Petitioner's Demonstratives

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 Nos. 10,702,600 and 10,933,127

Cases: IPR2023-01358, IPR2023-01359

Oral Hearing: December 10, 2024

BioNTech-Pfizer Exhibit 1320

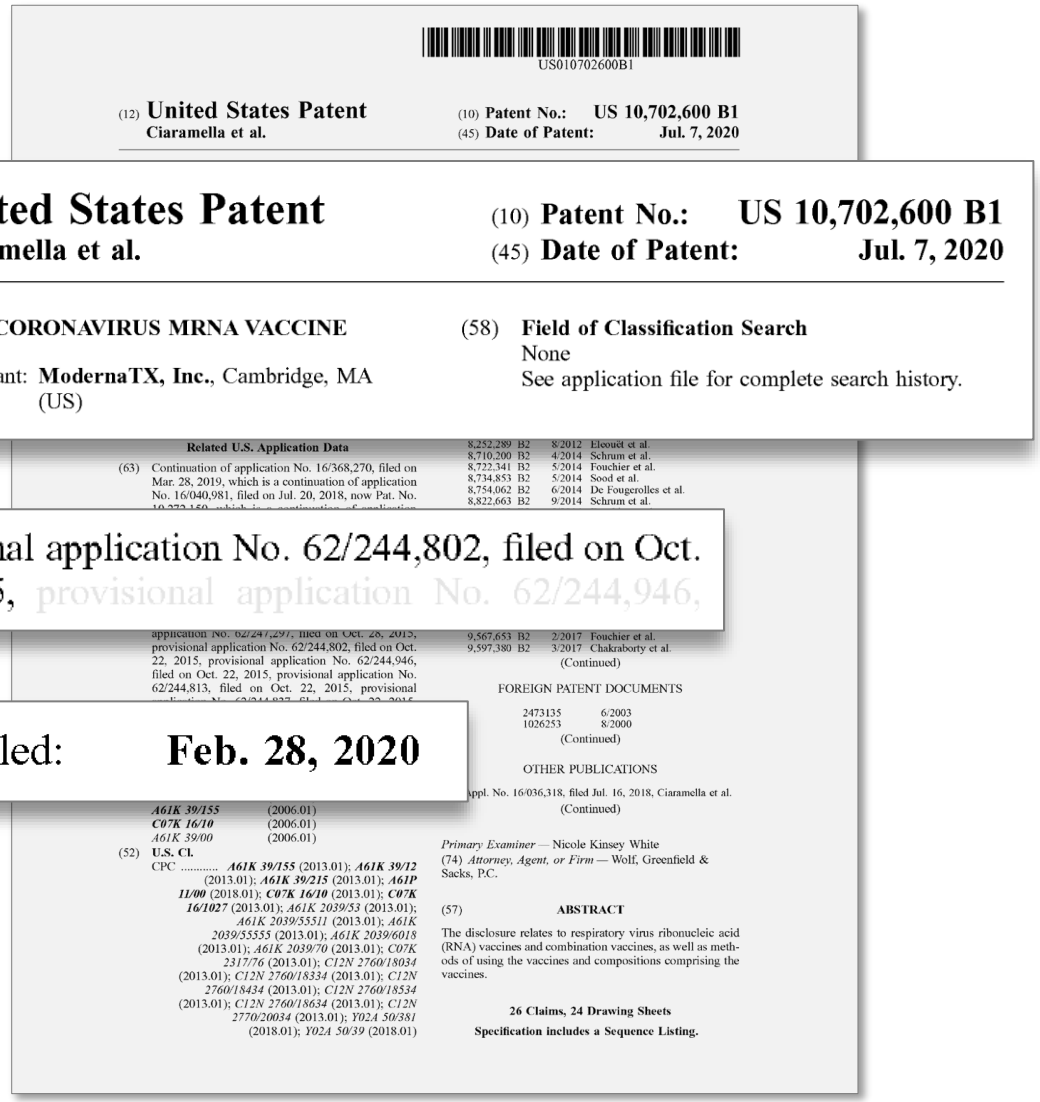
Agenda

- Overview of the challenged patents, the prior art & the instituted grounds
- Anticipation by Schrum (Ground 1)
- Obviousness in view of Schrum and Geall, Yang, or Altmeyer (Grounds 2-4)
- The testimony of Patent Owner's declarants should be afforded little weight

Agenda

- Overview of the challenged patents, the prior art & the instituted grounds
- Anticipation by Schrum (Ground 1)
- Obviousness in view of Schrum and Geall, Yang, or Altmeyer (Grounds 2-4)
- The testimony of Patent Owner's declarants should be afforded little weight

Challenged ’600 and ’127 Patents



US010702600B1

(12) **United States Patent**
Ciaramella et al.

(10) **Patent No.: US 10,702,600 B1**
(45) **Date of Patent: Jul. 7, 2020**

(54) **BETACORONAVIRUS MRNA VACCINE**

(71) Applicant: **ModernaTX, Inc.**, Cambridge, MA (US)

(58) **Field of Classification Search**
None
See application file for complete search history.

provisional application No. 62/244,802, filed on Oct. 22, 2015, provisional application No. 62/244,946,

Filed: **Feb. 28, 2020**

Related U.S. Application Data

(63) Continuation of application No. 16/368,270, filed on Mar. 28, 2019, which is a continuation of application No. 16/040,981, filed on Jul. 20, 2018, now Pat. No.

application No. 62/244,802, filed on Oct. 22, 2015, provisional application No. 62/244,946, filed on Oct. 22, 2015, provisional application No. 62/244,813, filed on Oct. 22, 2015, provisional

(52) **U.S. Cl.**
CPC ***A61K 39/155*** (2013.01); ***A61K 39/12*** (2013.01); ***A61K 39/215*** (2013.01); ***A61P 11/00*** (2018.01); ***C07K 16/10*** (2013.01); ***C07K 16/1027*** (2013.01); *A61K 2039/53* (2013.01); *A61K 2039/55511* (2013.01); *A61K 2039/55555* (2013.01); *A61K 2039/6018* (2013.01); *A61K 2039/70* (2013.01); *C07K 2317/76* (2013.01); *C12N 2760/18034* (2013.01); *C12N 2760/18334* (2013.01); *C12N 2760/18434* (2013.01); *C12N 2760/18534* (2013.01); *C12N 2760/18634* (2013.01); *C12N 2770/20034* (2013.01); *Y02A 50/381* (2018.01); *Y02A 50/39* (2018.01)

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Primary Examiner — Nicole Kinsey White
(74) *Attorney, Agent, or Firm* — Wolf, Greenfield & Sacks, P.C.

(57) **ABSTRACT**

The disclosure relates to respiratory virus ribonucleic acid (RNA) vaccines and combination vaccines, as well as methods of using the vaccines and compositions comprising the vaccines.

26 Claims, 24 Drawing Sheets
Specification includes a Sequence Listing.

Ex. 1001 (IPR2023-01358 (“-1358”))

US010933127B2

(12) **United States Patent**
Ciaramella et al.

(10) **Patent No.: US 10,933,127 B2**
(45) **Date of Patent: Mar. 2, 2021**

(54) **BETACORONAVIRUS MRNA VACCINE**

(71) Applicant: **ModernaTX, Inc.**, Cambridge, MA (US)

2317/76 (2013.01); *C12N 2760/18034* (2013.01); *C12N 2760/18334* (2013.01); *C12N 2760/18434* (2013.01); *C12N 2760/18534* (2013.01); *C12N 2760/18634* (2013.01); *C12N*

provisional application No. 62/244,802, filed on Oct. 22, 2015, provisional application No. 62/244,946,

Filed: **May 21, 2020**

US 2020/0282046 A1 Sep. 10, 2020

Related U.S. Application Data

PCT/US2016/058327, filed on Oct. 21, 2016.

(60) Provisional application No. 62/247,394, filed on Oct. 28, 2015, provisional application No. 62/247,362, filed on Oct. 28, 2015, provisional application No.

22, 2015.

(51) **Int. Cl.**
A61K 39/215 (2006.01)
A61K 39/12 (2006.01)
A61P 11/00 (2006.01)
A61K 39/155 (2006.01)
C07K 16/10 (2006.01)
A61K 39/00 (2006.01)

(52) **U.S. Cl.**
CPC ***A61K 39/155*** (2013.01); ***A61K 39/12*** (2013.01); ***A61K 39/215*** (2013.01); ***A61P 11/00*** (2018.01); ***C07K 16/10*** (2013.01); ***C07K 16/1027*** (2013.01); *A61K 2039/53* (2013.01); *A61K 2039/55511* (2013.01); *A61K 2039/55555* (2013.01); *A61K 2039/6018* (2013.01); *A61K 2039/70* (2013.01); *C07K*

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FOREIGN PATENT DOCUMENTS

2473135 6/2003
1026253 8/2000
(Continued)

OTHER PUBLICATIONS

Appl. No. 16/048,154, filed Jul. 27, 2018, Ciaramella et al.
(Continued)

Primary Examiner — Nicole Kinsey White
(74) *Attorney, Agent, or Firm* — Wolf, Greenfield & Sacks, P.C.

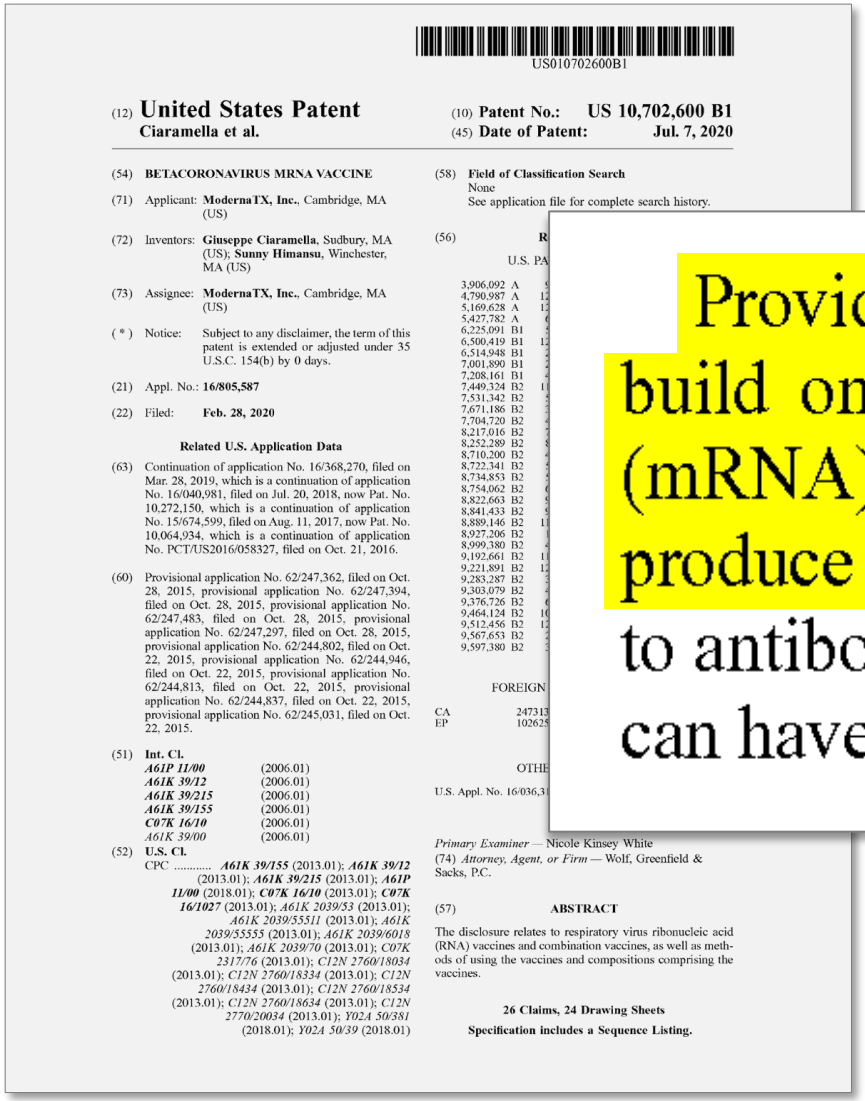
(57) **ABSTRACT**

The disclosure relates to respiratory virus ribonucleic acid (RNA) vaccines and combination vaccines, as well as methods of using the vaccines and compositions comprising the vaccines.

