section X.A.4. (Ex. 1002, ¶132.)

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

Schrum discloses this limitation, as discussed in Section X.A.5. (Ex. 1002, ¶133.)

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

Schrum discloses this limitation, as discussed in Section X.A.6. (Ex. 1002, ¶134.)

7. Claim 9: "The method of claim 1, wherein the mRNA further comprises a 5′ cap analog."

Schrum discloses this limitation, as discussed in Section X.A.7. (Ex. 1002, ¶135.)

8. Claim 11: "The method of claim 1, wherein the mRNA comprises a chemical modification."

Schrum discloses this limitation, as discussed in Section X.A.8. (Ex. 1002, ¶136.)

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

Schrum discloses this limitation, as discussed in Section X.A.9. (Ex. 1002, ¶137.) Should Patent Owner—erroneously—argue that Schrum is not anticipatory on account of disclosing more than one potential uracil modification, a POSA nonetheless would have reason to have included 1-methylpseudouridine as a uracil

modification in the disclosed immunogen-encoding mRNA sequence. Schrum discloses, consistent with the foundational teachings of Drs. 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. (*E.g.*, Ex. 1009, ¶¶26, 50, 1065-80, 1191-1198, 1204-10, 1222, 1266-68, 1300-1302, 1306-1309 (Examples 32, 59, 60, 63, 68, 75, 76, 87, 88, 90, 91); Ex. 1023 at 8:26-30, 26:22-29, 22:38-45.) Indeed, Schrum's examples confirm the use of mRNA including a 1-methylpseudouridine modification to promote protein expression. (*E.g.*, Ex. 1009, ¶¶26, 50, 1065-80, 1191-1198, 1204-10, 1266-68, 1300-1302, 1306-1309 (Examples 32, 59, 60, 63, 75, 76, 87, 88, 90, 91); Ex. 1023 at 8:26-30, 26:22-29, 22:38-45.) A POSA would have had reason to use mRNA including a 1-methylpseudouridine modification, and would reasonably have expected success in synthesizing such modified mRNA and using the same to express an encoded protein. (Ex. 1002, ¶136.)

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

Schrum discloses this limitation, as discussed in Section X.A.10. (Ex. 1002, ¶138.)

11. Claim 17

Schrum in view of Geall discloses every limitation of this claim for the reasons discussed below and in Section X.B.1. A POSA would have good reason to combine Schrum and Geall to arrive at the method of claim 17 with a reasonable expectation of success in doing so, as discussed in Section X.B.1.

i) [17.pre] "A method comprising administering to a subject"

Schrum discloses this limitation, as discussed in Section X.A.1.i. (Ex. 1002, ¶139.)

ii) [17.a] "an mRNA"

Schrum discloses this limitation, as discussed in Section X.A.1.ii. (Ex. 1002, ¶140.)

iii) [17.b] "comprising a 5′ cap analog,"

Schrum discloses this limitation for the reasons described in Section X.A.7. (Ex. 1002, ¶141.)

iv) [17.c] "a 5′ untranslated region,"

Schrum discloses this limitation for the reasons described in Section X.A.5. (Ex. 1002, ¶142.)

v) [17.d] "an open reading frame encoding a BetaCoV S protein or S protein subunit,"

Schrum, including in view of Geall, discloses or suggests this limitation, as discussed in Section X.B.1.iii. (Ex. 1002, ¶143.)

vi) [17.e] "a 3′ untranslated region,"

Schrum discloses this limitation, as discussed in Section X.A.5. (Ex. 1002, ¶144.)

vii) [17.f] "and a poly(A) tail"

Schrum discloses this limitation, as discussed in Section X.A.6. (Ex. 1002, ¶145.)

viii) [17.g] "formulated in a lipid nanoparticle"

Schrum discloses this limitation, as discussed in Section X.A.1.iv. Additionally, Geall discloses this limitation. (Ex. 1004, ¶¶91-93, 107; Ex. 1002, ¶146.)

ix) [17.h] "in an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit,"

Schrum, including in view of Geall, discloses or suggests this limitation, as discussed in Section X.B.1.v. (Ex. 1002, ¶147.)

x) [17.i] "wherein the lipid nanoparticle comprises 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid."

Schrum discloses this limitation, as discussed in Section X.A.1.vi. Additionally, Geall discloses this limitation. (Ex. 1004, ¶¶95-98, 110; Ex. 1002, ¶148.)

