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. 10,702,600

PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 10,702,600

TABLE OF CONTENTS

LIST OF EXHIBITS

Exhibit No.	Document
Ex. 1001	U.S. Patent No. 10,702,600
Ex. 1002	Declaration of Daniel O. Griffin, M.D., Ph.D.
Ex. 1003	Curriculum Vitae of Daniel O. Griffin, M.D., Ph.D.
Ex. 1004	Declaration of James J. Moon, Ph.D.
Ex. 1005	Curriculum Vitae of James J. Moon, Ph.D.
Ex. 1006	*Reserved*
Ex. 1007	*Reserved*
Ex. 1008	File History for U.S. Patent No. 10,702,600
Ex. 1009	U.S. Patent App. Publication 2013/0266640 ("Schrum")
Ex. 1010	International Patent App. Pub. No. WO 2012/006369 ("Geall")
Ex. 1011	Zhi-yong Yang et al., *A DNA vaccine induces SARS coronavirus neutralization and protective immunity in mice*, 428 NATURE 561 (2004) ("Yang")
Ex. 1012	International Patent App. Pub. No. WO 2005/118813 ("Altmeyer")
Ex. 1013	Jon A. Wolff et al., *Direct gene transfer into mouse muscle in vivo*, 247 SCIENCE 1465 (1990)
Ex. 1014	Frédéric Martinon et al., *Induction of virus-specific cytotoxic T lymphocytes in vivo by liposome-entrapped mRNA*, 23 EUR. J. IMMUNOL. 1719 (1993)
Ex. 1015	Matthew Cobb, *Who discovered messenger RNA?*, 25 CURRENT BIOLOGY R523 (2015)

Exhibit No.	Document
Ex. 1016	Andrew J. Geall et al., *RNA: The new revolution in nucleic acid vaccines*, 25 SEMIN. IMMUNOL. 152 (2013)
Ex. 1017	W. Michael McDonnell & Frederick K. Asari, *Molecular medicine – DNA vaccines,* 334 N. ENGL. J. MED. 42 (1996)
Ex. 1018	Suzanne Clancy & William Brown, *Translation: DNA to mRNA to Protein*, 1 NATURE EDUCATION 101 (2008) (https://www.nature.com/scitable/topicpage/translation-dna-to-mrna-to-protein-393/ (last accessed August 24, 2023))
Ex. 1019	Thomas Schlake et al., *Developing mRNA-vaccine technologies*, 9 RNA BIOLOGY 1319 (2012)
Ex. 1020	Karl-Josef Kallen & Andreas Theß, *A development that may evolve into a revolution in medicine: mRNA as the basis for novel, nucleotide-based vaccines and drugs*, 2 THER. ADV. VACCINES 10 (2014)
Ex. 1021	Katalin Karikó et al., *Suppression of RNA recognition by Toll-like receptors: The impact of nucleoside modification and the evolutionary origin of RNA*, 23 IMMUNITY 165 (2005)
Ex. 1022	Katalin Karikó et al., *Incorporation of pseudouridine into mRNA yields superior nonimmunogenic vector with increased translational capacity and biological stability*, 16 MOLECULAR THERAPY 1833 (2008)
Ex. 1023	U.S. Patent No. 8,691,966
Ex. 1024	Naomi Kresge, "The messenger RNA pioneers everyone ignored," *Bloomberg*, Nov. 23, 2021, https://www.bloomberg.com/news/newsletters/2021-11-23/the-messenger-rna-pioneers-everyone-ignored (last accessed August 24, 2023)

Exhibit No.	Document
Ex. 1025	"Katalin Karikó and Drew Weissman awarded Horwitz Prize for pioneering research on COVID-19 vaccines," *Columbia University Irving Medical Center*, Aug. 16, 2021, https://www.cuimc.columbia.edu/news/horwitz-prize-2021 (last accessed August 24, 2023)
Ex. 1026	Patent Sublicense Agreement Between Cellscript, LLC and ModernaTx, Inc.
Ex. 1027	*Reserved*
Ex. 1028	Katalin Karikó et al., *Increased eythropoiesis in mice injected with submicrogram quantities of pseudouridine-containing mRNA encoding erythropoietin*, 20 MOLECULAR THERAPY 948 (2012)
Ex. 1029	R. J. deGroot et al., *Part II – The Positive Sense Single Stranded RNA Viruses, Family Coronaviridae*, in VIRUS TAXONOMY: NINTH REPORT OF THE INTERNATIONAL COMMITTEE ON TAXONOMY OF VIRUSES 806 (2012)
Ex. 1030	Alimuddin Zumla et al., *Middle East respiratory syndrome*, 368 LANCET 995 (2015)
Ex. 1031	Lanying Du et al., *The spike protein of SARS-CoV – a target for vaccine and therapeutic development*, 7 NATURE REV. MICROBIOLOGY 226 (2009)
Ex. 1032	Patrick Midoux & Chantal Pichon, *Lipid-based mRNA vaccine delivery systems*, 14 EXPERT REV. VACCINES 221 (2015)
Ex. 1033	*Reserved*
Ex. 1034	*Reserved*
Ex. 1035	*ModernaTX, Inc. et al v. Pfizer Inc. et al.* (D. Mass. 22-11378-RGS) D.I. 105 - District Court Memorandum and Order on Claim Construction, August 1, 2023

Exhibit No.	Document
Ex. 1036	Notice of Allowance of U.S. Patent No. 10,933,127 (Application No. 16/880,829) (Sep. 18, 2020)
Ex. 1037	U.S. Provisional Patent App. titled "Measles Vaccine" (Moderna Measles Priority Application)
Ex. 1038	U.S. Provisional Patent App. No. 62/244,946 titled "Human Metapneumovirus Vaccine" (Moderna HMPV Priority Application)
Ex. 1039	Notice of Abandonment of U.S. Patent Application No. 13/917,720 (Aug. 12, 2015) (published as Ex. 1009)
Ex. 1040	Jesper Pallesen et al., *Immunogenicity and structures of a rationally designed prefusion MERS-CoV spike antigen*, 114 PROC NATL. ACAD. SCI. USA E7348 (2017)
Ex. 1041	*Reserved*
Ex. 1042	*Reserved*
Ex. 1043	*Excerpts from* Bruce Alberts et al., Chapters 1, 3, 5-7, 24, and 25 in MOLECULAR BIOLOGY OF THE CELL, 4th Ed. (2002)
Ex. 1044	*Excerpts from* Geoffrey M. Cooper & Robert E. Hausman, Chapters 1, 7, and 8 in THE CELL: A MOLECULAR APPROACH, 5th Ed. (2009)
Ex. 1045	Ayako Yamamoto et al., *Current prospects for mRNA gene delivery*, 71 EUR. J. PHARM. BIOPHARM. 484 (2009)
Ex. 1046	Katalin Karikó & Drew Weissman, *Naturally occurring nucleoside modifications suppress the immunostimulatory activity of RNA: Implication for therapeutic RNA development*, 10 CURR. OPIN. DRUG DISCOV. DEVEL. 523 (2007)
Ex. 1047	Kathryn A. Whitehead et al., *Knocking down barriers: Advances in siRNA delivery*, 8 NATURE REVIEWS DRUG DISCOVERY 129 (2009)