21 Claims, 24 Drawing Sheets
Specification includes a Sequence Listing.

Ex. 1001 (IPR2023-01359 (“-1359”))

Challenged ’600 and ’127 Patents



US010702600B1

(12) **United States Patent**
Ciaramella et al.

(10) **Patent No.: US 10,702,600 B1**
(45) **Date of Patent: Jul. 7, 2020**

(54) **BETACORONAVIRUS MRNA VACCINE**

(71) Applicant: **ModernaTX, Inc.**, Cambridge, MA (US)

(72) Inventors: **Giuseppe Ciaramella**, Sudbury, MA (US); **Sunny Himansu**, Winchester, MA (US)

(73) Assignee: **ModernaTX, Inc.**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **16/805,587**

(22) Filed: **Feb. 28, 2020**

Related U.S. Application Data

(63) Continuation of application No. 16/368,270, filed on Mar. 28, 2019, which is a continuation of application No. 16/040,981, filed on Jul. 20, 2018, now Pat. No. 10,272,150, which is a continuation of application No. 15/674,599, filed on Aug. 11, 2017, now Pat. No. 10,064,934, which is a continuation of application No. PCT/US2016/058327, filed on Oct. 21, 2016.

(60) Provisional application No. 62/247,362, filed on Oct. 28, 2015, provisional application No. 62/247,394, filed on Oct. 28, 2015, provisional application No. 62/247,483, filed on Oct. 28, 2015, provisional application No. 62/247,297, filed on Oct. 28, 2015, provisional application No. 62/244,802, filed on Oct. 22, 2015, provisional application No. 62/244,946, filed on Oct. 22, 2015, provisional application No. 62/244,813, filed on Oct. 22, 2015, provisional application No. 62/244,837, filed on Oct. 22, 2015, provisional application No. 62/245,031, filed on Oct. 22, 2015.

(51) **Int. Cl.**

A61P 11/00	(2006.01)
A61K 39/12	(2006.01)
A61K 39/215	(2006.01)
A61K 39/155	(2006.01)
C07K 16/10	(2006.01)
A61K 39/00	(2006.01)

(52) **U.S. Cl.**
CPC ***A61K 39/155*** (2013.01); ***A61K 39/12*** (2013.01); ***A61K 39/215*** (2013.01); ***A61P 11/00*** (2018.01); ***C07K 16/10*** (2013.01); ***C07K 16/1027*** (2013.01); *A61K 2039/53* (2013.01); *A61K 2039/55511* (2013.01); *A61K 2039/55555* (2013.01); *A61K 2039/6018* (2013.01); *A61K 2039/70* (2013.01); *C07K 2317/76* (2013.01); *C12N 2760/18034* (2013.01); *C12N 2760/18334* (2013.01); *C12N 2760/18434* (2013.01); *C12N 2760/18534* (2013.01); *C12N 2760/18634* (2013.01); *C12N 2770/20034* (2013.01); *Y02A 50/381* (2018.01); *Y02A 50/39* (2018.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **R**

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9,221,891 B2
9,283,287 B2
9,303,079 B2
9,376,726 B2
9,464,124 B2
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9,567,653 B2
9,597,380 B2

FOREIGN

CA 247313
EP 102625

OTHE

U.S. Appl. No. 16/036,31

Primary Examiner — Nicole Kinsey White
(74) *Attorney, Agent, or Firm* — Wolf, Greenfield & Sacks, P.C.

(57) **ABSTRACT**

The disclosure relates to respiratory virus ribonucleic acid (RNA) vaccines and combination vaccines, as well as methods of using the vaccines and compositions comprising the vaccines.

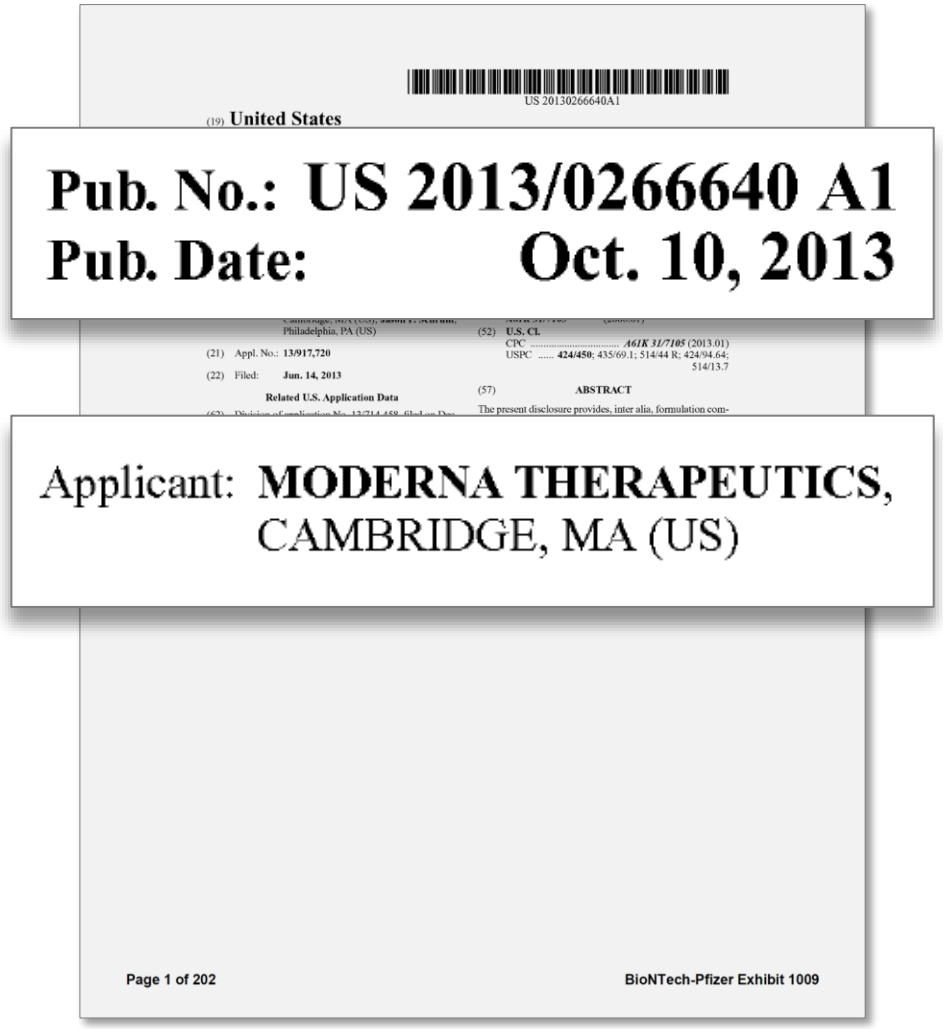
26 Claims, 24 Drawing Sheets

Specification includes a Sequence Listing.

Provided herein are ribonucleic acid (RNA) vaccines that build on the knowledge that RNA (e.g., messenger RNA (mRNA)) can safely direct the body’s cellular machinery to produce nearly any protein of interest, from native proteins to antibodies and other entirely novel protein constructs that can have therapeutic activity inside and outside of cells. The

Ex. 1001 (-1358) at 3:24-29; Ex. 1001(-1359) at 3:26-31

The "Schrum" Reference: US 2013/0266640


US 20130266640A1

(19) United States

Pub. No.: US 2013/0266640 A1

Pub. Date: Oct. 10, 2013

Philadelphia, PA (US)

(21) Appl. No.: 13/917,720

(22) Filed: Jun. 14, 2013

Related U.S. Application Data

(52) U.S. Cl.

CPC *A61K 31/7105* (2013.01)

USPC ..... 424/450; 435/69.1; 514/44 R; 424/94.64; 514/13.7

(57) ABSTRACT

The present disclosure provides, inter alia, formulation com-

Applicant: **MODERNA THERAPEUTICS**, CAMBRIDGE, MA (US)

Page 1 of 202

BioNTech-Pfizer Exhibit 1009

(57) **ABSTRACT**

The present disclosure provides, inter alia, formulation compositions comprising modified nucleic acid molecules which may encode a protein, a protein precursor, or a partially or fully processed form of the protein or a protein precursor. The formulation composition may further include a modified nucleic acid molecule and a delivery agent. The present

Ex. 1009, Cover

Schrum Was Abandoned on August 12, 2015

NOTIFICATION DATE	DELIVERY MODE
08/12/2015	ELECTRONIC

Notice of Abandonment	Application No.	Applicant(s)
	13/917,720	DE FOUGEROLLES ET AL.
	Examiner	**Art Unit**
	ARTHUR S. LEONARD	1633

is communication appears on the cover sheet with the correspondence address--

This application is abandoned in view of:

1. ☒ Applicant's failure to timely file a proper reply to the Office letter mailed on *14 January 2015*.
   (a) ☐ A reply was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply (including a total extension of time of _____ month(s)) which expired on _____.

7. ☒ The reason(s) below:

A telephone call was made to Mrs. Jennifer Bryan at (978) 448-8720 on Friday 8/7/2015 regarding the status of instant application, whereupon Mrs. Bryan stated that the Applicants were abandoning instant application.

Ex. 1039, 1-2

Schrum Describes mRNA Compositions Formulated in Lipid Nanoparticles

US 20130266640A1

(19) **United States**

(12) **Patent Application Publication**
de Fougerolles et al.

(10) **Pub. No.: US 2013/0266640 A1**
(43) **Pub. Date: Oct. 10, 2013**

(54) **MODIFIED NUCLEOSIDE, NUCLEOTIDE, AND NUCLEIC ACID COMPOSITIONS**

(71) Applicant: **MODERNA THERAPEUTICS**, CAMBRIDGE, MA (US)

(72) Inventors: **Antonin de Fougerolles**, Brookline, MA (US); **Kristy M. Wood**, Cambridge, MA (US); **Sayda M. Elbashir**, Cambridge, MA (US); **Noubar B. Afeyan**, Cambridge, MA (US); **Pedro Valencia**, Cambridge, MA (US); **Jason P. Schrum**, Philadelphia, PA (US)

(21) Appl. No.: **13/917,720**

(22) Filed: **Jun. 14, 2013**

Related U.S. Application Data

(62) Division of application No. 13/714,458, filed on Dec. 14, 2012.

(60) Provisional application No. 61/576,705, filed on Dec. 16, 2011, provisional application No. 61/618,957, filed on Apr. 2, 2012, provisional application No. 61/648,244, filed on May 17, 2012, provisional application No. 61/681,712, filed on Aug. 10, 2012, provisional application No. 61/696,381, filed on Sep. 4, 2012, provisional application No. 61/709,303, filed on Oct. 3, 2012, provisional application No. 61/712,490, filed on Oct. 11, 2012.

(30) **Foreign Application Priority Data**

Oct. 3, 2012 (US) PCT/US2012/058519

Publication Classification

(51) **Int. Cl.**
A61K 31/7105 (2006.01)

(52) **U.S. Cl.**
CPC ***A61K 31/7105*** (2013.01)
USPC ..... **424/450**; 435/69.1; 514/44 R; 424/94.64; 514/13.7

(57) **ABSTRACT**

The present disclosure provides, inter alia, formulation compositions comprising modified nucleic acid molecules which may encode a protein, a protein precursor, or a partially or fully processed form of the protein or a protein precursor. The formulation composition may further include a modified nucleic acid molecule and a delivery agent. The present invention further provides nucleic acids useful for encoding polypeptides capable of modulating a cell's function and/or activity.