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

Schrum, including in view of Geall, discloses or suggests this limitation, as discussed in Section X.B.1.iii. (Ex. 1002, ¶149.)

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

Schrum discloses this limitation, as discussed in Section X.A.13. (Ex. 1002, ¶¶106, 150.) As discussed in Section X.B.9, a POSA would have good reason to use mRNA including a 1-methylpseudouridine modification and would reasonably expect success in expressing an encoded protein using such mRNA. A POSA would further have good reason to use mRNA with 100% of the uracils replaced with 1-methylpseudouridine, as Schrum asserts that full (*i.e.*, "100% modification") results in increased protein expression (s*ee id.*, ¶1183-85) and demonstrates the use of such fully modified mRNA to express a protein. (*E.g.*, *id.* ¶¶1266-68, 1300-1302 (Examples 75, 76, 87, 88); Ex. 1002, ¶¶137, 150.)

C. Ground 3: Schrum in View of Yang Renders Claims 1-3, 6-9, 11-13, 17-18, and 20 Obvious

1. Claim 1

i) [1.pre] "A method comprising administering to a subject"

Schrum discloses this limitation, as discussed in Section X.A.1.i. (Ex. 1002, ¶¶151-52.)

ii) [1.a] "a messenger ribonucleic acid (mRNA)"

Schrum discloses this limitation, as discussed in Section X.A.1.ii. (Ex. 1002, ¶153.)

iii) [1.b] "comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit"

Schrum discloses this limitation, as discussed in Section X.A.1.iii. As yet another exemplary teaching, Schrum in view of Yang discloses or suggests this limitation. (Ex. 1002, ¶¶154-55.)

Schrum discloses modified mRNA molecules encoding an immunogen. Schrum discusses using "mRNA molecules . . . to elicit or provoke an immune response in an organism." (Ex. 1009, ¶340.) Schrum provides that "the modified nucleic acid molecules and/or mmRNA of the invention may encode an immunogen . . .[, which] may be delivered to a vertebrate in a dose amount large enough to be immunogenic to the vertebrate. (*Id.*, ¶342.)

Yang discloses that a "DNA vaccine encoding the spike (S) glycoprotein of the SARS-CoV induces T cell and neutralizing antibody responses, as well as protective immunity." (Ex. 1011 at 561.) Administration of the SARS-CoV spike protein-encoding nucleic acid vaccine reduced viral replication "by more than six orders of magnitude in the lungs of mice vaccinated" with the nucleic acid vaccine. (*Id.*) In addition, "a 60- to 300-fold reduction of virus titre in the nasal turbinates

was also observed" upon delivery of the SARS-CoV spike protein-encoding DNA vaccine described in Yang. (*Id.* at 562.) The results obtained in Yang provided good reason for a POSA to incorporate the SARS-CoV spike protein as the encoded immunogen in the mRNA vaccine of Schrum. (Ex. 1002, ¶157.)

iv) [1.c] "formulated in a lipid nanoparticle"

Schrum discloses this limitation, as discussed in Section X.A.1.iv. (Ex. 1004, ¶115; Ex. 1002, ¶158.)

v) [1.d] "in an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit,"

Schrum discloses this limitation, as discussed in Section X.A.1.v. As yet another exemplary teaching, Schrum in view of Yang discloses or suggests this limitation. (Ex. 1002, ¶¶159-61.)

Schrum states that the "mRNA molecules to be delivered may encode an immunogenic peptide or polypeptide" "in a dose amount large enough to be immunogenic." (Ex. 1009, ¶340-42.)

Yang, meanwhile, discloses a "DNA vaccine encoding the spike (S) glycoprotein of the SARS-CoV[, which] induces T cell and neutralizing antibody responses, as well as protective immunity." (Ex. 1011 at 561.) Administration of the SARS-CoV spike protein-encoding nucleic acid vaccine reduced viral

replication "by more than six orders of magnitude in the lungs of mice vaccinated" with the nucleic acid vaccine. (*Id.*)

vi) [1.e] "wherein the lipid nanoparticle comprises 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid."

Schrum discloses this limitation, as discussed in Section X.A.1.vi. (Ex. 1004, ¶117; Ex. 1002, ¶162.)