Exhibit No.	Document
Ex. 1048	Alison J. Lin et al., *Three-dimensional imaging of lipid gene-carriers: Membrane charge density controls universal transfection behavior in lamellar cationic liposome-DNA complexes*, 84 BIOPHYSICAL JOURNAL 3307 (2003)
Ex. 1049	Zhong Li et al. *Application of ultra-high performace liquid chromatography for chemical characterization of liposome-based therapeutic small-interfering RNA*, 13 AMERICAN PHARMACEUTICAL REVIEW 102 (2010)
Ex. 1050	S. S. Shidhaye et al., *Solid lipid nanoparticles and nanostructured lipid carriers – Innovative generations of solid lipid carriers*, 5 CURRENT DRUG DELIVERY 324 (2008)
Ex. 1051	Dhruba J. Bharali et al., *Nanoparticles and cancer therapy: A concise review with emphasis on dendrimers*, 4 INTERNATIONAL JOURNAL OF NANOMEDICINE 1 (2009)
Ex. 1052	*Reserved*
Ex. 1053	A. D. Bangham et al., *Diffusion of univalent ions across the lamellae of swollen phospholipids*, 13 J. MOL. BIOL. 238 (1965)
Ex. 1054	Marc J. Ostro et al., *Evidence for translation of rabbit globin mRNA after liposome-mediated insertion into a human cell line*, 274 NATURE 921 (1978)
Ex. 1055	Giorgos J. Dimitriadis, *Translation of rabbit globin mRNA introduced by liposomes into mouse lymphocytes*, 274 NATURE 923 (1978)
Ex. 1056	Laura J. Peek et al., *Nanotechnology in vaccine delivery*, 60 ADV. DRUG DELIV. REV. 915 (2008)
Ex. 1057	Center for Drug Evaluation and Research Approval Package for New Drug Application No. 50-718/S-50 for Doxil®
Ex. 1058	Jochen Probst et al., *Characterization of the ribonuclease activity on the skin surface*, 4 GENETIC VACCINES AND THERAPY (2006)

Exhibit No.	Document
Ex. 1059	Xiang Gao et al., *Nonviral gene delivery: What we know and what is next*, 9 THE AAPS JOURNAL E92 (2007)
Ex. 1060	Ayesha Ahmad et al., *New multivalent cationic lipids reveal bell curve for transfection efficiency versus membrane charge density: lipid–DNA complexes for gene delivery*, 7 J. GENE MED. 739 (2005)
Ex. 1061	Theresa M. Allen & Pieter R. Cullis, *Liposomal drug delivery systems: From concept to clinical applications*, 65 ADV. DRUG DELIV. REV. 36 (2013)
Ex. 1062	International Patent App. Pub. No. WO 2011/140627
Ex. 1063	*Reserved*
Ex. 1064	Rumiana Tenchov et al., *Lipid nanoparticles—From liposomes to mRNA vaccine delivery, a landscape of research diversity and advancement*, 15 ACS NANO 16982 (2021)
Ex. 1065	Sean C. Semple et al., *Rational design of cationic lipids for siRNA delivery*, 28 NATURE BIOTECHNOLOGY 172 (2010)
Ex. 1066	Robert Langer, *New methods of drug delivery*, 249 SCIENCE 1527 (1990)
Ex. 1067	Saba Ahmed et al., *Biochemistry, Lipids*, STATPEARLS PUBLISHING (2023) (https://www.ncbi.nlm.nih.gov/books/NBK525952/ (last accessed August 24, 2023))
Ex. 1068	Michael J. Bennett et al., *Cholesterol enhances cationic liposome-mediated DNA transfection of human respiratory epithelial cells*, 15 BIOSCIENCE REPORTS 47 (1995)
Ex. 1069	Zhaohua Huang et al. *Asymmetric 1-alkyl-2-acyl phosphatidylcholine: A helper lipid for enhanced non-viral gene delivery*, (Author Manuscript), published in final edited from as 427 INT. J. PHARM. 64 (2012)

Exhibit No.	Document
Ex. 1070	James Heyes et al., *Cationic lipid saturation influences intracellular delivery of encapsulated nucleic acids*, 107 J. CONTROLLED RELEASE 276 (2005)
Ex. 1071	International Patent App. Pub. No. WO 2012/031046
Ex. 1072	Moderna Therapeutics, Inc. Petition for *Inter Partes* Review of U.S. Patent No. 8,058,069 (IPR2019-00554)
Ex. 1073	Mikhail A. Zhukovsky et al., *Heterogeneity of early intermediates in cell-liposome fusion mediated by influenza hemagglutinin*, 91 BIOPHYSICAL JOURNAL 3349 (2006)
Ex. 1074	Yang Liu et al., *Influence of polyethylene glycol density and surface lipid on pharmacokinetics and biodistribution of lipid-calcium-phosphate nanoparticles*, (Author Manuscript), published in final edited form as 35 BIOMATERIALS 3027 (2014)
Ex. 1075	*Reserved*
Ex. 1076	*Reserved*
Ex. 1077	*Reserved*
Ex. 1078	*Excerpts from* Kenneth Murphy, JANEWAY'S IMMUNOBIOLOGY, 8th Ed. (2012)
Ex. 1079	Sander van Boheemen et al., *Genomic characterization of a newly discovered coronavirus associated with acute respiratory distress syndrome in humans*, 3 MBIO e00473 (2012)
Ex. 1080	Fang Li, *Receptor recognition mechanisms of coronaviruses: A decade of structural studies*, 89 J. VIROL. 1954 (2015)
Ex. 1081	Jason McLellan et al., *Structure and function of RSV surface glycoproteins*, (Author Manuscript), published in final edited form as 372 CURRENT TOPICS IN MICROBIOLOGY AND IMMUNOLOGY 83 (2014)

Exhibit No.	Document
Ex. 1082	Muthusamy Jayaraman et al., *Maximizing the potency of siRNA lipid nanoparticles for hepatic gene silencing in vivo*, 51 ANGEW. CHEM. INT. ED. 8259 (2012)
Ex. 1083	Alex K. K. Leung et al., *Chapter Four – Lipid nanoparticles for short interfering RNA delivery*, in ADVANCES IN GENETICS, Vol. 88, (2014)
Ex. 1084	Sean C. Semple et al., *Efficient encapsulation of antisense oligonucleotides in lipid vesicles using ionizable aminolipids: Formation of novel small multilamellar vesicle structures*, 1510 BIOCHIMICA ET BIOPHYSICA ACTA 152 (2001)
Ex. 1085	Rosemary Kanasty et al., *Delivery materials for siRNA therapeutics*, 12 NATURE MATERIALS 967 (2013)
Ex. 1086	*Reserved*
Ex. 1087	Shutao Guo & Leaf Huang, *Nanoparticles escaping RES and endosome: Challenges for siRNA delivery for cancer therapy*, 2011 JOURNAL OF NANOMATERIALS 1 (2011)
Ex. 1088	Philip L. Felgner et al., *Lipofection: A highly efficient, lipid-mediated DNA-transfection procedure*, 84 PROC. NATL. ACAD. SCI. USA 7413 (1987)
Ex. 1089	Erick J. Dufourc, *Sterols and membrane dynamics*, 1 J. CHEM. BIOL. 63 (2008)

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 – compositions of mRNA encoding any spike protein or spike protein subunit of any betacoronavirus, formulated in a broadly claimed lipid delivery system.

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 the use of antigen-encoding mRNA, scientists in the field worked to optimize mRNA vaccines. Before 2015, that work led to mRNA vaccines which 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 specific combination of these features claimed in the '600 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, with no data, directed to these same basic ideas. (*See, e.g.*, Ex. 1037, 1038.) In October 2016, Patent Owner then filed a non-provisional application containing two examples of betacoronavirus (specifically, MERS-CoV) mRNA vaccines tested in mice and rabbits: Application No. PCT/US2016/058327. The mRNA structure of the specific vaccines was not disclosed. After numerous continuations, Patent Owner eventually obtained, in July 2020, the subject of this petition, U.S. Patent No. 10,702,600 ("the '600 patent").

The '600 patent has, by Patent Owner's own arguments, unimaginably broad claims reciting an mRNA composition 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. Its broad claims encompass subject

matter disclosed in the art before October 22, 2015, the earliest date to which the '600 patent claims priority.