Page 1 of 202

BioNTech-Pfizer Exhibit 1009

SUMMARY OF THE INVENTION

[0004] The present disclosure provides, inter alia, formulation compositions comprising modified nucleic acid molecules which may encode a protein, a protein precursor, or a partially or fully processed form of the protein or a protein precursor. The formulation compositions may further include a modified nucleic acid molecule and a delivery agent. The

[0005] In one aspect a method of producing a polypeptide of interest in a mammalian cell or tissue is described. The method comprises contacting the mammalian cell or tissue with a formulation comprising a modified mRNA encoding a polypeptide of interest. The formulation may be, but is not limited to, nanoparticles, poly(lactic-co-glycolic acid)

[0006] In one embodiment, the formulation comprising the modified mRNA is a nanoparticle which may comprise at least one lipid. The lipid may be selected from, but is not

[0008] The formulations of modified mRNA may comprise a fusogenic lipid, cholesterol and a PEG lipid. The formulation may have a molar ratio 50:10:38.5:1.5-3.0 (cationic lipid: fusogenic lipid:cholesterol:PEG lipid). The PEG lipid may be selected from, but is not limited to PEG-c-DOMG, PEG-DMG. The fusogenic lipid may be DSPC.

Ex. 1009, ¶¶ 4-6, 8

Schrum Describes Using Its mRNA Compositions as Vaccines Encoding an Immunogen

US 20130266640A1

(19) **United States**

(12) **Patent Application Publication**
de Fougerolles et al.

(10) **Pub. No.: US 2013/0266640 A1**
(43) **Pub. Date: Oct. 10, 2013**

(54) **MODIFIED NUCLEOSIDE, NUCLEOTIDE, AND NUCLEIC ACID COMPOSITIONS**

(71) Applicant: **MODERNA THERAPEUTICS**, CAMBRIDGE, MA (US)

(72) Inventors: **Antonin de Fougerolles**, Brookline, MA (US); **Kristy M. Wood**, Cambridge, MA (US); **Sayda M. Elbashir**, Cambridge, MA (US); **Noubar B. Afeyan**, Cambridge, MA (US); **Pedro Valencia**, Cambridge, MA (US); **Jason P. Schrum**, Philadelphia, PA (US)

(21) Appl. No.: **13/917,720**

(22) Filed: **Jun. 14, 2013**

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(60) Provisional application No. 61/576,705, filed on Dec. 16, 2011, provisional application No. 61/618,957, filed on Apr. 2, 2012, provisional application No. 61/648,244, filed on May 17, 2012, provisional application No. 61/681,712, filed on Aug. 10, 2012, provisional application No. 61/696,381, filed on Sep. 4, 2012, provisional application No. 61/709,303, filed on Oct. 3, 2012, provisional application No. 61/712,490, filed on Oct. 11, 2012.

(30) **Foreign Application Priority Data**

Oct. 3, 2012 (US) PCT/US2012/058519

Publication Classification

(51) **Int. Cl.**
A61K 31/7105 (2006.01)

(52) **U.S. Cl.**
CPC ***A61K 31/7105*** (2013.01)
USPC ..... **424/450**; 435/69.1; 514/44 R; 424/94.64; 514/13.7

(57) **ABSTRACT**

The present disclosure provides, inter alia, formulation compositions comprising modified nucleic acid molecules which may encode a protein, a protein precursor, or a partially or fully processed form of the protein or a protein precursor. The formulation composition may further include a modified nucleic acid molecule and a delivery agent. The present invention further provides nucleic acids useful for encoding polypeptides capable of modulating a cell's function and/or activity.

Page 1 of 202

BioNTech-Pfizer Exhibit 1009

Activation of the Immune Response: Vaccines

[0340] In one embodiment of the present invention, mRNA molecules may be used to elicit or provoke an immune response in an organism. The mRNA molecules to be delivered may encode an immunogenic peptide or polypeptide and may encode more than one such peptide or polypeptide.

* * *

[0342] In one embodiment, the modified nucleic acid molecules and/or mmRNA of the invention may encode an immunogen. The delivery of modified nucleic acid molecules and/or mmRNA encoding an immunogen may activate the immune response. As a non-limiting example, the modified nucleic acid molecules and/or mmRNA encoding an immunogen may be delivered to cells to trigger multiple innate response pathways (see International Pub. No. WO2012006377; herein incorporated by reference in its entirety). As another non-limiting example, the modified nucleic acid molecules and mmRNA of the present invention encoding an immunogen may be delivered to a vertebrate in a dose amount large enough to be immunogenic to the vertebrate (see International Pub. No. WO2012006372 and WO2012006369; each of which is herein incorporated by reference in their entirety).

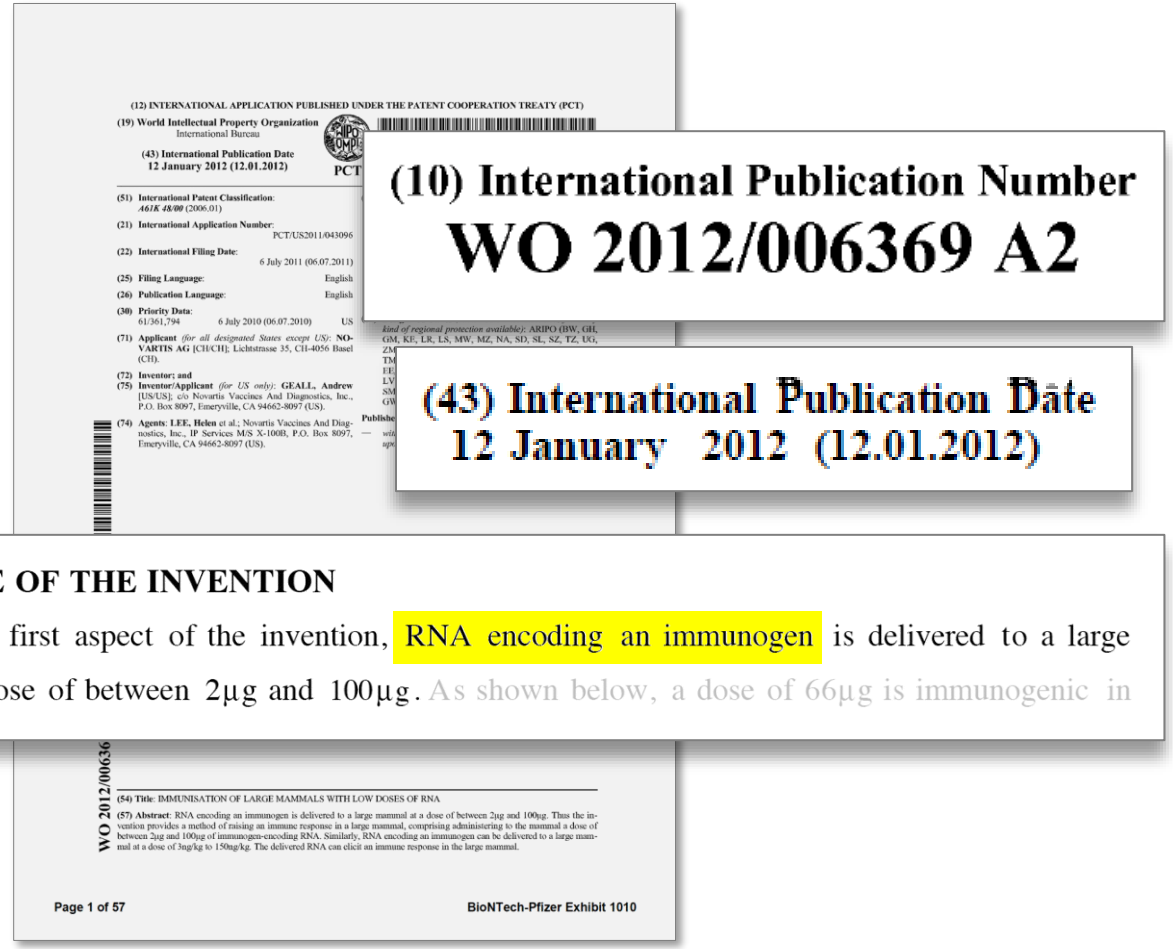
Ex. 1009, ¶¶ 340, 342

Schrum Incorporates Geall "in [its] entirety" & Geall Likewise Describes RNA Vaccines Encoding an Immunogen

Schrum

[0342] In one embodiment, the modified nucleic acid molecules and/or mmRNA of the invention may encode an immunogen. The delivery of modified nucleic acid molecules and/or mmRNA encoding an immunogen may activate the immune response. As a non-limiting example, the modified nucleic acid molecules and/or mmRNA encoding an immunogen may be delivered to cells to trigger multiple innate response pathways (see International Pub. No. WO2012006377; herein incorporated by reference in its entirety). As another non-limiting example, the modified nucleic acid molecules and mmRNA of the present invention encoding an immunogen may be delivered to a vertebrate in a dose amount large enough to be immunogenic to the vertebrate (see International Pub. No. WO2012006372 and WO2012006369; each of which is herein incorporated by reference in their entirety).

Ex. 1009, ¶ 342


(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 January 2012 (12.01.2012)

(10) International Publication Number
WO 2012/006369 A2

(43) International Publication Date
12 January 2012 (12.01.2012)

DISCLOSURE OF THE INVENTION

According to a first aspect of the invention, RNA encoding an immunogen is delivered to a large mammal at a dose of between 2µg and 100µg. As shown below, a dose of 66µg is immunogenic in

(54) Title: IMMUNISATION OF LARGE MAMMALS WITH LOW DOSES OF RNA

(57) Abstract: RNA encoding an immunogen is delivered to a large mammal at a dose of between 2µg and 100µg. Thus the invention provides a method of raising an immune response in a large mammal, comprising administering to the mammal a dose of between 2µg and 100µg of immunogen-encoding RNA. Similarly, RNA encoding an immunogen can be delivered to a large mammal at a dose of 3ng/kg to 150ng/kg. The delivered RNA can elicit an immune response in the large mammal.

Page 1 of 57

BioNTech-Pfizer Exhibit 1010

Ex. 1010 at Cover, 1:23-25

Dr. Griffin Explained How a POSA Reads Schrum's Interconnected Teachings

Daniel Griffin, M.D., Ph.D.

1. "I started reading Schrum. And I'm reading the beginning of Schrum where I get an overview. Then, I move onto where I am taught about modified mRNA. I am taught about delivery systems, including LNP. Then, after a very long section on the nucleotide modifications, when I'm wondering what I'm going to do with this technology."

2. "I then come across a section that starts bottom of the right page` just right above paragraph 340, where I am now taught I can use this technology to make a vaccine."

3. "I am directed to reference Geall, which is incorporated in its entirety as if it were stapled to the back of Schrum. There's a list of pathogens for which I can use this technology to make a vaccine, and in the list of pathogens is coronavirus, which is in the list of top ten pathogens of emerging pathogens of pandemic potential in 2015."

4. "As I'm reading this as a POSA, and I see not only is coronavirus mentioned on the bottom of page 19, but specifically the S protein is called out as a protein that I can make with this technology in vaccine design."

Ex. 2114 at 72:17-73:20

Schrum Provides, in a Single Embodiment, mRNA-LNP Vaccines

[0397] In one embodiment, an immune response may be elicited by delivering a lipid nanoparticle which may include a nanospecies, a polymer and an immunogen. (U.S. Publication No. 20120189700 and International Publication No. WO2012099805; each of which is herein incorporated by reference in their entirety). The polymer may encapsulate the nanospecies or partially encapsulate the nanospecies. The immunogen may be a recombinant protein, a modified RNA described herein. In one embodiment, the lipid nanoparticle may be formulated for use in a vaccine such as, but not limited to, against a pathogen.

Ex. 1009, ¶ 397

Schrum's Written Disclosure & Claims

SUMMARY OF THE INVENTION

[0004] The present disclosure provides, inter alia, formulation compositions comprising modified nucleic acid molecules which may encode a protein, a protein precursor, or a partially or fully processed form of the protein or a protein precursor. The formulation compositions may further include a modified nucleic acid molecule and a delivery agent. The

[0005] In one aspect a method of producing a polypeptide of interest in a mammalian cell or tissue is described. The method comprises contacting the mammalian cell or tissue with a formulation comprising a modified mRNA encoding a polypeptide of interest. The formulation may be, but is not limited to, nanoparticles, poly(lactic-co-glycolic acid)

[0006] In one embodiment, the formulation comprising the modified mRNA is a nanoparticle which may comprise at least one lipid. The lipid may be selected from, but is not

[0008] The formulations of modified mRNA may comprise a fusogenic lipid, cholesterol and a PEG lipid. The formulation may have a molar ratio 50:10:38.5:1.5-3.0 (cationic lipid:fusogenic lipid:cholesterol:PEG lipid). The PEG lipid may be selected from, but is not limited to PEG-c-DOMG, PEG-DMG. The fusogenic lipid may be DSPC.