* * *

It would have been obvious for a POSA to combine the teachings of Schrum and Yang to arrive at the method of claim 1. Schrum discloses using an mRNA vaccine—having identical mRNA and lipid nanoparticle components to that claimed in the '127 patent—encoding an immunogen to induce an immune response thereto. Yang discloses the immunogenic use of a nucleic acid vaccine encoding the S protein of SARS-CoV, which was known to be the most promising antigen for development of a SARS-CoV vaccine. As discussed above, the immunogen (SARS-CoV S protein) would be encoded by the ORF of the mRNA. (*Supra* Section X.A.1.iii.) Combining these known elements to achieve the method of claim 1 involves only a

"combination of familiar elements" to "yield predictable results," and would have been obvious to a POSA.[17] *KSR*, 550 U.S. at 401.

A POSA would have had good reason to combine Schrum's disclosure of an mRNA vaccine encoding an "immunogenic peptide or polypeptide"—*i.e.*, "mmRNA encoding an immunogen"—with Yang's disclosure of a nucleic acid vaccine encoding the spike protein of SARS-CoV. (Ex. 1009, ¶342; Ex. 1002, ¶¶163-64.) Both references are in the same field of endeavor, and a POSA would have good reason to apply the choice of antigen in the DNA vaccine of Yang—the SARS-CoV spike protein—to the mRNA vaccine construct disclosed in Schrum.[18]

[17] The '127 patent does not disclose or claim a clinically effective mRNA vaccine—*i.e.*, an mRNA vaccine shown to be effective in humans. In fact, the patent includes animal data, just as disclosed in Yang, and claims priority to applications with no data. Accordingly, Patent Owner cannot argue that animal data would be insufficient to render obvious the broad scope of the '127 patent claims.

[18] Patent Owner correctly represented the applicability of DNA-based disclosures to the mRNA context to the Board. *See, e.g.*, *ModernaTX, Inc. v. CureVac AG*, IPR2017-02194, Paper 44 at 22:17-21 (Patent Owner stating in the context of nucleic acid purification, "And what the references we've cited, the numerous references

It was known well before 2015 that mRNA vaccines encoding a viral antigen could be used to induce an immune response. Such mRNA vaccines were known to have significant advantages over DNA vaccines, including better safety profiles and increased antigen production. (*Id.*; *see e.g.*, Ex. 1020 at 10.)

A POSA would have reasonably expected success in combining the disclosures of Schrum and Yang to arrive at the method of claim 1. First, a POSA would have reasonably expected success in making an mRNA vaccine encoding the SARS-CoV S protein following well-known methods in the art, as discussed above. (*E.g.*, Ex. 1009, ¶¶291, 320, 995-99; Ex. 1002, ¶165.) Second, a POSA would have reasonably expected success in inducing an immune response to the SARS-CoV spike protein using such a vaccine. Yang demonstrates that a nucleic acid vaccine encoding a betacoronavirus spike protein induced "T cell and neutralizing antibody responses, as well as protective immunity, in a mouse model." (Ex. 1011 at 561.) In fact, the disclosed nucleic acid vaccine achieved a "$>10^6$-fold reduction in viral

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we've cited show, the expectations of a person of ordinary skill in the art, they expected these methods that were developed for DNA to also work for RNA, and in numerous instances, they demonstrated that the methods developed for DNA also worked for RNA.")

load in the lungs compared with a control group" and a "60- to 300-fold reduction of virus titre in the nasal turbinates." (*Id.* at 562.)

A POSA would have additionally understood that the betacoronavirus-encoding DNA in the efficacious vaccine of Yang was necessarily transcribed into mRNA encoding the SARS-CoV S protein upon administration of the DNA vaccine, before subsequent translation of the mRNA into the spike protein antigen. (*See* Ex. 1002, ¶166.) A POSA would therefore reasonably have expected that direct administration of mRNA encoding the SARS-CoV spike protein would result in production of the spike protein antigen, which proved in Yang to induce a strong immune response.

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

Schrum in view of Yang discloses or suggests this limitation, as discussed in Section X.C.1.iii. (Ex. 1002, ¶167.)