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

II. MANDATORY NOTICES

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 '600 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 '600 patent issued in July 2020 from Application No. 16/805,587 ("the '587 application"). Thereafter, Application No. 16/880,829 was filed as a continuation of the '587 application and issued in March 2021 as U.S. Patent No. 10,933,127 ("the '127 patent"). The '127 patent is asserted in the above-cited district court case and is the subject of a separate *inter partes* review petition concurrently filed by Petitioner.

Counsel and Service Information: Lead counsel is David Krinsky (Reg. No. 72,339). Backup counsel are (1) Stanley Fisher (Reg. No. 55,820), (2) Naveen Modi (Reg. No. 46,224), (3) Bruce Wexler (Reg. No. 35,409), (4) Eric Dittmann (Reg. No.

51,188), (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 Williams & Connolly LLP, 680 Maine Avenue SW, Washington, D.C. 20024, Tel.: 202.434.5000, Fax: 202.4345029, email: COVIDPatentPfizer@wc.com and BioNTech-Moderna-IPR@paulhastings.com. Petitioner consents to electronic service.

III. PAYMENT OF FEES UNDER 37 C.F.R. §§ 42.15 AND 42.103

The PTO is authorized to charge any fees due during this proceeding to Deposit Account No. 50-6403.

IV. STANDING

Petitioner certifies under 37 C.F.R. § 42.104(a) that the '600 patent is available for review and 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, 2, 4-6, 8-12, 16-17, 20-21, and 26 of the '600 patent and cancellation of these claims as unpatentable. The challenged claims should be found unpatentable based on the following grounds:

Ground 1: Claims 1, 2, 4-6, 8-12, 16-17, 20-21, and 26 are unpatentable under 35 U.S.C. § 102(a) as anticipated by US 2013/026640 ("Schrum") (Ex. 1009).

Ground 2: Claims 1, 2, 4-6, 8-12, 16-17, 20-21, and 26 are unpatentable under 35 U.S.C. § 103 as being obvious based on Schrum in view of WO 2012/006369 ("Geall") (Ex. 1010).

Ground 3: Claims 1, 2, 4-6, 8-12, 16-17, 20-21, and 26 are unpatentable under 35 U.S.C. § 103 as being 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, 2, 4-6, 8-12, 16-17, 20-21, and 26 are unpatentable under 35 U.S.C. § 103 as being 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 system response. (*Id.*)

In the context of betacoronaviruses,[1] the subject of the '600 patent claims, the "spike protein" was well-established as the most promising antigen for vaccine development long before October 2015. (Ex. 1031 at 227; Ex. 1002, ¶¶45-47.) Betacoronaviruses comprise four structural proteins: the spike, envelope, nucleocapsid, and membrane proteins. (Ex. 1002, ¶¶28-31; Ex. 1029 at 811-12.) By at least 2009, scientists recognized that, of those proteins, only 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 attachment and entry, it represents one of the most

[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.)

important targets for the development of SARS vaccines and therapeutics." (*Id.* at 227; *see also id.* at 229 ("Among all structural proteins of SARS-CoV, S protein is the main antigenic component that is responsible for inducing host immune responses, neutralizing antibodies and/or protective immunity against virus infection.").)

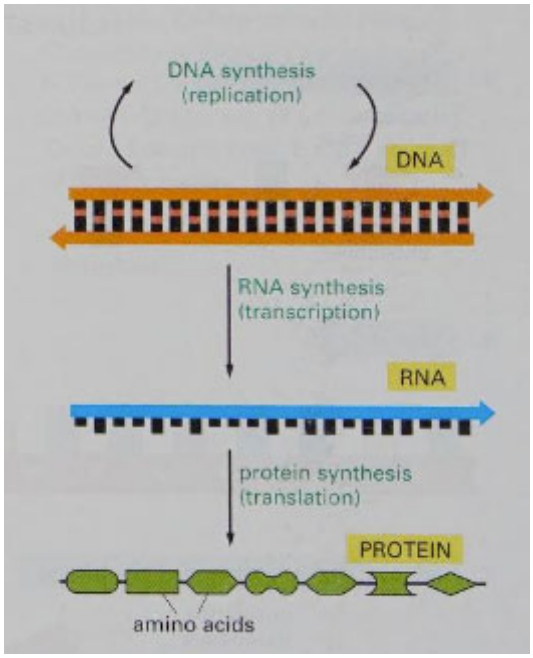
2. Nucleic Acid Vaccines

A traditional vaccine contains an antigen itself, such as a weakened or inactivated part of a virus. (Ex. 1002, ¶¶36.) But scientific advances long pre-dating the claimed priority date of the '600 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, thereby 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; Ex. 1002, ¶40.)

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:

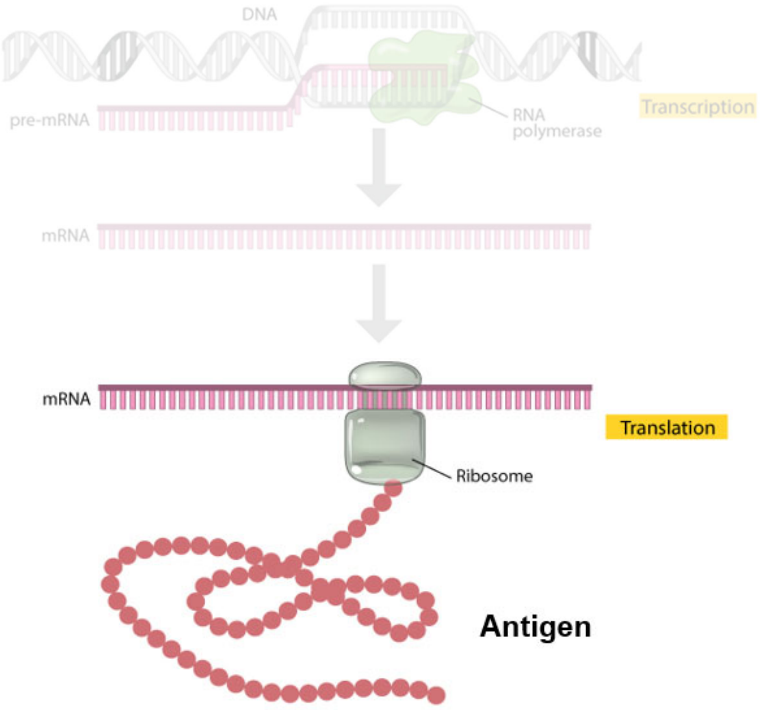
Flow of Genetic Information for Protein Synthesis



(Ex. 1043 at 6.) mRNA carries genetic information from the cell nucleus into the cytoplasm. (Ex. 1002, ¶¶21-27, 38.) There, mRNA binds to a cellular component called a 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 subsequently translated into the antigen, which induces a protective immune response. (Ex. 1002, ¶38.)

mRNA vaccines rely on an abbreviated, 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 serious problem for vaccine development because it could destroy mRNA before it achieved sufficient production of the encoded antigen.[2] (Ex. 1002, ¶¶42-43; Ex. 1021 at 165.) In that timeframe, there was instead significant attention to nucleic acid vaccines using DNA.

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]

[2] The "innate immune response" is distinct from the body's "adaptive immune response," which vaccines engage. (Ex. 1002, ¶¶32-35.) In the context of viruses, for example, the innate immune response is a relatively non-specific protective response that destroys pathogens, rather than creating cells that remember and protect against a virus. (*Id.*, ¶.) The "adaptive immune response," meanwhile, identifies a virus and creates particularized antibodies (B cell responses) and T cells that recognize and neutralize the virus, storing the information for efficient and rapid future responses when needed. (*Id.*, ¶.)