Ex. 1009, ¶¶ 4-6, 8

What is claimed is:

1. A method of producing a polypeptide of interest in a mammalian cell or tissue, the method comprising, contacting said mammalian cell or tissue with a formulation comprising a modified mRNA encoding the polypeptide of interest, wherein the formulation is selected from the group consisting of nanoparticles, poly(lactic-co-glycolic acid) (PLGA) microspheres, lipidoid, lipoplex, liposome, polymers, carbohydrates (including simple sugars), cationic lipids, fibrin gel, fibrin hydrogel, fibrin glue, fibrin sealant, fibrinogen, thrombin, rapidly eliminated lipid nanoparticles (reLNPs) and combinations thereof.

3. The method of claim **1**, wherein the formulation comprising the modified mRNA is a nanoparticle and wherein said nanoparticle comprises at least one lipid.

11. The method of claim **7**, wherein the nanoparticle formulation comprising the modified mRNA further comprises a fusogenic lipid, cholesterol, and a PEG lipid.

12. The method of claim **11**, wherein the nanoparticle formulation comprising the modified mRNA has a molar ratio of 50:10:38.5:1.5-3.0 (Cationic Lipid:fusogenic lipid:Cholesterol:PEG lipid).

Ex. 1009, Claims 1, 3, 11-12

Challenged Claims Broadly Recite What Schrum Already Disclosed

1. A composition, comprising: a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit formulated in a lipid nanoparticle.

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

What is claimed:

- mRNA encoding a protein
- Where the mRNA is formulated in a lipid nanoparticle
- Where the encoded protein is a betacoronavirus S protein
- Administering the mRNA-LNP formulation to induce an immune response to the encoded immunogen ('127 patent)

Schrum's Claims Compared to the Challenged Claims

Schrum

What is claimed is:

1. A method of producing a polypeptide of interest in a mammalian cell or tissue, the method comprising, contacting said mammalian cell or tissue with a formulation comprising a modified mRNA encoding the polypeptide of interest, wherein the formulation is selected from the group consisting of nanoparticles, poly(lactic-co-glycolic acid) (PLGA) microspheres, lipidoid, lipoplex, liposome, polymers, carbohydrates (including simple sugars), cationic lipids, fibrin gel, fibrin hydrogel, fibrin glue, fibrin sealant, fibrinogen, thrombin, rapidly eliminated lipid nanoparticles (reLNPs) and combinations thereof.

11. The method of claim **7**, wherein the nanoparticle formulation comprising the modified mRNA further comprises a fusogenic lipid, cholesterol, and a PEG lipid.

12. The method of claim **11**, wherein the nanoparticle formulation comprising the modified mRNA has a molar ratio of 50:10:38.5:1.5-3.0 (Cationic Lipid:fusogenic lipid:Cholesterol:PEG lipid).

Ex. 1009, Claims 1, 11, 12

'600 and '127 Patents, Claim 1

1. A composition, comprising: a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit formulated in a lipid nanoparticle.

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

Ex. 1001 (-1358), Claim 1 ; Ex. 1001 (-1359), Claim 1

Under Patent Owner's Interpretation, the Breadth of the Claims Is Unbounded

- Any mRNA structure, with a coding region defined only by reference to the polypeptides it encodes
- The polypeptide is generically any betacoronavirus S protein – known, unknown, and even unknowable as of the alleged invention date
- The formulation of the mRNA is generically any lipid nanoparticle, known or unknown as of the alleged invention date (using the four known generic LNP components)
- The generic mRNA composition, when administered to any mammal, induces any level of immune response

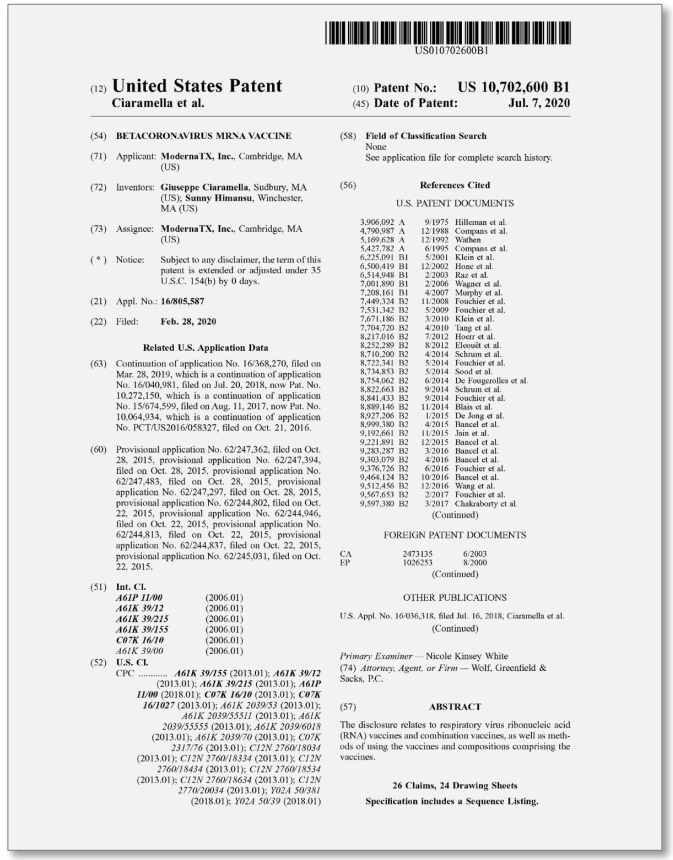
Instituted Grounds of Review

Ground 1	Anticipation by Schrum
Ground 2	Obviousness over Schrum and Geall
Ground 3	Obviousness over Schrum and Yang
Ground 4	Obviousness over Schrum and Altmeyer

Agenda

- Overview of the challenged patents, the prior art & the instituted grounds
- Anticipation by Schrum (Ground 1)
  - Schrum discloses each limitation as arranged in the challenged claims
  - Patent Owner fails to rebut anticipation by Schrum
- Obviousness in view of Schrum and Geall, Yang, or Altmeyer
- The testimony of Patent Owner's declarants should be afforded little weight

Disputed Claim of the ’600 Patent



US010702600B1

(12) **United States Patent**
Ciaramella et al.

(10) **Patent No.: US 10,702,600 B1**
(45) **Date of Patent: Jul. 7, 2020**

(54) **BETACORONAVIRUS MRNA VACCINE**

(71) Applicant: **ModernaTX, Inc.**, Cambridge, MA (US)

(72) Inventors: **Giuseppe Ciaramella**, Sudbury, MA (US); **Sunny Himansu**, Winchester, MA (US)

(73) Assignee: **ModernaTX, Inc.**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **16/805,587**

(22) Filed: **Feb. 28, 2020**

Related U.S. Application Data

(63) Continuation of application No. 16/368,270, filed on Mar. 28, 2019, which is a continuation of application No. 16/040,981, filed on Jul. 20, 2018, now Pat. No. 10,272,150, which is a continuation of application No. 15/674,599, filed on Aug. 11, 2017, now Pat. No. 10,064,934, which is a continuation of application No. PCT/US2016/058327, filed on Oct. 21, 2016.

(60) Provisional application No. 62/247,362, filed on Oct. 28, 2015, provisional application No. 62/247,394, filed on Oct. 28, 2015, provisional application No. 62/247,483, filed on Oct. 28, 2015, provisional application No. 62/247,297, filed on Oct. 28, 2015, provisional application No. 62/244,802, filed on Oct. 22, 2015, provisional application No. 62/244,946, filed on Oct. 22, 2015, provisional application No. 62/244,813, filed on Oct. 22, 2015, provisional application No. 62/244,837, filed on Oct. 22, 2015, provisional application No. 62/245,031, filed on Oct. 22, 2015.

(51) **Int. Cl.**

A61P 11/00	(2006.01)
A61K 39/12	(2006.01)
A61K 39/215	(2006.01)
A61K 39/155	(2006.01)
C07K 16/10	(2006.01)
A61K 39/00	(2006.01)

(52) **U.S. Cl.**
CPC ***A61K 39/155*** (2013.01); ***A61K 39/12*** (2013.01); ***A61K 39/215*** (2013.01); ***A61P 11/00*** (2018.01); ***C07K 16/10*** (2013.01); ***C07K 16/1027*** (2013.01); *A61K 2039/53* (2013.01); *A61K 2039/55511* (2013.01); *A61K 2039/55555* (2013.01); *A61K 2039/6018* (2013.01); *A61K 2039/70* (2013.01); *C07K 2317/76* (2013.01); *C12N 2760/18034* (2013.01); *C12N 2760/18334* (2013.01); *C12N 2760/18434* (2013.01); *C12N 2760/18534* (2013.01); *C12N 2760/18634* (2013.01); *C12N 2770/20034* (2013.01); *Y02A 50/381* (2018.01); *Y02A 50/39* (2018.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

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(Continued)

OTHER PUBLICATIONS

U.S. Appl. No. 16/036,318, filed Jul. 16, 2018, Ciaramella et al.

(Continued)

Primary Examiner — Nicole Kinsey White
(74) *Attorney, Agent, or Firm* — Wolf, Greenfield & Sacks, P.C.

(57) **ABSTRACT**

The disclosure relates to respiratory virus ribonucleic acid (RNA) vaccines and combination vaccines, as well as methods of using the vaccines and compositions comprising the vaccines.

26 Claims, 24 Drawing Sheets

Specification includes a Sequence Listing.

Ex. 1001 (-1358), Claim 1

1. A composition, comprising: a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit formulated in a lipid nanoparticle.

-1358 Petition (Paper 3), 22-27; -1358 Reply (Paper 59), 4-10, 4 n.4; 1358 Decision (Paper 17), 79-89

Schrum Anticipates Every Challenged Claim of the ’600 Patent

- Moderna cannot credibly dispute that Schrum discloses administering mRNA encoding a protein, where the mRNA is encapsulated in a lipid nanoparticle, as claimed

E.g., Decision (-1358), 34-35; Ex. 1009, ¶¶ 4-8, 378, 397

The only claim limitation alleged to be missing is a well-known, prior art antigen—the betacoronavirus S protein

1	mRNA encoding a protein	
2	Where the mRNA is formulated in a lipid nanoparticle	
3	Where the encoded protein is a betacoronavirus S protein	

-1358 Petition (Paper 3), 16-17, 22-23, 26-27; -1358 Reply (Paper 59), 4-6, 9-10; -1358 Decision (Paper 17), 34-36

Schrum Describes mRNA Compositions Formulated in Lipid Nanoparticles

1. mRNA encoding a protein
2. Where the mRNA is formulated in a lipid nanoparticle
3. Where the encoded protein is a betacoronavirus S protein

SUMMARY OF THE INVENTION

[0004] The present disclosure provides, inter alia, formulation compositions comprising modified nucleic acid molecules which may encode a protein, a protein precursor, or a partially or fully processed form of the protein or a protein precursor. The formulation compositions may further include a modified nucleic acid molecule and a delivery agent. The

[0005] In one aspect a method of producing a polypeptide of interest in a mammalian cell or tissue is described. The method comprises contacting the mammalian cell or tissue with a formulation comprising a modified mRNA encoding a polypeptide of interest. The formulation may be, but is not limited to, nanoparticles, poly(lactic-co-glycolic acid)

[0006] In one embodiment, the formulation comprising the modified mRNA is a nanoparticle which may comprise at least one lipid. The lipid may be selected from, but is not

[0008] The formulations of modified mRNA may comprise a fusogenic lipid, cholesterol and a PEG lipid. The formulation may have a molar ratio 50:10:38.5:1.5-3.0 (cationic lipid: fusogenic lipid:cholesterol:PEG lipid). The PEG lipid may be selected from, but is not limited to PEG-c-DOMG, PEG-DMG. The fusogenic lipid may be DSPC.