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

Schrum in view of Yang discloses or suggests this limitation. (Ex. 1002, ¶¶168-70.) Yang teaches that a nucleic acid vaccine encoding the spike protein of SARS-CoV "induces T cell and neutralizing antibody responses." (Ex. 1011 at 561.) In fact, Yang reports that "DNA vaccination has been used to induce cellular and

humoral immunity to the SARS-CoV S glycoprotein. The humoral immune response includes the generation of neutralizing antibodies." (*Id.* at 563.)

Even if, *quod non*, Schrum in view of Yang did not disclose or suggest inducing a neutralizing antibody response, claim 3 is merely directed to the body's reaction to the mRNA vaccine of claims 1 and 2, which is an intended effect or result entitled to no patentable weight. *Allergan*, 726 F.3d at 1296.

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

Schrum discloses this limitation, as discussed in Section X.A.4. (Ex. 1002, ¶171.)

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

Schrum discloses this limitation, as discussed in Section X.A.5. (Ex. 1002, ¶172.)

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

Schrum discloses this limitation, as discussed in Section X.A.6. (Ex. 1002, ¶173.)

7. Claim 9: "The method of claim 1, wherein the mRNA further comprises a 5′ cap analog."

Schrum discloses this limitation, as discussed in Section X.A.7. (Ex. 1002, ¶174.)

8. Claim 11: "The method of claim 1, wherein the mRNA comprises a chemical modification."

Schrum discloses this limitation, as discussed in Section X.A.8. (Ex. 1002, ¶175.)

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

Schrum discloses this limitation, as discussed in Section X.A.9. A POSA would have good reason to use immunogen-encoding mRNA including this modification with a reasonable expectation of success, as discussed in Section X.B.9. (Ex. 1002, ¶176.)

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

Schrum discloses this limitation, as discussed in Section X.A.10. (Ex. 1002, ¶177.)

11. Claim 17

Schrum in view of Yang discloses every limitation of this claim for the reasons discussed below and in Section X.C.1. A POSA would have good reason to

combine Schrum and Yang to arrive at the method of claim 17 with a reasonable expectation of success in doing so, as discussed in Section X.C.1.

i) [17.pre] "A method comprising administering to a subject"

Schrum discloses this limitation, as discussed in Section X.A.1.i. (Ex. 1002, ¶178.)

ii) [17.a] "an mRNA"

Schrum discloses this limitation, as discussed in Section X.A.1.ii. (Ex. 1002, ¶179.)

iii) [17.b] "comprising a 5′ cap analog,"

Schrum discloses this limitation, as discussed in Section X.A.7. (Ex. 1002, ¶180.)

iv) [17.c] "a 5′ untranslated region,"

Schrum discloses this limitation, as discussed in Section X.A.5. (Ex. 1002, ¶181.)

v) [17.d] "an open reading frame encoding a BetaCoV S protein or S protein subunit,"

Schrum in view of Yang discloses or suggests this limitation, as discussed in Section X.C.1.iii. (Ex. 1002, ¶182.)

vi) [17.e] "a 3′ untranslated region,"

Schrum discloses this limitation, as discussed in Section X.A.5. (Ex. 1002, ¶183.)

vii) [17.f] "and a poly(A) tail"

Schrum discloses this limitation, as discussed in Section X.A.6. (Ex. 1002, ¶184.)

viii) [17.g] "formulated in a lipid nanoparticle"

Schrum discloses this limitation, as discussed in Section X.A.1.v. (Ex. 1004, ¶125; Ex. 1002, ¶185.)

ix) [17.h] "in an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit,"

Schrum in view of Yang discloses or suggests this limitation, as discussed in Section X.C.1.v. (Ex. 1002, ¶186.)

x) [17.i] "wherein the lipid nanoparticle comprises 20-60 mol % ionizable cationic lipid, 5-25 mol % neutral lipid, 25-55 mol % cholesterol, and 0.5-15 mol % PEG-modified lipid."

Schrum discloses this limitation, as discussed in Section X.A.1.vi. (Ex. 1004, ¶127; Ex. 1002, ¶187.)

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

Schrum in view of Yang discloses or suggests this limitation, as discussed in Section X.C.1.iii. (Ex. 1002, ¶188.)

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

Schrum discloses this limitation, as discussed in Section X.A.13. (Ex. 1002, ¶¶106, 189.) A POSA would have good reason to use immunogen-encoding mRNA including at least 80% of such modification with a reasonable expectation of success, as discussed in Section X.B.9 and X.B.13. (Ex. 1002, ¶¶137, 150, 189.)