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

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 any mRNA therapeutics down the road." (Ex. 1024; *see* Ex. 1025 (Columbia University identifying Drs. Karikó and Weissman's discoveries as "[the] key insight [that] finally transformed mRNA into a viable and highly effective vaccine platform").)

Following Drs. Karikó and Weissman's publications, and before the priority date of the '600 patent, mRNA vaccines were recognized as more promising than DNA vaccines. (*See* Ex. 1020 at Abstract ("Recent advances strongly suggest that

[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.)

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 is 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 the use of lipid nanoparticles for mRNA delivery).)

Before 2015, the use of certain lipid components in lipid nanoparticle formulations had been well-established. (Ex. 1004, ¶¶33-44.) Lipid nanoparticles, for delivery of nucleic acids like mRNA, were known to be made up of (1) a cationic lipid, (2) a phospholipid, (3) a PEG-lipid, and (4) a sterol. (*Id.*; *see* Ex. 1009, ¶¶8, 36; Ex. 1062 at 2:33-34; Ex. 1010 at 5:3.)[5] Each component serves a purpose. For

[5] Indeed, 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)

example, the cationic lipid facilitates encapsulation of negatively charged 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 in the body. (*See* Ex. 1004, ¶¶35-44.)

B. '600 Patent Overview

The '600 patent issued on July 7, 2020 from U.S. Application No. 16/805,587, filed February 28, 2020. Through a chain of applications, the '600 patent claims priority to nine U.S. provisional applications, four filed on October 28, 2015 and five filed on October 22, 2015.

The '600 patent claims a combination of disclosed technologies, as discussed herein. Claim 1, the first independent claim, is directed to:

> 1. A composition comprising: a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding

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("[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.").)

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

(Ex. 1001 at 737:26-29.)

The claim comprises three broad features: (1) an mRNA composition (*i.e.*, an mRNA vaccine); (2) the use of a betacoronavirus spike protein or subunit thereof as an antigen (*i.e.*, including known targets for a vaccine);[6] and (3) formulation of the mRNA in lipid particles. (Ex. 1002, ¶¶14-19; Ex. 1004, ¶¶45-47.)

The claims that depend from claim 1 recite various attributes that add nothing to patentability—for example, that the mRNA composition includes known structural components (claims 4-6) and/or uridine modifications previously disclosed in the art (claims 8-10), or includes known specific lipid components at known ratio ranges (claims 11-12). The second independent claim (claim 16), as well as the claims that depend therefrom (claims 17 and 20) recite the same added

[6] The only betacoronavirus vaccine Patent Owner describes making and using in the '600 patent specification was for MERS, in one lipid nanoparticle formulation, and without disclosing its mRNA sequence. (*Id.* at 213:57-214:56.) In allowing the claims of the related '127 patent to issue, the Examiner said she was interpreting the claims as limited to mRNA producing viruses known at the time of filing, but Patent Owner refused to accept this interpretation. (Ex. 1036 at 4.)

features of the earlier dependent claims. (Ex. 1001 at 738:25-42.) The final independent claim (claim 26) combines the same mRNA and lipid nanoparticle components of the earlier claims. (*Id.* at 738:64-739:2.)

VII. LEVEL OF ORDINARY SKILL

With respect to the '600 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. 1004, ¶16; Ex. 1002, ¶11.)

Patent Owner advanced the following definition of a POSA in litigation: a POSA with respect to the '600 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. 1004, ¶17-18; Ex. 1002, ¶¶11-13.)

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, which published on October 10, 2013. Schrum is prior art to the '600 patent under 35 U.S.C. §§ 102(a)(1) and 102(a)(2).[7] During prosecution, Schrum was included only in an information disclosure statement with more than three hundred other documents.

Schrum "provides, *inter alia*, formulation compositions comprising modified nucleic acid molecules which may encode a protein. . . . The formulation compositions may further include a modified nucleic acid molecule and a delivery agent." (Ex. 1009, ¶4; *see also* Ex. 1002, ¶¶51-57; Ex. 1004, ¶¶50-53.) The nucleic acids were "modified mRNA." (Ex. 1009, ¶53.) Schrum further 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.)

[7] 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 '600 patent. (Ex. 1039.)

Further, 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; *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 immunogen (*i.e.*, antigen[8]) 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.)

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

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 to the '600 patent under 35 U.S.C. § 102(a)(1). Like Schrum, Geall was listed only on an information disclosure statement among hundreds of references.

Geall discloses the use of RNA vaccines encoding the spike protein of a betacoronavirus. (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 further specifies that the immunogen-encoding RNA is "+-stranded, and so it can be translated without needing any intervening replication steps such as reverse transcription." (*Id.* at 12:4-5.) 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 19:27-30.)

Geall confirms that lipid-based delivery vehicles are preferred for RNA administration *in vivo*. (Ex. 1004, ¶¶54-57.) Geall teaches that "to enhance both entry to immune and non-immune cells and also subsequent intercellular effects, and

also to reduce the amount of RNA required for a good immunogenic effect, the RNA is preferably administered with a delivery system. . . . Liposomes[9] are a preferred delivery system." (*Id.* at 3:25-31.) 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.)

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 to the '600 patent 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 652-53.) 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

[9] Geall's reference to lipid particles of nanometer size, matching the components and molar ratios discussed in the '600 patent, are lipid nanoparticles, as explained by Dr. Moon. (Ex. 1004, ¶¶22, 99-100.)

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.*; Ex. 1002, ¶¶60-63.)

D. Altmeyer

WO2005/118813 is a patent application published on December 15, 2005. (Ex. 1012 at Cover). Altmeyer is prior art to the '600 patent 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, ¶98.) 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.*) 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."[10]

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).

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

X. DETAILED EXPLANATION OF GROUNDS

As detailed below, each challenged claim is unpatentable. Schrum discloses an mRNA composition encoding an antigen. In Schrum, Patent Owner disclosed the same standard mRNA and lipid nanoparticle components that it later claimed in the '600 patent. And, through its incorporation of Geall, Schrum discloses encoding the spike (S) protein of a betacoronavirus, SARS-CoV, in an mRNA composition, *i.e.*, an mRNA vaccine (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 '600 patent are unpatentable as both anticipated by and obvious in view of the prior art cited by Petitioner.

A. Ground 1: Schrum Anticipates Claims 1, 2, 4-6, 8-12, 16, 17, 20, 21, and 26 of the '600 Patent

1. Claim 1

i) [1.pre] "A composition comprising:"

Schrum discloses this limitation. (Ex. 1002, ¶¶67-68.) Schrum is titled "Modified Nucleoside, Nucleotide, and Nucleic Acid Compositions" and discloses "formulation compositions comprising modified nucleic acid molecules which may encode a protein." (Ex. 1009, Cover, ¶3.) In one aspect of Schrum, the "mammalian cell or tissue" is contacted "with a formulation comprising a modified mRNA

encoding a polypeptide of interest." (*Id.*, ¶5, claim 1.) In addition to the modified mRNA, the "formulation" (*i.e.*, composition) includes a "delivery agent." (*Id.*, ¶¶4-5, 22.) Schrum further discloses administering the modified mRNA formulation for vaccination, as the "mRNA molecules may be used to elicit or provoke an immune response in an organism," such as a mammal (an exemplary "subject" in the '600 patent, Ex. 1001 at 68:3-5). (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.) Within Schrum's disclosure of formulation compositions comprising modified mRNA, Schrum provides that the modified "mRNA molecules to be delivered may encode an immunogenic peptide or polypeptide." (Ex. 1009, ¶340.) Schrum continues, "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 accordingly incorporates these references for their teaching of disclosed immunogens and dose amounts necessary to achieve an immunogenic effect.

One of these references 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, which is incorporated expressly for its disclosure of RNA encoding immunogens, further 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, ¶59 n.92), 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).[11]

[11] 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

Indeed, Schrum later recognizes that "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," which would include Geall's disclosure of the betacoronavirus spike polypeptide. (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 by the mRNA. Ex. 1002, ¶73.) 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.