Ex. 1009, ¶¶ 4-6, 8

Schrum Discloses That the Encoded Protein Is an Immunogenic Polypeptide

The first application Schrum teaches of its disclosed mRNA composition technology is an mRNA vaccine encoding for an immunogenic protein

1	mRNA encoding a protein
2	Where the mRNA is formulated in a lipid nanoparticle
3	Where the encoded protein is a betacoronavirus S protein

Activation of the Immune Response: Vaccines

* * *

[0342] In one embodiment, the modified nucleic acid molecules and/or mmRNA of the invention may encode an immunogen. The delivery of modified nucleic acid molecules and/or mmRNA encoding an immunogen may activate the immune response. As a non-limiting example, the modified nucleic acid molecules and/or mmRNA encoding an immunogen may be delivered to cells to trigger multiple innate response pathways (see International Pub. No. WO2012006377; herein incorporated by reference in its entirety). As another non-limiting example, the modified nucleic acid molecules and mmRNA of the present invention encoding an immunogen may be delivered to a vertebrate in a dose amount large enough to be immunogenic to the vertebrate (see International Pub. No. WO2012006372 and WO2012006369; each of which is herein incorporated by reference in their entirety).

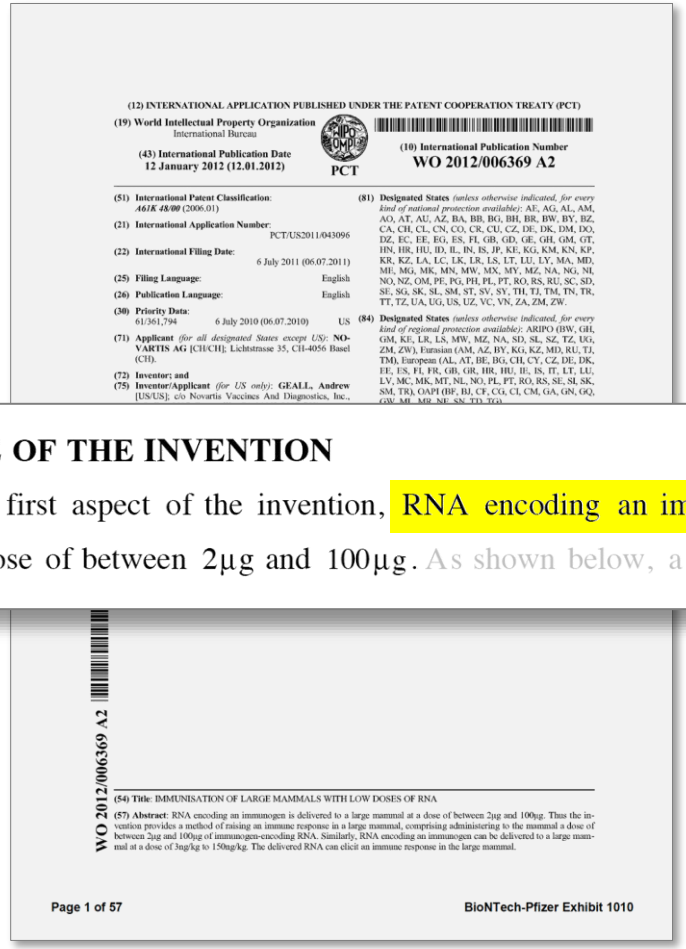
Ex. 1009, ¶ 342

Incorporated into Schrum "in [its] entirety," Geall Describes RNA Vaccines Encoding an Immunogen and Identifies Known Immunogens To Be Encoded

Schrum

[0342] In one embodiment, the modified nucleic acid molecules and/or mmRNA of the invention may encode an immunogen. The delivery of modified nucleic acid molecules and/or mmRNA encoding an immunogen may activate the immune response. As a non-limiting example, the modified nucleic acid molecules and/or mmRNA encoding an immunogen may be delivered to cells to trigger multiple innate response pathways (see International Pub. No. WO2012006377; herein incorporated by reference in its entirety). As another non-limiting example, the modified nucleic acid molecules and mmRNA of the present invention encoding an immunogen may be delivered to a vertebrate in a dose amount large enough to be immunogenic to the vertebrate (see International Pub. No. WO2012006372 and WO2012006369; each of which is herein incorporated by reference in their entirety).

Ex. 1009, ¶ 342



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 January 2012 (12.01.2012)

PCT

(10) International Publication Number
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(51) International Patent Classification:
A61K 48/00 (2006.01)

(21) International Application Number:
PCT/US2011/043096

(22) International Filing Date:
6 July 2011 (06.07.2011)

(25) Filing Language: English

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(30) Priority Data:
61/361,794 6 July 2010 (06.07.2010) US

(71) Applicant *(for all designated States except US)*: NOVARTIS AG [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: GEALL, Andrew [US/US]; c/o Novartis Vaccines And Diagnostics, Inc.,

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

DISCLOSURE OF THE INVENTION

According to a first aspect of the invention, RNA encoding an immunogen is delivered to a large mammal at a dose of between 2µg and 100µg. As shown below, a dose of 66µg is immunogenic in

WO 2012/006369 A2

(54) Title: IMMUNISATION OF LARGE MAMMALS WITH LOW DOSES OF RNA

(57) Abstract: RNA encoding an immunogen is delivered to a large mammal at a dose of between 2µg and 100µg. Thus the invention provides a method of raising an immune response in a large mammal, comprising administering to the mammal a dose of between 2µg and 100µg of immunogen-encoding RNA. Similarly, RNA encoding an immunogen can be delivered to a large mammal at a dose of 3ng/kg to 150ng/kg. The delivered RNA can elicit an immune response in the large mammal.

Page 1 of 57

BioNTech-Pfizer Exhibit 1010

Ex. 1010 (-1358) at Cover, 1:23-25

Schrum, through Geall's Incorporation, Discloses a Beta CoV S protein as the "Immunogenic" Polypeptide Encoded by Schrum's mRNA Vaccine

1. mRNA encoding a protein
2. Where the mRNA is formulated in a lipid nanoparticle
3. Where the encoded protein is a betacoronavirus S protein

Geall (WO '369)

The immunogen

RNA molecules used with the invention encode a polypeptide immunogen. After administration of

Coronavirus: Viral immunogens include, but are not limited to, those derived from a SARS coronavirus, avian infectious bronchitis (IBV), Mouse hepatitis virus (MHV), and Porcine transmissible gastroenteritis virus (TGEV). The coronavirus immunogen may be a spike polypeptide.

Ex. 1010 at 15:32-33, 19:27-30

Schrum anticipates Patent Owner's claims to an mRNA composition encoding for that previously disclosed immunogen

Geall's Disclosure of the S Protein Immunogen Is Incorporated in Schrum

ADVANCED DISPLAY SYSTEMS, INC., Plaintiff–Appellee,

and

Bao Gang Wu, Third Party Defendant–Appellee.

v.

KENT STATE UNIVERSITY and Kent Research Corporation, Defendants/Third–Party Plaintiffs–Appellants,

May 18, 2000

To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents.

Advanced Display Systems, Inc. v. Kent State University, 212 F.3d 1272, 1282 (Fed. Cir. 2000)

Schrum identifies:

1. **Where the incorporated material is found:** "WO2012006369" (Geall)
2. **What specific material it incorporates:** Geall's "entirety"

entirety). As another non-limiting example, the modified nucleic acid molecules and mmRNA of the present invention encoding an immunogen may be delivered to a vertebrate in a dose amount large enough to be immunogenic to the vertebrate (see International Pub. No. WO2012006372 and WO2012006369; each of which is herein incorporated by reference in their entirety).

Ex. 1009, ¶ 342

Federal Circuit Law Confirms That Geall's Disclosure of the S Protein Immunogen Is Incorporated into Schrum

Incorporation in *Paice*

The '817 application expressly incorporates Severinsky in the following passage:

> This application discloses a number of improvements over and enhancements to the hybrid vehicles disclosed in the inventor's *U.S. Pat. No. 5,343,970 (the "'970 patent") [Severinsky], which is incorporated herein by this reference.*

Incorporation by Schrum

entirety). As another non-limiting example, the modified nucleic acid molecules and mmRNA of the present invention encoding an immunogen may be delivered to a vertebrate in a dose amount large enough to be immunogenic to the vertebrate (see International Pub. No. WO2012006372 and WO2012006369; each of which is herein incorporated by reference in their entirety).

Ex. 1009, ¶ 342

PAICE LLC, The Abell Foundation, Inc., Appellants

v.

FORD MOTOR COMPANY, Appellee

Decided: February 1, 2018

The first sentence of this passage is broad and unambiguous. It states that Severinsky "*is*," without qualification, incorporated into the '817 application "by *this* reference"—i.e., the reference contained in the sentence. The sentence identifies with detailed particularity the specific material subject to incorporation (Severinsky, and not just particular portions thereof) and where that material can be found (U.S. Patent No. 5,343,970). Such language is plainly sufficient to incorporate Severinsky in its entirety.

Paice LLC v. Ford Motor Co., 881 F.3d 894, 907 (Fed. Cir. 2018)

-1358 Petition (Paper 3), 24-25; -1358 Reply (Paper 59), 6-8

Geall's Disclosure of the SARS-CoV S Protein Immunogen in a List Anticipates

In re Martin GLEAVE and Maxim Signaevsky.

No. 2008–1453.

United States Court of Appeals, Federal Circuit.

March 26, 2009.

In Wraight, the applicants listed every fifteen-base-long sense oligodeoxynucleotide in the IGFBP-2 gene. The list includes more than 1400 sequences . . . For the purposes of whether they are anticipatory, lists and genera are often treated differently under our case law. *Compare Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1376 (Fed. Cir. 2005) (rejecting "the notion that [a compound] cannot anticipate because it appears without special emphasis in a longer list") . . . In this case, Gleave's arguments fail for two reasons. First, Wraight expressly lists every possible fifteen-base-long oligodeoxynucleotide sequence in IGFBP-2, and under our precedent, this list anticipates Gleave's claims.

In re Gleave, 560 F.3d 1331, 1333, 1337-38 (Fed. Cir. 2009)

Coronavirus: Viral immunogens include, but are not limited to, those derived from a SARS coronavirus, avian infectious bronchitis (IBV), Mouse hepatitis virus (MHV), and Porcine transmissible gastroenteritis virus (TGEV). The coronavirus immunogen may be a spike polypeptide.

Ex. 1010 at 19:27-30

Geall, incorporated into Schrum, discloses a list of immunogens including the SARS-CoV S protein

Patent Owner Cannot Avoid Anticipation by Pointing to the Length of Geall's List of Immunogens

Patent Owner

portion of Geall, and Geall contains a ***seven-page*** list of potential immunogens, which includes no fewer than ***500*** different immunogens with non-viral targets such as bacteria, fungi, and parasites. *Id.*, 15:32-22:35. It lists 21 different families of

-1358 POR (Paper 41), 19

In re Martin GLEAVE and Maxim Signaevsky.

No. 2008–1453.

United States Court of Appeals, Federal Circuit.

March 26, 2009.

The examiner initially rejected the claims over the published PCT application 00/78341 of Wraight et al. ("Wraight"). In Wraight, the applicants listed every fifteen-base-long *sense* oligodeoxynucleotide in the IGFBP–2 gene. The list includes more than 1400 sequences. Wraight also

F.3d at 1377. In this case, Gleave's arguments fail for two reasons. First, Wraight expressly lists every possible fifteen-base-long oligodeoxynucleotide sequence in IGFBP–2, and under our precedent, this list anticipates Gleave's claims. Second,

In re Gleave, 560 F.3d at 1333, 1338

-1358 Petition (Paper 3), 25-26; -1358 Reply (Paper 59), 9-10; Decision (Paper 17), 85 n.39

Schrum Discloses Each Limitation as Arranged in the Claims

Dr. Griffin confirmed in detailed deposition testimony, elicited by Patent Owner, that a POSA would understand that Schrum discloses each limitation of the challenged claims as arranged therein

Daniel Griffin, M.D., Ph.D.