D. Ground 4: Schrum in View of Altmeyer Renders Claims 1-3, 6-9, 11-13, 17-18, and 20 Obvious

1. Claim 1:

i) [1.pre][19]

Schrum discloses this limitation, as discussed in Section X.A.1.i. (Ex. 1002, ¶¶190-91.)

ii) [1.a]

Schrum discloses this limitation, as discussed in Section X.A.1.ii. (Ex. 1002, ¶192.)

iii) [1.b]

Schrum discloses this limitation, as discussed in Section X.A.1.iii. As yet another exemplary teaching, Schrum in view of Altmeyer discloses or suggests this limitation. (Ex. 1002, ¶¶193-97.)

[19] Petitioner does not repeat the claim language previously set forth in Grounds 1-3.

Schrum discloses modified mRNA molecules encoding an immunogen. Schrum discusses using "mRNA molecules . . . to elicit or provoke an immune response in an organism." (Ex. 1009, ¶340.) Schrum provides that "the modified nucleic acid molecules and/or mmRNA of the invention may encode an immunogen . . .[, which] may be delivered to a vertebrate in a dose amount large enough to be immunogenic to the vertebrate." (*Id.*, ¶342.)

Altmeyer further discloses "[n]ucleic acid molecules, polypeptides . . . and methods of making and using the nucleotides and encoded polypeptides associated with the Spike protein of SARS Corona Virus (SARS CoV)." (Ex. 1012 at Abstract.) Altmeyer provides "immunogenic compositions [*i.e.*, vaccines] . . . comprising nucleic acids encoding Spike polypeptides." (*Id.*, ¶98.) As the nucleic acids to be used, Altmeyer states that "[n]ucleic acid sequences within the scope of the invention include isolated . . . RNA sequences that hybridize to SEQ ID NOS: 2, 3 & 6 herein under conditions of moderate or severe stringency, and *which encode* Spike polypeptides." (*Id.*, ¶60 (emphasis added).) A POSA would understand Altmeyer's disclosure of "RNA sequences" encoding a SARS-CoV spike protein as encompassing messenger RNA. (Ex. 1002, ¶195-97.) The results obtained in Altmeyer provided good reason to incorporate the SARS-CoV spike protein as the encoded immunogen in the mRNA vaccine disclosed in Schrum. (Ex. 1031 at 229; Ex. 1002, ¶197.)

iv) [1.c]

Schrum discloses this limitation, as discussed in Section X.A.1.iv. (Ex. 1002, ¶132; Ex. 1002, ¶198.)

v) [1.d]

Schrum discloses this limitation, as discussed in Section X.A.1.v. As yet another exemplary teaching, Schrum in view of Altmeyer discloses or suggests this limitation. (Ex. 1002, ¶¶199-202.)

Schrum states that the "mRNA molecules to be delivered may encode an immunogenic peptide or polypeptide" "in a dose amount large enough to be immunogenic." (Ex. 1009, ¶340-42.)

Altmeyer discloses a "method of RNA and/or DNA vaccination" that "includes administering any combination of the nucleic acids encoding Spike polypeptides . . . to an individual." (Ex. 1012, ¶97.) The disclosed SARS-CoV spike protein-encoding vaccine "can be employed to stimulate a B-cell response to Spike polypeptides, as well as immunity mediated by a CTL response following viral infection."). (Ex. 1012, ¶93.) Altmeyer demonstrates that administration of RNA-encoding spike protein induced a robust immune response thereto, including "high titer anti-SARS antibodies in mice." (*Id.*, ¶116.)

vi) [1.e]

Schrum discloses this limitation, as discussed in Section X.A.1.vi. (Ex. 1002, ¶203.)

* * *

It would have been obvious for a POSA to combine the teachings of Schrum and Altmeyer to arrive at the method of claim 1. Schrum discloses using an mRNA vaccine—having identical mRNA and lipid nanoparticle components to that claimed in the '127 patent—encoding an immunogen to induce an immune response thereto. Altmeyer discloses the immunogenic use of an RNA vaccine encoding the S protein of SARS-CoV, which was known to be the most promising antigen for development of a SARS-CoV vaccine. As discussed above, the immunogen (SARS-CoV S protein) would be encoded by the ORF of the mRNA. (*Supra* Section X.A.1.iii.) Combining these known elements to achieve the method of claim 1 involves only a "combination of familiar elements" to "yield predictable results," and would have been obvious to a POSA. *KSR*, 550 U.S. at 401.