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

2005). Equally, "anticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabling 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, ¶74-76.) Schrum discloses that "the formulation comprising the modified mRNA is a nanoparticle which may comprise at least one lipid." (Ex. 1009, ¶6.) Schrum further discloses 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."[12] (Ex. 1009 at Abstract, ¶34.) Schrum provide that 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 further contemplates the use of mRNA encoding an immunogen encapsulated in a lipid nanoparticle "for use in a vaccine such as . . . against a

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

pathogen." (*See id.*, ¶397.) And, Schrum reports successful administration of modified mRNA encapsulated in a lipid nanoparticle in multiple examples. (*E.g.*, *id*., ¶¶995-1000, 1002-20, 1022-36, 1046-51.)

* * *

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." (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, 72.) 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 creating the modified mRNA compositions (*i.e.*, vaccines) described in Schrum—including those encoding the betacoronavirus S protein—using the disclosed lipid nanoparticles. Indeed, Schrum expressly states as much, disclosing that "[t]he modified nucleic acid molecules and mmRNA of the invention can be formulated using one or more liposomes, lipoplexes, *or 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 composition of claim 1, wherein the open reading frame encodes a BetaCoV S protein."

Schrum discloses this limitation. (Ex. 1002, ¶77.) As discussed in Section X.A.1.iii, Schrum describes mRNA compositions comprising an open reading frame encoding a betacoronavirus spike protein.

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

Schrum discloses this limitation. (Ex. 1002, ¶78.) Schrum discloses a formulation including (1) a modified mRNA, (2) encoding a polypeptide of interest, and (3) a delivery agent for delivery. (Ex. 1009, ¶¶4-5, claim 1.) Describing the structure of 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.").[13]) 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

[13] The '600 patent admits that a 5' UTR and a 3' UTR are "basic components of an mRNA molecule." (Ex. 1001, 42:3-5.)

both elements. *See Upsher-Smith Labs., Inc. v. Pamlab L.L.C.*, 412 F.3d 1319, 1322 (Fed. Cir. 2005).

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

Schrum discloses this limitation. (Ex. 1002, ¶79.) As discussed in Section X.A.3, 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 long chain of nucleotides (poly-A tail) [that] may be added to a modified nucleic acid molecule . . . in order to increase stability." (Ex. 1009, ¶89.) The "length of a poly-A tail of the present invention is greater than 30 nucleotides in length." (*Id.*, ¶91.[14]) Schrum exemplifies administration of modified mRNA comprising a polyA tail. (*Id*., ¶¶995-99.)

5. Claim 6: "The composition of claim 4, wherein the mRNA further comprises a 5′ cap analog."

Schrum discloses this limitation. (Ex. 1002, ¶80.) As discussed above in Sections X.A.3 and X.A.4, Schrum describes the structure of the modified mRNA molecule including various parts thereof. Schrum explains that "the nucleic acid molecule, [*i.e.*, mRNA] may comprise at least one 5′ terminal cap." (Ex. 1009, ¶29,

[14] The 600 patent admits that a 5' UTR and a 3' UTR are "basic components of an mRNA molecule." (Ex. 1001, 42:3-5.)

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 '600 patent. (Ex. 1001 at 11:46-47, claim 7.)[15]

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

Schrum discloses this limitation. (Ex. 1002, ¶81.) 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" refers to mRNA "which contain[s] one or more modified nucleosides or nucleotides." (*Id.*, ¶53.) Schrum further discloses that the "modified nucleic acid molecules may be chemically modified." (Ex. 1009, ¶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

[15] The 600 patent admits that a 5' cap is a "basic component[] of an mRNA molecule." (Ex. 1001, 42:3-5.)

successful delivery of mRNA comprising a chemical modification to express a protein. (*E.g.*, *id*., ¶¶995-99.)

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

Schrum discloses this limitation. (Ex. 1002, ¶82.) Schrum identifies 1-methylpseudouridine as a chemical modification included in the immunogenic mRNA compositions. (Ex. 1009, ¶26.) Additionally, 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 (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).)

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

Schrum discloses this limitation. (Ex. 1002, ¶83.) 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 further discusses mRNA sequences "fully modified" at each cytosine and uridine replacement site, *i.e.*, chemically modifies 100% of the uracils in the mRNA sequence, including the open reading frame. (Ex. 1009, ¶936; *see also*

id., ¶¶940, 942. 963, 979, 981.) Schrum asserts that full modification results in an increase in protein expression. (*See id.*, ¶1183.)

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

Schrum discloses this limitation. (Ex. 1004, ¶¶67-73; Ex. 1002, ¶¶84-85.) Schrum discloses a "lipid nanoparticle" as the delivery agent for the mRNA vaccines disclosed therein. Schrum further provides that the lipid nanoparticles have the four lipid components of 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 '600 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 '600 patent. (Ex. 1004, ¶¶ 67-73.)

DSPC is the lipid disclosed and claimed in the '600 patent as "neutral." (*See* Ex. 1001 at 73:16-17, claim 15 (737:63-67). Similarly, Schrum refers to "PEG"

lipids and provides that "the PEG lipid is PEG-DMG." (Ex. 1009, ¶37). PEG-DMG is a "PEG-modified lipid" per the '600 patent specification and claims. (Ex. 1001 at 73:18-19, claim 15.) Finally, Schrum discloses that "the cationic lipid may be . . . DLin-MC3-DMA . . . and DLin-KC2-DMA" (Ex. 1009, ¶34), which are the same lipids identified in the '600 patent as exemplary "ionizable" cationic lipids. (Ex. 1001 at 73:1-5 ("Lipid nanoparticle formulations typically comprise a lipid, in particular, an ionizable cationic lipid, for example . . . (DLin-KC2-DMA) . . . [and] (DLin-MC3-DMA)".)

Indeed, Schrum and the '600 patent disclose precisely the same lipid formulations. The '600 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 74:65-75:1.) Schrum teaches the same, providing that "the formulation may have a molar ratio of 50:10:38.5:1.5-3.0 (cationic lipid:fusogenic lipid [encompassing "neutral" lipids]: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 phospholipid component, Schrum explains that "the fusogenic lipid is disteroylphophatidyl choline (DSPC)," which is a neutral lipid. (Ex. 1009, ¶37).

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

Schrum discloses this limitation. (Ex. 1004, ¶¶74-82; Ex. 1002, ¶¶86-87.) As discussed above in Section X.A.9, Schrum discloses the same specific lipids and same molar ratios that the '600 patent discloses and claims. 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.) That, again, is the same lipid formulation disclosed in the '600 patent. (*See* Ex. 1001 at 74:65-75:1.) ("In 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.").)

Schrum further claims mRNA-encapsulating lipid nanoparticles with a molar ratio falling within the ranges claimed in the '600 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. (Ex, 1009, ¶8, claims 1, 3, 11, and 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) (affirming Patent Owner's successful *inter partes* review invalidating patent claims to, *inter alia*, lipid nanoparticles comprising 10-50 mol % cationic lipid)).

11. Claim 16

For the reasons discussed below and in Section X.A.1, Schrum discloses every limitation of claim 16, as arranged in in the claim.

i) [16.pre] "A composition, comprising:"

Schrum discloses this limitation for the reasons discussed in Section X.A.1.i. (Ex. 1002, ¶88.)

ii) [16.a] "a messenger ribonucleic acid (mRNA)"

Schrum discloses this limitation for the reasons discussed in Section X.A.1.ii. (Ex. 1002, ¶89.)

iii) [16.b] "comprising a 5′ untranslated region (UTR),"

Schrum discloses this limitation for the reasons discussed in Section X.A.3. (Ex. 1002, ¶90.)

iv) [16.c] "an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit"

Schrum discloses this limitation for the reasons discussed in Section X.A.1.iii. (Ex. 1002, ¶91.)

v) [16.d] "a 3′ UTR,"

Schrum discloses this limitation for the reasons discussed in Section X.A.3. (Ex. 1002, ¶92.)

vi) [16.e] "and a poly(A) tail,"

Schrum discloses this limitation for the reasons discussed in Section X.A.4. (Ex. 1002, ¶93.)

vii) [16.f] "formulated in a lipid nanoparticle that comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid."