1. "I started reading Schrum. And I'm reading the beginning of Schrum where I get an overview. Then, I move onto where I am taught about modified mRNA. I am taught about delivery systems, including LNP. Then, after a very long section on the nucleotide modifications, when I'm wondering what I'm going to do with this technology."

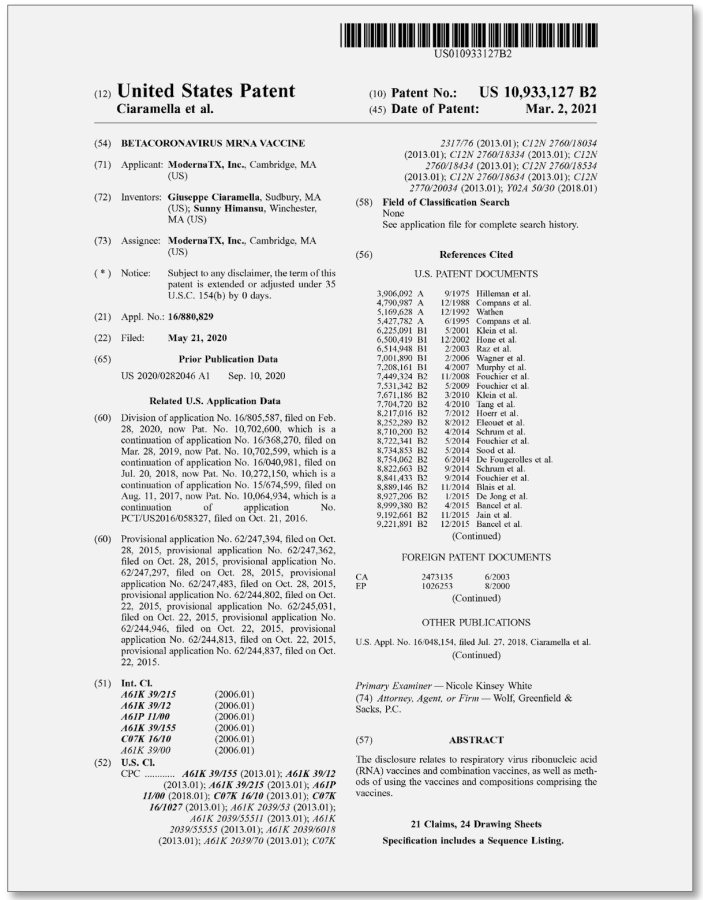
2. "I then come across a section that starts bottom of the right page, just right above paragraph 340, where I am now taught I can use this technology to make a vaccine."

3. "I am directed to reference Geall, which is incorporated in its entirety as if it were stapled to the back of Schrum. There's a list of pathogens for which I can use this technology to make a vaccine, and in the list of pathogens is coronavirus, which is in the list of top ten pathogens of emerging pathogens of pandemic potential in 2015."

4. "As I'm reading this as a POSA, and I see not only is coronavirus mentioned on the bottom of page 19, but specifically the S protein is called out as a protein that I can make with this technology in vaccine design."

Ex. 2114 at 72:17-73:20

Disputed Claims of the ’127 Patent



US010933127B2

(12) **United States Patent**
Ciaramella et al.

(10) **Patent No.: US 10,933,127 B2**
(45) **Date of Patent: Mar. 2, 2021**

(54) **BETACORONAVIRUS MRNA VACCINE**

(71) Applicant: **ModernaTX, Inc.**, Cambridge, MA (US)

(72) Inventors: **Giuseppe Ciaramella**, Sudbury, MA (US); **Sunny Himansu**, Winchester, MA (US)

(73) Assignee: **ModernaTX, Inc.**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **16/880,829**

(22) Filed: **May 21, 2020**

(65) **Prior Publication Data**

US 2020/0282046 A1 Sep. 10, 2020

Related U.S. Application Data

(60) Division of application No. 16/805,587, filed on Feb. 28, 2020, now Pat. No. 10,702,600, which is a continuation of application No. 16/368,270, filed on Mar. 28, 2019, now Pat. No. 10,702,599, which is a continuation of application No. 16/040,981, filed on Jul. 20, 2018, now Pat. No. 10,272,150, which is a continuation of application No. 15/674,599, filed on Aug. 11, 2017, now Pat. No. 10,064,934, which is a continuation of application No. PCT/US2016/058327, filed on Oct. 21, 2016.

(60) Provisional application No. 62/247,394, filed on Oct. 28, 2015, provisional application No. 62/247,362, filed on Oct. 28, 2015, provisional application No. 62/247,297, filed on Oct. 28, 2015, provisional application No. 62/247,483, filed on Oct. 28, 2015, provisional application No. 62/244,802, filed on Oct. 22, 2015, provisional application No. 62/245,031, filed on Oct. 22, 2015, provisional application No. 62/244,946, filed on Oct. 22, 2015, provisional application No. 62/244,813, filed on Oct. 22, 2015, provisional application No. 62/244,837, filed on Oct. 22, 2015.

(51) **Int. Cl.**

A61K 39/215	(2006.01)
A61K 39/12	(2006.01)
A61P 11/00	(2006.01)
A61K 39/155	(2006.01)
C07K 16/10	(2006.01)
A61K 39/00	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 39/155*** (2013.01); ***A61K 39/12*** (2013.01); ***A61K 39/215*** (2013.01); ***A61P 11/00*** (2018.01); ***C07K 16/10*** (2013.01); ***C07K 16/1027*** (2013.01); *A61K 2039/53* (2013.01); *A61K 2039/55511* (2013.01); *A61K 2039/55555* (2013.01); *A61K 2039/6018* (2013.01); *A61K 2039/70* (2013.01); *C07K 2317/76* (2013.01); *C12N 2760/18034* (2013.01); *C12N 2760/18334* (2013.01); *C12N 2760/18434* (2013.01); *C12N 2760/18534* (2013.01); *C12N 2760/18634* (2013.01); *C12N 2770/20034* (2013.01); *Y02A 50/30* (2018.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

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(Continued)

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EP	1026253	8/2000

(Continued)

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U.S. Appl. No. 16/048,154, filed Jul. 27, 2018, Ciaramella et al.
(Continued)

Primary Examiner — Nicole Kinsey White
(74) *Attorney, Agent, or Firm* — Wolf, Greenfield & Sacks, P.C.

(57) **ABSTRACT**

The disclosure relates to respiratory virus ribonucleic acid (RNA) vaccines and combination vaccines, as well as methods of using the vaccines and compositions comprising the vaccines.

21 Claims, 24 Drawing Sheets
Specification includes a Sequence Listing.

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

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

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

Ex. 1001 (-1359), Claims 1, 3

Schrum Anticipates Every Challenged Claim of the ’127 Patent

- Schrum discloses a composition comprising mRNA encoding for a betacoronavirus S protein formulated in a lipid nanoparticle, *i.e.* each limitation of the challenged claims of the ’600 patent

The only additional language in the claims of the ’127 patent is the use of such a composition to induce an immune response, but Schrum discloses this, too

1	mRNA encoding a protein	Already required by the ’600 patent
2	Where the mRNA is formulated in a lipid nanoparticle	
3	Where the encoded protein is a betacoronavirus S protein	
4	Administering the mRNA-LNP formulation to induce any level of immune response to the encoded immunogen	Only additional language found in the ’127 patent

-1359 Petition (Paper 1), 25; -1359 Reply (Paper 59), 4-6, 9-10; -1359 Decision (Paper 18), 80-81

Schrum Teaches the Additional Language of the Challenged Claims of the '127 Patent

1. mRNA encoding a protein
2. Encapsulating that mRNA in a lipid nanoparticle
3. Where the mRNA is formulated in a lipid nanoparticle
4. Administering the mRNA-LNP formulation to induce an immune response to the encoded immunogen

Activation of the Immune Response: Vaccines

[0340] In one embodiment of the present invention, mRNA molecules may be used to elicit or provoke an immune response in an organism. The mRNA molecules to be delivered may encode an immunogenic peptide or polypeptide and may encode more than one such peptide or polypeptide.

* * *

[0342] In one embodiment, the modified nucleic acid molecules and/or mmRNA of the invention may encode an immunogen. The delivery of modified nucleic acid molecules and/or mmRNA encoding an immunogen may activate the immune response. As a non-limiting example, the modified nucleic acid molecules and/or mmRNA encoding an immunogen may be delivered to cells to trigger multiple innate response pathways (see International Pub. No. WO2012006377; herein incorporated by reference in its entirety). As another non-limiting example, the modified nucleic acid molecules and mmRNA of the present invention encoding an immunogen may be delivered to a vertebrate in a dose amount large enough to be immunogenic to the vertebrate (see International Pub. No. WO2012006372 and WO2012006369; each of which is herein incorporated by reference in their entirety).

Ex. 1009, ¶¶ 340, 342

-1359 Petition (Paper 1), 25, 28-29; -1359 Reply (Paper 59), 4-6, 9-10; -1359 Decision (Paper 18), 35-36

Geall, Incorporated into Schrum, Teaches Inducing an Immune Response to the Encoded Immunogen, Including Against Disclosed SARS-CoV S Protein Immunogen

Schrum

[0342] In one embodiment, the modified nucleic acid molecules and/or mmRNA of the invention may encode an immunogen. The delivery of modified nucleic acid molecules and/or mmRNA encoding an immunogen may activate the immune response. As a non-limiting example, the modified nucleic acid molecules and/or mmRNA encoding an immunogen may be delivered to cells to trigger multiple innate response pathways (see International Pub. No. WO2012006377; herein incorporated by reference in its entirety). As another non-limiting example, the modified nucleic acid molecules and mmRNA of the present invention encoding an immunogen may be delivered to a vertebrate in a dose amount large enough to be immunogenic to the vertebrate (see International Pub. No. WO2012006372 and WO2012006369; each of which is herein incorporated by reference in their entirety).

Ex. 1009, ¶ 342

Geall (WO '369)

The immunogen

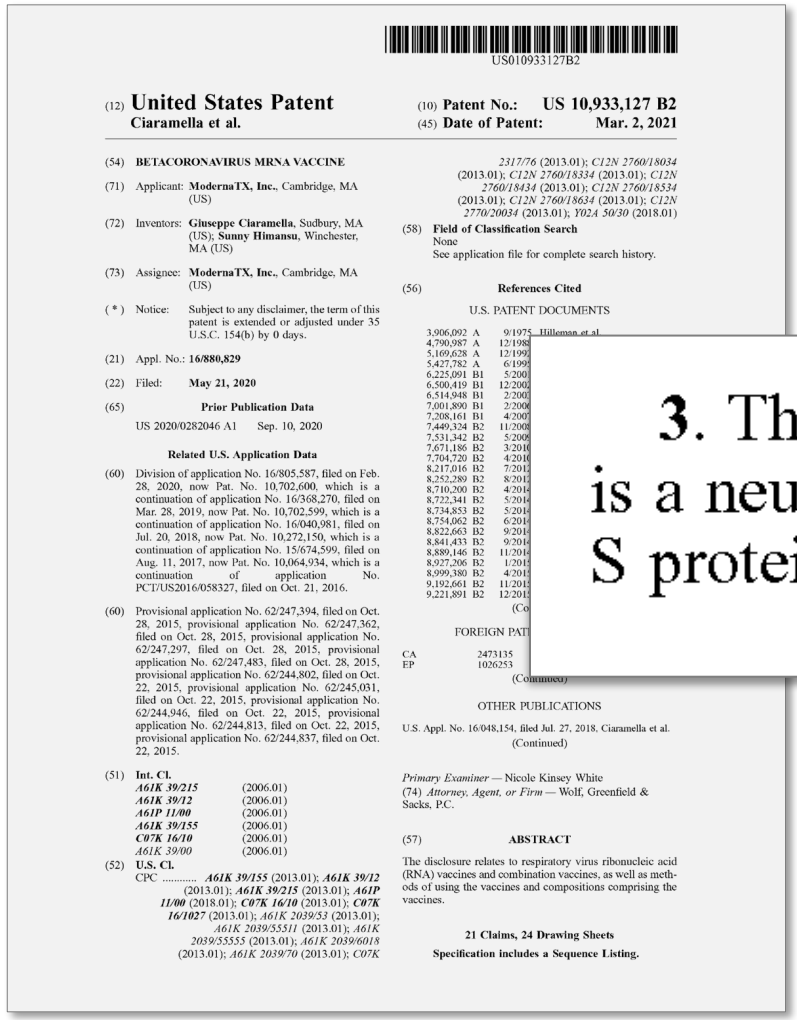
RNA molecules used with the invention encode a polypeptide immunogen. After administration of the RNA the immunogen is translated *in vivo* and can elicit an immune response in the recipient. The immunogen may elicit an immune response against a bacterium, a virus, a fungus or a parasite (or, in

Coronavirus: Viral immunogens include, but are not limited to, those derived from a SARS coronavirus, avian infectious bronchitis (IBV), Mouse hepatitis virus (MHV), and Porcine transmissible gastroenteritis virus (TGEV). The coronavirus immunogen may be a spike polypeptide.