A POSA would have good reason to combine Schrum's disclosure of an mRNA vaccine encoding an "immunogenic peptide or polypeptide"—*i.e.*, "mmRNA encoding an immunogen"—with Altmeyer's disclosure of an RNA vaccine encoding the spike protein of SARS-CoV. (Ex. 1009, ¶342; Ex. 1002, ¶204.) Both references are in the same field of endeavor, and a POSA would have

good reason to apply the choice of antigen in Altmeyer—the SARS-CoV spike protein—to the mRNA vaccine construct disclosed in Schrum. Altmeyer reports that administering SARS-CoV spike protein-encoding RNA induced an immune response and resulted in the "presence of recombinant Spike-specific antibodies . . . and SARS CoV-specific antibodies." (Ex. 1012, ¶116, Figs. 6-8.) Altmeyer's findings are consistent with the knowledge in the field that nucleic acid vaccines encoding the spike protein of SARS-CoV "induc[e] T cell and neutralizing antibody responses, as well as protective immunity" *in vivo*. (Ex. 1011, Yang at 561; *see also* Ex. 1031 at 229.)

Further, a POSA would have reasonably expected success in combining the disclosures of Schrum and Altmeyer to arrive at the method of claim 1. (Ex. 1002, ¶205.) First, a POSA would have reasonably expected success in making an mRNA vaccine encoding the SARS-CoV S protein following well-known methods in the art, as discussed above. (*Id.*; *E.g.*, Ex. 1009, ¶¶291, 320, 995-99.) Second, a POSA would have reasonably expected success in inducing an immune response to the SARS-CoV spike protein using such a vaccine. Altmeyer demonstrates that a RNA vaccine-encoding the SARS-CoV spike protein induces "[s]pike-specific antibodies" and "SARS CoV-specific antibodies." (Ex. 1012, ¶116.) Those results were consistent with the immunogenic use of other nucleic acid vaccines encoding a betacoronavirus spike protein. (Ex. 1011 at 561.) Further, a POSA would have

been aware that the SARS-CoV S protein "represents one of the most important targets for the development of SARS vaccines and therapeutics." (Ex. 1031 at 227; Ex. 1002, ¶205.)

2. Claim 2

Schrum in view of Altmeyer discloses or suggests this limitation, as discussed in Section X.D.1.iii. (Ex. 1002, ¶206.)

3. Claim 3

Schrum in view of Altmeyer discloses or suggests this limitation. (Ex. 1002, ¶¶207-09.) Altmeyer discloses that the nucleic acid vaccine encoding the spike protein of SARS-CoV "induces high titer anti-SARS antibodies" in Spike-encoding RNA immunized mice. (Ex. 1012, ¶¶114-116.) Further, Altmeyer demonstrates that analyzed sera from mice immunized with the Spike protein ("TriSpike") raised both reactive antibody responses and neutralizing activity against SARS CoV infection. (*Id.*, ¶56, Figure 17.) And, Altmeyer provides that "[t]he polypeptides of the invention can also be employed to raise neutralizing antibodies that either inactivate the virus, reduce the viability of the virus in vivo, or inhibit or prevent viral replication." (*Id.*, ¶34.)

Even if, *quod non*, Schrum in view of Altmeyer did not disclose or suggest inducing a neutralizing antibody response, claim 3 is merely directed to the body's

reaction to the mRNA vaccine of claims 1 and 2, which is an intended effect or result entitled to no patentable weight. *Allergan*, 726 F.3d at 1296.

4. Claim 6

Schrum discloses this limitation, as discussed in Section X.A.4. (Ex. 1002, ¶210.)

5. Claim 7

Schrum discloses this limitation, as discussed in Section X.A.5. (Ex. 1002, ¶211.)

6. Claim 8

Schrum discloses this limitation, as discussed in Section X.A.6. (Ex. 1002, ¶212.)

7. Claim 9

Schrum discloses this limitation, as discussed in Section X.A.7. (Ex. 1002, ¶213.)

8. Claim 11

Schrum discloses this limitation, as discussed in Section X.A.8. (Ex. 1002, ¶214.)