Schrum discloses this limitation for the reasons discussed in Sections X.A.9 and X.A.10. (Ex. 1004, ¶¶ 67-82, 89, Ex. 1002, ¶¶94-95.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.1.iii. (Ex. 1002, ¶96.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.8. (Ex. 1002, ¶97.)

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

Schrum discloses this limitation for the reasons discussed in Sections X.A.6 and X.A.7. (Ex. 1002, ¶98.)

15. Claim 26

For the reasons discussed below and in Section X.A.1, Schrum discloses every limitation of claim 26, as arranged in the claim.

i) [26.pre] "A lipid nanoparticle, comprising:"

Schrum discloses this limitation for the reasons discussed in Section X.A.1.iv. (Ex. 1004, ¶¶ 62-66, 90; Ex. 1002, ¶99.)

ii) [26.a] "a messenger ribonucleic acid (mRNA)"

Schrum discloses this limitation for the reasons discussed in Section X.A.1.ii. (Ex. 1002, ¶100.)

iii) [26.b] "comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit;"

Schrum discloses this limitation for the reasons discussed in Section X.A.1.iii. (Ex. 1002, ¶101.)

iv) [26.c] "wherein the lipid nanoparticle comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid."

Schrum discloses this limitation for the reasons discussed in Sections X.A.9 and X.A.10. (Ex. 1004, ¶ 67-82, 93; Ex. 1002, ¶¶102-03.)

B. Ground 2: Schrum in View of Geall Renders Claims 1, 2, 4-6, 8-12, 16, 17, 20, 21, and 26 Obvious

1. Claim 1

i) [1.pre] "A composition comprising:"

Schrum discloses this limitation for the reasons discussed in Section X.A.1.i. (Ex. 1002, ¶¶104-05.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.1.ii. (Ex. 1002, ¶106.)

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, including by incorporating Geall. 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, ¶¶107-10.)

Schrum discloses modified mRNA molecules encoding an immunogen and their use in a vaccine "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 instructs that the immunogen-encoding RNA "is +-stranded, and so it can be translated without needing any intervening replication steps such as reverse transcription." (*Id.* at 12:4-5.) 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, ¶109.) And, the "coronavirus immunogen" is taught to be a "spike polypeptide," or "spike protein" as claimed in the '600 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, ¶109 n.168.)

The knowledge that the spike protein had "been selected as an important target for vaccine and anti-viral development," as well as demonstrated immunostimulatory benefits demonstrated by nucleic acid vaccines encoding the

SARS-CoV spike protein provided good reason for a POSA to incorporate such protein as the encoded immunogen in the mRNA vaccine disclosed in Schrum. (Ex. 1031 at 229; Ex. 1002, ¶110.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.1.iv. (Ex. 1004, ¶62-66, 98.) Additionally, Geall discloses this limitation, providing an identical lipid nanoparticle formulation to that disclosed and claimed in the '600 patent. (Ex. 1004, ¶¶94, 99-100; Ex. 1002, ¶111.)

* * *

It would have been obvious for a POSA to combine the teachings of Schrum and Geall to arrive at the composition of claim 1. (Ex. 1002, ¶¶112-16.) Schrum discloses mRNA vaccines—having identical mRNA and lipid nanoparticle components to that claimed in the '600 patent—encoding an immunogen. Geall discloses the immunogenic RNA vaccines 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 an mRNA composition encoding the SARS-CoV S protein—a known betacoronavirus—accordingly 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; Ex. 1002, ¶¶112-14.) 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. (*Id.*.) Moreover, a POSA would have good reason to create an mRNA vaccine encoding the spike protein of SARS-CoV, given the knowledge 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; *see also* Ex. 1031 at 229 ("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.").)

A POSA would have reasonably expected success in making an mRNA composition encoding a SARS-CoV spike protein following well-known methods. (Ex. 1002, ¶¶115-16.) 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 additionally provides examples of the administration of protein-encoding mRNA formulated in lipid nanoparticles to express the encoded protein. (*E.g.*, *id.*, ¶942, 963, 995-99, 1000-01; Ex. 1002, ¶115; Ex. 1004, ¶¶72, 81.)

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

Schrum in view of Geall discloses or suggests this limitation for the reasons discussed in Section X.B.1.iii. (Ex. 1002, ¶117.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.3. (Ex. 1002, ¶118.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.4. (Ex. 1002, ¶119.)

5. Claim 6: "The composition of claim 4, wherein the mRNA further comprises a 5′ cap analog."

Schrum discloses this limitation for the reasons discussed in Section X.A.5. (Ex. 1002, ¶120.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.6. (Ex. 1002, ¶121.)

7. Claim 9: "The composition of claim 8, 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. 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; Ex. 1002, ¶118.) 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; Ex. 1002, ¶118.) 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, ¶122.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.8. (Ex. 1002, ¶123.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.9. (Ex. 1004, ¶¶67-73, 101; Ex. 1002, ¶124.)Additionally, Geall discloses this limitation, providing an identical lipid nanoparticle formulation to that disclosed and claimed in the '600 patent. (Ex. 1004, ¶¶102-04.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.10. (Ex. 1004, ¶¶74-82, 105; Ex. 1002, ¶125.) Additionally, Geall discloses this limitation, providing an identical lipid nanoparticle formulation to that disclosed and claimed in the '600 patent. (Ex. 1004, ¶¶106-08).

11. Claim 16

For the reasons discussed below and in sections X.A.1 and X.B.1, Schrum and Geall disclose every limitation of claim 16. The POSA would have been motivated to combine Schrum and Geall with a reasonable expectation of success for the reasons discussed in Section X.B.1.

i) [16.pre] "A composition, comprising:"

Schrum discloses this limitation for the reasons discussed in Section X.A.1.i. (Ex. 1002, ¶126.)

ii) [16.a] "a messenger ribonucleic acid (mRNA)"

Schrum discloses this limitation for the reasons discussed in Section X.A.1.ii. (Ex. 1002, ¶127.)

iii) [16.b] "comprising a 5′ untranslated region (UTR),"

Schrum discloses this limitation for the reasons discussed in Section X.A.3. (Ex. 1002, ¶128.)

iv) [16.c] "an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit"

Schrum in view of Geall discloses or suggests this limitation for the reasons discussed in Section X.B.1.iii. (Ex. 1002, ¶129.)

v) [16.d] "a 3′ UTR,"

Schrum discloses this limitation for the reasons discussed in Section X.A.3. (Ex. 1002, ¶130.)

vi) [16.e] "and a poly(A) tail,"

Schrum discloses this limitation for the reasons discussed in Section X.A.4. (Ex. 1002, ¶131.)

vii) [16.f] "formulated in a lipid nanoparticle that comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid."

Schrum discloses this limitation for the reasons discussed in Sections X.A.9 and X.A.10. (Ex. 1004, ¶¶67-82, 115; Ex. 1002, ¶132.) Additionally, Geall discloses this limitation. (Ex. 1004, ¶¶102-08, 116.)

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

Schrum in view of Geall discloses or suggests this limitation for the reasons discussed in Section X.B.1.iii. (Ex. 1002, ¶133.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.8. (Ex. 1002, ¶134.)