Ex. 1010 at 15:32-35, 19:27-30

Schrum anticipates Patent Owner's claims to inducing an immune response using an mRNA vaccine encoding for that previously disclosed immunogen

To the Extent Required, Schrum Discloses a Neutralizing Antibody Response



US010933127B2

(12) **United States Patent**
Ciaramella et al.

(10) **Patent No.: US 10,933,127 B2**
(45) **Date of Patent: Mar. 2, 2021**

(54) **BETACORONAVIRUS MRNA VACCINE**

(71) Applicant: **ModernaTX, Inc.**, Cambridge, MA (US)

(72) Inventors: **Giuseppe Ciaramella**, Sudbury, MA (US); **Sunny Himansu**, Winchester, MA (US)

(73) Assignee: **ModernaTX, Inc.**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **16/880,829**

(22) Filed: **May 21, 2020**

(65) **Prior Publication Data**

US 2020/0282046 A1 Sep. 10, 2020

Related U.S. Application Data

(60) Division of application No. 16/805,587, filed on Feb. 28, 2020, now Pat. No. 10,702,600, which is a continuation of application No. 16/368,270, filed on Mar. 28, 2019, now Pat. No. 10,702,599, which is a continuation of application No. 16/040,981, filed on Jul. 20, 2018, now Pat. No. 10,272,150, which is a continuation of application No. 15/674,599, filed on Aug. 11, 2017, now Pat. No. 10,064,934, which is a continuation of application No. PCT/US2016/058327, filed on Oct. 21, 2016.

(60) Provisional application No. 62/247,394, filed on Oct. 28, 2015, provisional application No. 62/247,362, filed on Oct. 28, 2015, provisional application No. 62/247,297, filed on Oct. 28, 2015, provisional application No. 62/247,483, filed on Oct. 28, 2015, provisional application No. 62/244,802, filed on Oct. 22, 2015, provisional application No. 62/245,031, filed on Oct. 22, 2015, provisional application No. 62/244,946, filed on Oct. 22, 2015, provisional application No. 62/244,813, filed on Oct. 22, 2015, provisional application No. 62/244,837, filed on Oct. 22, 2015.

(51) **Int. Cl.**

A61K 39/215	(2006.01)
A61K 39/12	(2006.01)
A61P 11/00	(2006.01)
A61K 39/155	(2006.01)
C07K 16/10	(2006.01)
A61K 39/00	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 39/155*** (2013.01); ***A61K 39/12*** (2013.01); ***A61K 39/215*** (2013.01); ***A61P 11/00*** (2018.01); ***C07K 16/10*** (2013.01); ***C07K 16/1027*** (2013.01); *A61K 2039/53* (2013.01); *A61K 2039/55511* (2013.01); *A61K 2039/55555* (2013.01); *A61K 2039/6018* (2013.01); *A61K 2039/70* (2013.01); *C07K 2317/76* (2013.01); *C12N 2760/18034* (2013.01); *C12N 2760/18334* (2013.01); *C12N 2760/18434* (2013.01); *C12N 2760/18534* (2013.01); *C12N 2760/18634* (2013.01); *C12N 2770/20034* (2013.01); *Y02A 50/30* (2018.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

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8,710,200 B2 4/2014
8,722,341 B2 5/2014
8,734,853 B2 5/2014
8,754,062 B2 6/2014
8,822,663 B2 9/2014
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8,889,146 B2 11/2014
8,927,206 B2 1/2015
8,999,380 B2 4/2015
9,192,661 B2 11/2015
9,221,891 B2 12/2015
(Co

FOREIGN PAT

CA 2473135
EP 1026253
(Continued)

OTHER PUBLICATIONS

U.S. Appl. No. 16/048,154, filed Jul. 27, 2018, Ciaramella et al.
(Continued)

Primary Examiner — Nicole Kinsey White
(74) *Attorney, Agent, or Firm* — Wolf, Greenfield & Sacks, P.C.

(57) **ABSTRACT**

The disclosure relates to respiratory virus ribonucleic acid (RNA) vaccines and combination vaccines, as well as methods of using the vaccines and compositions comprising the vaccines.

21 Claims, 24 Drawing Sheets

Specification includes a Sequence Listing.

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

Ex. 1001 (-1359), Claim 3

Petitioner Has Explained—and Patent Owner Has Not Contested—That Claim 3 Is Entitled to No Independent Patentable Weight

Petition for *Inter Partes* Review

Moreover, claim 3 is merely directed to the body's reaction to the mRNA vaccine of claims 1 and 2, which is an intended effect or result entitled to no patentable weight. *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1296 (Fed. Cir. 2013) ("a newly-discovered *result or property* of an existing (or obvious) *method of use* is not patentable") (emphasis in original). Regardless, a POSA would have

-1359 Petition (Paper 1), 30-31

Patent Owner

Third, without working examples of vaccines with betacoronavirus antigens in Schrum/Geall, neither reference discloses the immune response required by claims 1, 3, and 17 or the neutralizing antibodies required by claim 3. Ex. 1001, Claims. Schrum discloses ***no working examples*** of an infectious disease vaccine,

-1359 POR (Paper 42), 18

Ex. 1010, 29:1-43:9 (RSV-F only). Petitioners cite no example or data in Schrum (or Geall) of neutralizing antibody generation to a betacoronavirus immunogen as claim 3 requires. Ex. 2114, 211:6-214:1; Ex. 1010, 29:1-43:9; Ex. 2199, ¶¶337-339.

-1359 Sur-Reply (Paper 72), 7-8

Claim 3 is Therefore Entitled to No Independent Patentable Weight

Allergan, Inc
v.
Sandoz Inc.
726 F.3d 1286 (Fed. Cir. 2013)

While a new and nonobvious *method of using* an existing (or obvious) composition may itself be patentable, *see Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1378 (Fed. Cir. 2005), a newly-discovered *result or property* of an existing (or obvious) *method of use* is not patentable. *See Abbott Labs. v. Baxter Pharm. Prods.*, 471 F.3d 1363, 1368–69 (Fed. Cir. 2006)

Allergan, Inc v. Sandoz Inc., 726 F.3d 1286, 1295-96 (Fed. Cir. 2013) (Dyk, T., concurring-in-part, dissenting-in-part) (emphasis in original)

Claim 3 is merely directed to the "result or property" of the method of claims 1 and 2

Even if Afforded Any Independent Weight, Schrum Anticipates Claim 3 of the '127 Patent

Activation of the Immune Response: Vaccines

[0340] In one embodiment of the present invention, mRNA molecules may be used to elicit or provoke an immune response in an organism. The mRNA molecules to be delivered may encode an immunogenic peptide or polypeptide and may encode more than one such peptide or polypeptide.

* * *

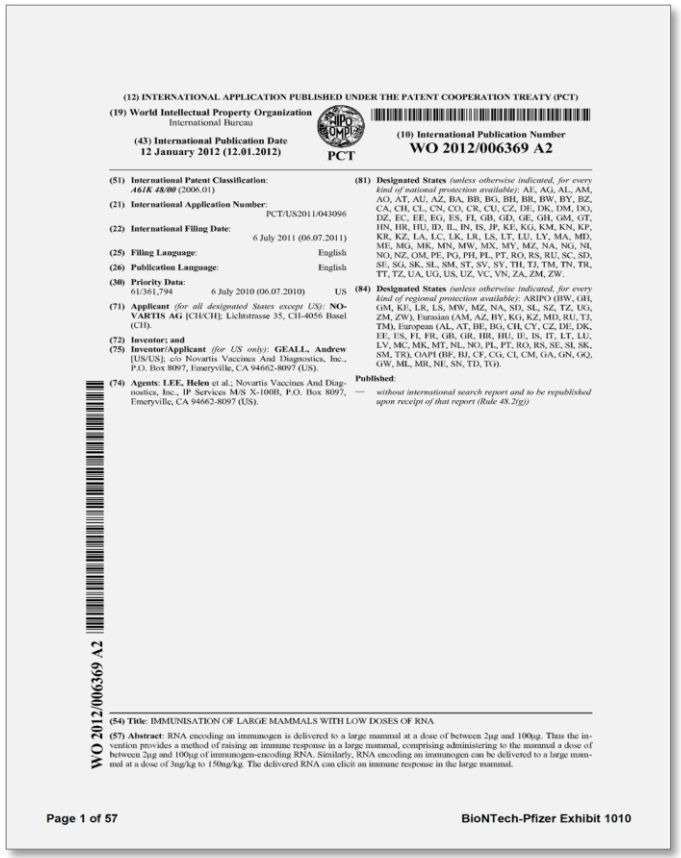
[0342] In one embodiment, the modified nucleic acid molecules and/or mmRNA of the invention may encode an immunogen. The delivery of modified nucleic acid molecules and/or mmRNA encoding an immunogen may activate the immune response. As a non-limiting example, the modified nucleic acid molecules and/or mmRNA encoding an immunogen may be delivered to cells to trigger multiple innate response pathways (see International Pub. No. WO2012006377; herein incorporated by reference in its entirety). As another non-limiting example, the modified nucleic acid molecules and mmRNA of the present invention encoding an immunogen may be delivered to a vertebrate in a dose amount large enough to be immunogenic to the vertebrate (see International Pub. No. WO2012006372 and WO2012006369; each of which is herein incorporated by reference in their entirety).

Ex. 1009, ¶¶ 340, 342

Even if Afforded Any Independent Weight, Schrum Anticipates Claim 3 of the '127 Patent

Schrum, through its incorporation of Geall, discloses a neutralizing antibody response

Geall



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(30) Priority Data:
61/361,794 6 July 2010 (06.07.2010) US

(71) Applicant (*for all designated States except US*): NOVARTIS AG [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(72) Inventor; and
(75) Inventor/Applicant (*for US only*): GEALL, Andrew [US/US]; c/o Novartis Vaccines And Diagnostics, Inc., P.O. Box 8097, Emeryville, CA 94662-8097 (US).

(74) Agents: LEE, Helen et al.; Novartis Vaccines And Diagnostics, Inc., IP Services M/S X-100H, P.O. Box 8097, Emeryville, CA 94662-8097 (US).

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Published:
— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2012/006369 A2

(54) Title: IMMUNISATION OF LARGE MAMMALS WITH LOW DOSES OF RNA

(57) Abstract: RNA encoding an immunogen is delivered to a large mammal at a dose of between 2μg and 100μg. Thus the invention provides a method of raising an immune response in a large mammal, comprising administering to the mammal a dose of between 2μg and 100μg of immunogen-encoding RNA. Similarly, RNA encoding an immunogen can be delivered to a large mammal at a dose of 3ng/kg to 150ng/kg. The delivered RNA can elicit an immune response in the large mammal.