9. Claim 12

Schrum discloses this limitation, as discussed in Section X.A.9. Schrum discloses this limitation, as discussed in Section X.A.9. A POSA would have good

reason to use immunogen-encoding mRNA including this modification with a reasonable expectation of success, as discussed in Section X.B.9. (Ex. 1002, ¶215.)

10. Claim 13

Schrum discloses this limitation, as discussed in Section X.A.10. (Ex. 1002, ¶216.)

11. Claim 17

Schrum in view of Altmeyer discloses every limitation of this claim for the reasons discussed below and in Section X.D.1. A POSA would have good reason to combine Schrum and Geall to arrive at the method of claim 17 with a reasonable expectation of success in doing so, as discussed in Section X.D.1.

i) [17.pre]

Schrum discloses this limitation, as discussed in Section X.A.1.i. (Ex. 1002, ¶217.)

ii) [17.a]

Schrum discloses this limitation, as discussed in Section X.A.1.ii. (Ex. 1002, ¶218.)

iii) [17.b]

Schrum discloses this limitation, as discussed in Section X.A.7. (Ex. 1002, ¶219.)

iv) [17.c]

Schrum discloses this limitation, as discussed in Section X.A.5. (Ex. 1002, ¶220.)

v) [17.d]

Schrum in view of Altmeyer discloses or suggests this limitation, as discussed in Section X.D.1.iii. (Ex. 1002, ¶221.)

vi) [17.e]

Schrum discloses this limitation, as discussed in Section X.A.5. (Ex. 1002, ¶222.)

vii) [17.f]

Schrum discloses this limitation, as discussed in Section X.A.6. (Ex. 1002, ¶223.)

viii) [17.g]

Schrum discloses this limitation, as discussed in Section X.A.1.iv. (Ex. 1004, ¶142; Ex. 1002, ¶224.)

ix) [17.h]

Schrum in view of Altmeyer discloses or suggests this limitation, as discussed in Section X.D.1.v. (Ex. 1002, ¶225.)

x) [17.i]

Schrum discloses this limitation, as discussed in Section X.A.1.vi. (Ex. 1004, ¶144; Ex. 1002, ¶226.)

12. Claim 18

Schrum in view of Altmeyer discloses or suggests this limitation, as discussed in Section X.D.1.iii. (Ex. 1002, ¶227.)

13. Claim 20

Schrum discloses this limitation, as discussed in Section X.A.13. (Ex. 1002, ¶¶106, 228.) A POSA would have good reason to use immunogen-encoding mRNA including at least 80% of such modification with a reasonable expectation of success, as discussed in Section X.B.9 and X.B.13. (Ex. 1002, ¶¶137, 150, 228.)

XI. DISCRETIONARY DENIAL IS NOT APPROPRIATE

A. *Fintiv* Does Not Justify Denial

The merits of Petitioner's arguments are strong and the evidence in support of them is substantial, and, if the Board agrees, "that determination alone demonstrates that the PTAB should not discretionarily deny institution under *Fintiv*." (Memorandum from Director Vidal dated June 21, 2022, 4-5.) Even if the Board necessitates the *Fintiv* analysis, the *Fintiv* factors do not justify denying institution. 35 U.S.C. § 314(a); *Apple Inc. v. Fintiv, Inc*., IPR2020-00019, Paper 11 (P.T.A.B. Mar. 20, 2020) (precedential).

The **first factor** (existence or possibility of a stay) is neutral because the Board need not speculate as to the likelihood of the district court entering a stay. *See*

Hulu LLC v. SITO Mobile R&D IP, LLC et al., IPR2021-00298, Paper 11 at 10-11 (P.T.A.B. May 19, 2021).

The **second factor** (proximity of trial dates) weighs in favor of institution, or is at least neutral, because trial is not yet scheduled.

The **third factor** (investment in parallel proceeding) weighs against discretionary denial. Fact discovery is still ongoing, with no witnesses having been deposed, and expert discovery has yet to begin. *Huawei Techs. Co. Ltd. v. Wsou Inv., LLC*, IPR2021-00228, Paper 9 at 11-12 (P.T.A.B. June 10, 2021) (factor three weighed in favor of institution where "discovery is not over and much remains to be completed in advance of trial"). After that, substantive motion practice would still need to occur. *See Fintiv*, IPR2020-00019 at 9-10. Thus, the investments that remain substantially outweigh those incurred so far.