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

Schrum discloses this limitation for the reasons discussed in Sections X.A.6 and X.A.7. (Ex. 1002, ¶135.)

15. Claim 26

For the reasons discussed below and in sections X.A.1 and X.B.1, Schrum and Geall disclose every limitation of claim 26. The POSA would have been motivated to combine Schrum and Geall with a reasonable expectation of success for the reasons discussed in Section X.B.1.

i) [26.pre] "A lipid nanoparticle, comprising:"

Schrum discloses this limitation for the reasons discussed in Section X.A.1.iv. (Ex. 1004, ¶¶62-66, 117; Ex. 1002, ¶136.) Additionally, Geall discloses this limitation. (Ex. 1004, ¶¶99-100, 118, 116.)

ii) [26.a] "a messenger ribonucleic acid (mRNA)"

Schrum discloses this limitation for the reasons discussed in Section X.A.1.ii. (Ex. 1002, ¶137.)

iii) [26.b] "comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit;"

Schrum in view of Geall discloses or suggests this limitation for the reasons discussed in Section X.B.1.iii. (Ex. 1002, ¶138.)

iv) [26.c] "wherein the lipid nanoparticle comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid."

Schrum discloses this limitation for the reasons discussed in Sections X.A.9 and X.A.10. (Ex. 1004, ¶¶67-82, 121; Ex. 1002, ¶139.) Additionally, Geall discloses this limitation. (Ex. 1004, ¶¶102-108, 122.)

C. Ground 3: Schrum in view of Yang Renders Claims 1, 2, 4-6, 8-12, 16, 17, 20, 21, and 26 Obvious

1. Claim 1

i) [1.pre] "A composition comprising:"

Schrum discloses this limitation for the reasons discussed in Section X.A.1.i. (Ex. 1002, ¶141.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.1.ii. (Ex. 1002, ¶142.)

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, ¶¶143-46.)

Schrum discloses modified mRNA molecules encoding an immunogen and their use in a vaccine "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.) Yang teaches that 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 immunostimulatory results obtained in Yang via administration of a nucleic acid vaccine encoding the SARS-CoV spike protein, consistent with the knowledge that the spike protein had "been selected as an important target for vaccine and anti-viral development," provided good reason for a POSA to incorporate such protein as the encoded immunogen in the mRNA vaccine disclosed in Schrum. (Ex. 1031 at 229; Ex. 1002, ¶146.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.1.iv. (Ex. 1004, ¶¶62-66, 127; Ex. 1002, ¶147.)

* * *

It would have been obvious for a POSA to combine the teachings of Schrum and Yang to arrive at the composition of claim 1. (Ex. 1002, ¶¶148-50.) Schrum discloses an mRNA vaccine—having identical mRNA and lipid nanoparticle components to that claimed in the '600 patent—encoding an immunogen. 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. Combining these known elements to achieve an mRNA composition, *i.e.*, an mRNA vaccine, encoding the S protein of SARS-CoV involves only a "combination of familiar elements" to "yield predictable results," and would have been obvious to a POSA.[16] *KSR*, 550 U.S. at 401.

[16] The '600 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 '600 patent claims.

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; ¶¶148-49.) Specifically, 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.[17] As discussed above, the immunogen (SARS-CoV S protein) would be encoded by the ORF of the mRNA. (*Supra* Section X.A.1.iii.)

By 2015, it was known that mRNA vaccines encoding a viral antigen could be used to induce an immune response. (Ex. 1002, ¶¶ 36-47.) Such mRNA vaccines were known to have significant advantages over DNA vaccines, including better

[17] 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 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 demonstrate that the methods developed for DNA also worked for RNA.")

safety profiles and increased antigen production. (*Id.*; *see e.g.*, Ex. 1020 at 10 ("Recent advances strongly suggest that mRNA rather than DNA will be the nucleotide basis for a new class of vaccines and drugs").)

A POSA would have reasonably expected success in making an mRNA composition encoding a SARS-CoV spike protein following well-known methods. (Ex. 1002, ¶150.) 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 additionally provides examples of the administration of protein-encoding mRNA formulated in lipid nanoparticles to express the encoded protein. (*E.g.*, *id.*, ¶942, 963, 995-99, 1000-01; Ex. 1002, ¶150; Ex. 1004, ¶¶72, 81.)

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

Schrum in view of Yang discloses or suggests this limitation for the reasons discussed in Section X.C.1.iii. (Ex. 1002, ¶151.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.3. (Ex. 1002, ¶152.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.4. (Ex. 1002, ¶153.)

5. Claim 6: "The composition of claim 4, wherein the mRNA further comprises a 5′ cap analog."

Schrum discloses this limitation for the reasons discussed in Section X.A.5. (Ex. 1002, ¶154.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.6. (Ex. 1002, ¶155.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.7. 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.7. (Ex. 1002, ¶156.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.8. (Ex. 1002, ¶157.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.9. (Ex. 1004, ¶¶67-73, 128; Ex. 1002, ¶158.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.10. (Ex. 1004, ¶¶74-82, 129; Ex. 1002, ¶159.)

11. Claim 16

For the reasons discussed below and in sections X.A.1 and X.C.1, Schrum and Yang disclose every limitation of claim 16. The POSA would have been motivated to combine Schrum and Yang with a reasonable expectation of success for the reasons discussed in Section X.C.1.

i) [16.pre] "A composition, comprising:"

Schrum discloses this limitation for the reasons discussed in Section X.A.1.i. (Ex. 1002, ¶160.)

ii) [16.a] "a messenger ribonucleic acid (mRNA)"

Schrum discloses this limitation for the reasons discussed in Section X.A.1.ii. (Ex. 1002, ¶161.)

iii) [16.b] "comprising a 5′ untranslated region (UTR),"

Schrum discloses this limitation for the reasons discussed in Section X.A.3. (Ex. 1002, ¶162.)

iv) [16.c] "an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit"

Schrum in view of Yang discloses or suggests this limitation for the reasons discussed in Section X.C.1.iii. (Ex. 1002, ¶163.)

v) [16.d] "a 3′ UTR,"

Schrum discloses this limitation for the reasons discussed in Section X.A.3. (Ex. 1002, ¶164.)

vi) [16.e] "and a poly(A) tail,"

Schrum discloses this limitation for the reasons discussed in Section X.A.4. (Ex. 1002, ¶165.)

vii) [16.f] "formulated in a lipid nanoparticle that comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid."

Schrum discloses this limitation for the reasons discussed in Section X.A.9 and X.A.10. (Ex. 1004, ¶¶67-82; 136; Ex. 1002, ¶166.)

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

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

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

Schrum discloses this limitation for the reasons discussed in Section X.A.8. (Ex. 1002, ¶168.)

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

Schrum discloses this limitation for the reasons discussed in Sections X.A.6 and X.A.7. (Ex. 1002, ¶169.)

15. Claim 26

For the reasons discussed below and in sections X.A.1 and X.C.1, Schrum and Yang disclose every limitation of claim 26. The POSA would have been motivated to combine Schrum and Yang with a reasonable expectation of success for the reasons discussed in Section X.C.1.

i) [26.pre] "A lipid nanoparticle, comprising:"

Schrum discloses this limitation for the reasons discussed in Section X.A.1.iv. (Ex. 1004, ¶62-66, 137; Ex. 1002, ¶170.)

ii) [26.a] "a messenger ribonucleic acid (mRNA)"

Schrum discloses this limitation for the reasons discussed in Section X.A.1.ii. (Ex. 1002, ¶171.)

iii) [26.b] "comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit;"

Schrum in view of Yang discloses or suggests this limitation for the reasons discussed in Section X.A.1.iii. (Ex. 1002, ¶172.)

iv) [26.c] "wherein the lipid nanoparticle comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid."