The **fourth factor** (overlap in parallel proceedings) is neutral. Patent Owner's litigation positions continue to be disclosed and Petitioner continues to respond. Neither party has identified final positions on issues of validity. *See One World Techs., Inc. v. Chervon (HK) Ltd.*, IPR2020-00887, Paper 20, at 15 (P.T.A.B. Nov. 6, 2020).

The **fifth factor** (same parties) is neutral, and the Board should give no weight to the fact that Petitioner and Patent Owner are the same parties as in district court.

See Weatherford U.S., L.P., v. Enventure Global Tech., Inc., IPR2020-01666, Paper 16 at 11-13 (P.T.A.B. Apr. 14, 2021).

The **sixth factor** (other circumstances) strongly favors institution. As argued herein, the claims of the '127 patent should never have been granted, being broadly directed to subject matter anticipated and/or obvious over art that was not substantively considered during prosecution. And, when the Examiner allowed the claims, she expressly disclosed her interpretation, but Patent Owner has refused to agree to that scope, resulting in enforcement proceedings of a patent that again never should have been granted. (Ex. 1036 at 4.) There is significant public interest against "leaving bad patents enforceable." *Thryv, Inc v. Click-To-Call Techs., LP*, 140 S. Ct. 1367, 1374 (2020).

B. Discretionary Denial Under 35 U.S.C. § 325(d) Is Not Appropriate

Discretionary denial pursuant to 35 U.S.C. § 325(d) is inappropriate under the two-part framework set forth in *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 8 (P.T.A.B. Feb. 13, 2020) (precedential).

As to part one of the *Advanced Bionics* framework, this Petition relies on art (Schrum and Geall) that was presented to the Office only in an IDS amongst hundreds of other references and not substantively considered. And, the Petition also relies on art (Yang and Altmeyer) that was not previously before the Office.

For instance, grounds 3 and 4 rely on Schrum in combination with Yang or Altmeyer.

Regardless of whether part one of the *Advanced Bionics* framework is satisfied, the Office materially erred in allowing the claims of the '127 patent under part two of the *Advanced Bionics* framework. Schrum and Geall, were cited in an information disclosure statement along with hundreds of other references, but there is no indication that they were substantively considered by the Examiner and certainly, were never used to reject the claims. *See Hum Industrial Tech., Inc. v. Amsted Rail Co., Inc.*, IPR2023-00539, Paper 10 at 51 (P.T.A.B. July 26, 2023) (declining to exercise discretion under § 325(d)).

In fact, the Examiner issued a single rejection during the prosecution of the application that issued as the '127 patent, based solely on 35 U.S.C. § 112. (*See* Ex. 1008 at 448 of 554.) The Examiner did not raise an anticipation or obviousness rejection based upon the Petitioner's prior art grounds in this petition, and factors (d), (e), and (f) therefore weigh against discretionary denial under 35 U.S.C. § 325(d). *See Progenity, Inc. v. Natera, Inc.*, IPR2021-00279, Paper 12 at 41-45 (P.T.A.B. Jun. 11, 2021). As this Petition and supporting testimony demonstrates, Schrum anticipates all challenged claims and further renders it obvious based on Geall, Yang, and Altmeyer. Thus, the Office materially erred by allowing the claims over the prior art cited in this Petition.

XII. CONCLUSION

Petitioner requests institution of IPR for claims 1-3, 6-9, 11-13, 17-18 and 20 of the '127 patent.

Respectfully submitted,

Dated: August 28, 2023

By: /Naveen Modi/
Naveen Modi (Reg. No. 46,224)
Counsel for Petitioner

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 10,933,127 contains, as measured by the word-processing system used to prepare this paper, 13,836 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

Respectfully submitted,

Dated: August 28, 2023

By: /Naveen Modi/
Naveen Modi (Reg. No. 46,224)
Counsel for Petitioner

CERTIFICATE OF SERVICE

I hereby certify that on August 28, 2023, I caused a true and correct copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 10,933,127 and supporting exhibits to be served by Federal Express Priority Overnight on the Patent Owner at the following correspondence address of record as listed on Patent Center:

WOLF GREENFIELD & SACKS, P.C.
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A courtesy copy was also sent by electronic mail to the Patent Owner's litigation counsel at the following addresses:

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