Schrum discloses this limitation for the reasons discussed in Section X.A.9 and X.A.10. (Ex. 1004, ¶¶67-82, 140; Ex. 1002, ¶173.)

D. Ground 4: Schrum in View of Altmeyer Renders Claims 1, 2, 4-6, 8-12, 16, 17, 20, 21, and 26 Obvious

1. Claim 1

i) [1.pre] "A composition comprising:"

Schrum discloses this limitation for the reasons discussed in Section X.A.1.i. (Ex. 1002, ¶¶174-75.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.1.ii. (Ex. 1002, ¶176.)

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, including by incorporating Geall. As yet another exemplary teaching, Schrum in view of Altmeyer discloses or suggests this limitation. (Ex. 1002, ¶¶177-81.)

Schrum discloses modified mRNA molecules encoding an immunogen and their use in a vaccine "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.) A POSA would understand Altmeyer's disclosure

of "RNA sequences" encoding a SARS-CoV spike protein as encompassing messenger RNA. (Ex. 1002, ¶179.) The immunostimulatory results obtained in Altmeyer via administration of an RNA vaccine encoding the SARS-CoV spike protein, consistent with the knowledge that the spike protein had "been selected as an important target for vaccine and anti-viral development," provided good reason for a POSA to incorporate such protein as the encoded immunogen in the mRNA vaccine disclosed in Schrum. (Ex. 1031 at 229; Ex. 1002, ¶181.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.1.iv. (Ex. 1004, ¶¶62-66, 145; Ex. 1002, ¶182.)

* * *

It would have been obvious for a POSA to combine the teachings of Schrum and Altmeyer to arrive at the composition of claim 1. (Ex. 1002, ¶¶183-84.) Schrum discloses an mRNA vaccine—having identical mRNA and lipid nanoparticle components to that claimed in the '600 patent—encoding an immunogen. 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. Combining these known elements to achieve an mRNA composition, *i.e.*, an mRNA vaccine, encoding the S protein of SARS-CoV 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, ¶183.) 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. As discussed above, the immunogen (SARS-CoV S protein) would be encoded by the ORF of the mRNA. (*Supra* Section X.A.1.iii.)

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. 7-8.) 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 861; *see also* Ex. 1031 at 229.)

A POSA would further have reasonably expected success in making an mRNA composition encoding a SARS-CoV spike protein following well-known

methods. (Ex. 1002, ¶184.) 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 additionally provides examples of the administration of protein-encoding mRNA formulated in lipid nanoparticles to express the encoded protein. (*E.g.*, *id.*, ¶942, 963, 995-99, 1000-01; Ex. 1002, ¶184; Ex. 1004, ¶¶72, 81.)

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

Schrum in view of Altmeyer discloses or suggests this limitation for the reasons discussed in Section X.C.1.iii. (Ex. 1002, ¶185.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.3. (Ex. 1002, ¶186.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.4. (Ex. 1002, ¶187.)

5. Claim 6: "The composition of claim 4, wherein the mRNA further comprises a 5′ cap analog."

Schrum discloses this limitation for the reasons discussed in Section X.A.5. (Ex. 1002, ¶188.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.6. (Ex. 1002, ¶189.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.7. (Ex. 1002, ¶190.) 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.7.

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

Schrum discloses this limitation for the reasons discussed in Section X.A.8. (Ex. 1002, ¶191.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.9. (Ex. 1004, ¶67-73, 146; Ex. 1002, ¶192.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.10. (Ex. 1004, ¶¶74-82, 147; Ex. 1002, ¶193.)

11. Claim 16

For the reasons discussed below and in sections X.A.1 and X.D.1, Schrum and Altmeyer disclose every limitation of claim 16. The POSA would have been motivated to combine Schrum and Altmeyer with a reasonable expectation of success for the reasons discussed in Section X.D.1.

i) [16.pre] "A composition, comprising:"

Schrum discloses this limitation for the reasons discussed in Section X.A.1.i. (Ex. 1002, ¶194.)

ii) [16.a] "a messenger ribonucleic acid (mRNA)"

Schrum discloses this limitation for the reasons discussed in Section X.A.1.ii. (Ex. 1002, ¶195.)

iii) [16.b] "comprising a 5′ untranslated region (UTR),"

Schrum discloses this limitation for the reasons discussed in Section X.A.3. (Ex. 1002, ¶196.)

iv) [16.c] "an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit"

Schrum in view of Altmeyer discloses or suggests this limitation for the reasons discussed in Section X.C.1.iii. (Ex. 1002, ¶197.)

v) [16.d] "a 3′ UTR,"

Schrum discloses this limitation for the reasons discussed in Section X.A.3. (Ex. 1002, ¶198.)

vi) [16.e] "and a poly(A) tail,"

Schrum discloses this limitation for the reasons discussed in Section X.A.4. (Ex. 1002, ¶199.)

vii) [16.f] "formulated in a lipid nanoparticle that comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid."

Schrum discloses this limitation for the reasons discussed in Section X.A.9 and X.A.10. (Ex. 1004, ¶¶ 67-82, 154; Ex. 1002, ¶200.)

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

Schrum in view of Altmeyer discloses or suggests this limitation for the reasons discussed in Section X.C.1.iii. (Ex. 1002, ¶201.)

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

Schrum discloses this limitation for the reasons discussed in Section X.A.8. (Ex. 1002, ¶202.)

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

Schrum discloses this limitation for the resaons discussed in Sections X.A.6 and X.A.7. (Ex. 1002, ¶203.)

15. Claim 26

For the reasons discussed below and in sections X.A.1 and X.D.1, Schrum and Altmeyer disclose every limitation of claim 26. The POSA would have been motivated to combine Schrum and Altmeyer with a reasonable expectation of success for the reasons discussed in Section X.D.1.

i) [26.pre] "A lipid nanoparticle, comprising:"

Schrum discloses this limitation for the reasons discussed in Section X.A.1.iv. (Ex. 1004, ¶¶62-66, 155; Ex. 1002, ¶204.)

ii) [26.a] "a messenger ribonucleic acid (mRNA)"

Schrum discloses this limitation for the reasons discussed in Section X.A.1.ii. (Ex. 1002, ¶205.)

iii) [26.b] "comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit;"

Schrum in view of Altmeyer discloses or suggests this limitation for the reasons discussed in Section X.A.1.iii. (Ex. 1002, ¶206.)

iv) [26.c] "wherein the lipid nanoparticle comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid."

Schrum discloses this limitation for the reasons discussed in Section X.A.9 and X.A.10. (Ex. 1004, ¶¶67-82, 158; Ex. 1002, ¶207.)

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 Investments, 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 Glob. 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 '600 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 of the related '600 patent, 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. 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 '600 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 only a restriction requirement and did not issue a single rejection—whether on the basis of prior art or otherwise—during prosecution of the application that led to the '600 patent. (*See* Ex. 1008 at 449-454 of 507.) Patent Owner overcame the restriction requirement by electing the composition claims that were then allowed to issue without further rejection. (*See* Ex. 1008 at 456-460 of 507.) Issuing no rejections, 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. June 11, 2021) (finding these factors to weigh against discretionary

denial where "no prior art was asserted by the Examiner during prosecution . . . and we are directed to no substantive evaluation by the Examiner or the applicant of any reference."). 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, 2, 4-6, 8-12, 16-17, 20-21, and 26 of the '600 patent.

Respectfully submitted,

Dated: August 28, 2023

By: /David Krinsky/
David Krinsky (Reg. No. 72,339)
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. 10,702,600 contains, as measured by the word-processing system used to prepare this paper, 13,412 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: /David Krinsky/
David Krinsky (Reg. No. 72,339)
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. 10,702,600 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.
600 Atlantic Avenue
Boston, MA 02210

A courtesy copy was also sent by electronic mail to the Patent Owner's litigation counsel at the following addresses:

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