Page 1 of 57

BioNTech-Pfizer Exhibit 1010

The immunogen

RNA molecules used with the invention encode a polypeptide immunogen. After administration of the RNA the immunogen is translated *in vivo* and can elicit an immune response in the recipient. The immunogen may elicit an immune response against a bacterium, a virus, a fungus or a parasite (or, in some embodiments, against an allergen; and in other embodiments, against a tumor antigen). The immune response may comprise an antibody response (usually including IgG) and/or a cell-mediated immune response. The polypeptide immunogen will typically elicit an immune response which

Methods of treatment and medical uses

RNA delivery according to the invention is for eliciting an immune response *in vivo* against an immunogen of interest. The immune response is preferably protective and preferably involves antibodies and/or cell-mediated immunity. The method may raise a booster response.

By raising an immune response the mammal can be protected against various diseases and/or infections *e.g.* against bacterial and/or viral diseases as discussed above. RNA-containing

Ex. 1010 at 15:32-16:3, 24:14-19

The Law Does Not Require Data

Bristol-Myers Squibb Co.
v.
Ben Venue Labs., Inc.,

246 F.3d 1368, 1379
(Fed. Cir. 2001)

Furthermore, although he did not actually premedicate the patients himself, anticipation does not require actual performance of suggestions in a disclosure.

Agenda

- Overview of the challenged patents, the prior art, & the instituted grounds
- Anticipation by Schrum (Ground 1)
  - Schrum discloses each limitation as arranged in the challenged claims
  - Patent Owner fails to rebut anticipation by Schrum
- Obviousness in view of Schrum and Geall, Yang, or Altmeyer
- The testimony of Patent Owner's declarants should be afforded little weight

Patent Owner's Erroneous Defenses to Anticipation

Patent Owner makes three arguments against anticipation:

1. Schrum does not incorporate Geall's disclosure of the SARS-CoV S protein immunogen
2. Geall does not disclose the same "S protein" recited in the challenged claims
3. Ground 1 requires "picking and choosing"

None is supported by the evidence

-1358 Reply (Paper 59), 4-10; -1359 Reply (Paper 59), 4-10

Argument # 1 Is Meritless: Schrum Incorporates Geall's Disclosure of the SARS-CoV S Protein Immunogen

Patent Owner:

"Given Geall's focus on dosing and the explicit statement that Geall is being incorporated for immunogen dose amounts, the only portions of Geall incorporated are dose disclosures."

-1359 POR (Paper 42), 16-17 (citing *Cook BioTech Inc. v. Acell, Inc.*, 460 F.3d 1365, 1376 (Fed. Cir. 2006))

Cook BioTech Inc. v. Acell, Inc.

460 F.3d 1365, 1376 (Fed. Cir. 2006)

The preparation of UBS from a segment of urinary bladder is similar to the procedure for preparing intestinal submucosa detailed in U.S. Patent No. 4,902,508, the disclosure of which is expressly incorporated herein by reference.

Cook BioTech Inc., 460 F.3d at 1373

Schrum

entirety). As another non-limiting example, the modified nucleic acid molecules and mmRNA of the present invention encoding an immunogen may be delivered to a vertebrate in a dose amount large enough to be immunogenic to the vertebrate (see International Pub. No. WO2012006372 and WO2012006369; each of which is herein incorporated by reference in their entirety).

Ex. 1009, ¶ 342

Patent Owner, the applicant of Schrum, elected to incorporate Geall "in its entirety"

-1358 Reply (Paper 59), 6-7; -1359 Reply (Paper 59), 6-7

Schrum Incorporates Geall's Disclosure of the SARS-CoV S Protein Immunogen

- Patent Owner's suggestion that Schrum incorporates Geall for "dose amounts"—and nothing else—makes little scientific sense, and is inconsistent with a POSA's interpretation

- Dr. Fuller conceded that the choice of immunogen influences dosage amounts

Patent Owner's Declarant, Dr. Fuller

Q. Is it fair to say that [self-amplifying mRNA is] typically administered at a different dose [than non-amplifying mRNA]?

A. So regardless of what vaccine that you have, you have to – multiple things can influence a dose. So that can be the immunogen that you use. Some immunogens are more immunogenic than others.

Ex. 1104 at 119:20-120:5

- **Dr. Griffin agreed:** "Given that interrelatedness, a POSA would not consider Geall's teachings of dosage levels without also considering its discussion of immunogens, particularly where Geall is expressly incorporated 'in [its] entirety.'"

Ex. 1159 (-1359), ¶ 39

Argument # 2 Is Meritless: Geall Discloses the Claimed "betacoronavirus (BetaCoV) S protein" Immunogen

'127 Patent, Claim 1

1. A method comprising administering to a subject a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit formulated in a lipid nanopar-

In some embodiments, at least one antigenic polypeptide is a SARS-CoV structural protein. For example, a SARS-CoV structural protein may be spike protein (S), envelope protein (E), nucleocapsid protein (N), membrane protein (M) or an immunogenic fragment thereof. In some embodiments, the SARS-CoV structural protein is a spike protein (S). In some embodiments, the SARS-CoV structural protein

Ex. 1001 (-1359), Claim 1, 8:40-46

Geall

Coronavirus: Viral immunogens include, but are not limited to, those derived from a SARS coronavirus, avian infectious bronchitis (IBV), Mouse hepatitis virus (MHV), and Porcine transmissible gastroenteritis virus (TGEV). The coronavirus immunogen may be a spike polypeptide.

Ex. 1010 at 19:27-30

- Geall, incorporated into Schrum, discloses the same immunogen as the challenged claims, using near-identical terminology

Geall Discloses the Claimed "betacoronavirus (BetaCoV) S protein" Immunogen

Patent Owner relies on an incorrect claim construction to evade Geall's disclosure

"Geall does not actually disclose betacoronavirus S protein, properly construed . . . because Geall does not (1) specify 'full-length'"

-1359 POR (Paper 42), 17

Patent Owner

The Board should add to this agreed construction that the "S protein" is "a full-length spike protein." This clarifies, consistent with the claims and specification, that "S protein" does not refer to a subunit, separately claimed as "S protein subunit," or any truncated form. The specification uses "S protein" interchangeably with full-length spike protein, while distinguishing from subunits.

-1359 POR (Paper 42), 8

-1358 Reply (Paper 59), 3, 6-8; -1359 Reply (Paper 59), 3, 6-8

Patent Owner's "S Protein" Construction Lacks Support

- Patent Owner does not rely on lexicography or disavowal to support its construction of "S protein"

Patent Owner

The Board should add to this agreed construction that the "S protein" is "a full-length spike protein." This clarifies, consistent with the claims and specification, that "S protein" does not refer to a subunit, separately claimed as "S protein subunit," or any truncated form. The specification uses "S protein" interchangeably with full-length spike protein, while distinguishing from subunits.

-1359 POR (Paper 42), 8

'600 and '127 Patents

In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) poly-nucleotide encoding S protein (S, S1 and/or S2), E protein, N protein and M protein.

Ex. 1001 (-1358) at 35:9-12

In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) poly-nucleotide encoding S protein (S, S1 and/or S2), E protein, N protein and M protein.

Ex. 1001 (-1359) at 35:5-8

-1358 Reply (Paper 59), 3; -1359 Reply (Paper 59), 3

Patent Owner's "S Protein" Construction Lacks Support

- Dr. Fuller recognized that there is also a "truncated version of a spike protein"

Patent Owner's Declarant, Dr. Fuller

"As discussed below in Section VIII.B, Geall . . . does not say whether the 'spike polypeptide' it lists is a full-length spike protein, a subunit of a spike protein, a ***truncated version of a spike protein***, or something else."

Ex. 2199 (-1359), ¶ 193

-1358 Reply (Paper 59), 3; -1359 Reply (Paper 59), 3

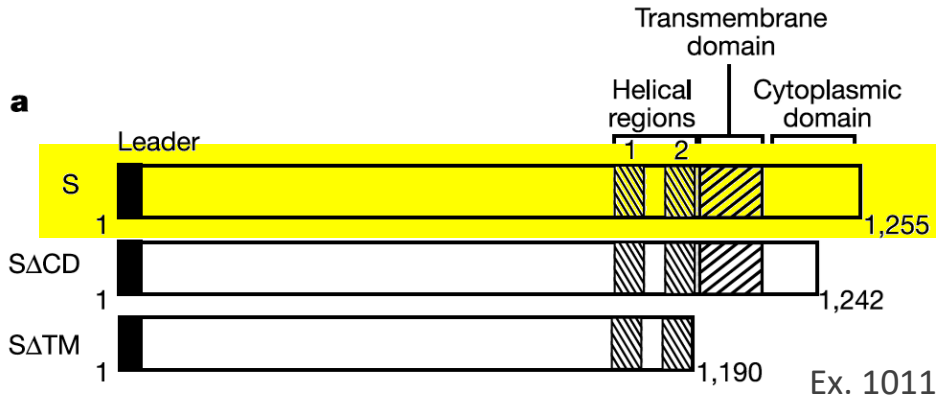
Even Accepting Moderna's Erroneous Construction, Geall Discloses the Claimed "betacoronavirus (BetaCoV) S protein" Immunogen

Daniel Griffin, M.D., Ph.D.

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

Ex. 1159 (-1359), ¶ 46

Yang 2004



Ex. 1011 at 561

Du 2009

paramyxovirus F and Ebola virus glycoprotein[28]. The SARS-CoV S protein encodes a surface glycoprotein precursor that is predicted to be 1,255 amino acids in length, and the amino terminus and most of the protein is predicted to be on the outside of the cell surface or the virus particles[3]. The predicted S protein consists of a

Ex. 1031 at 227

POSA would understand that "spike protein" refers to the "full-length" spike protein

Patent Owner Misstates Dr. Griffin's Testimony

Patent Owner:

"As Dr. Griffin concedes, when Geall intends to refer to 'full-length' protein, it does so."

-1359 Sur-reply (Paper 72), 7

Geall

Large mammal study

A large-animal study was performed in cattle. Calves (4-6 weeks old, ~60-80 kg, 5 per group) were immunised with 66µg of replicon vA317 encoding full-length RSV F protein at days 0, 21, 86 and 146. The replicons were formulated either inside liposomes or with the CNE17 emulsion. PBS alone was used as a negative control, and a licensed vaccine was used as a positive control ("Triangle 4" from Fort Dodge, containing killed virus). All calves received 15µg F protein adjuvanted with the MF59 emulsion on day 146. One cow was mistakenly vaccinated with the CNE17-based vaccine on day 86 instead of Triangle 4 and so its data were excluded from day 100 onwards.

Ex. 1010 at 40:13-20

Daniel Griffin, M.D., Ph.D.

Q. So Geall makes multiple references to a full-length protein; right?

A. So this same paragraph, just to put it in context, starts off by saying: A large-animal study was performed in cattle. . . . .

It then goes on to say: All calves received 15 micrograms F protein adjuvanted with the MF59 emulsion on day 146.

So we are seeing, just for context, full-length RSV F protein, and then we are also seeing just F protein.

Ex. 2253 at 91:6-21

-1358 Reply (Paper 59), 7-8; -1359 Reply (Paper 59), 7-8

Geall Discloses the Claimed "betacoronavirus (BetaCoV) S protein" Immunogen

Patent Owner's other attempt at injecting an additional claim limitation fails

"[A]ccordingly, without data, Geall does not disclose a 'structural protein forming a spike.' Petitioners' unsupported conclusion that 'administering mRNA encoding for a betacoronavirus spike protein would result in expression of a protein that forms spikes' is contrary to Dr. Griffin's admission that proteins can fail to express or misfold."

-1359 Sur-reply (Paper 72), 7 (internal citation omitted)

- Challenged claims only require mRNA "encoding" the S protein, and "do not require that the protein the recited composition causes to be expressed have any particular properties, much less that it fold to form a spike."

-1358 Decision (Paper 18), 59

'127 Patent

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

Ex. 1001(-1359), Claim 1

'600 Patent

1. A composition, comprising: a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit formulated in a lipid nanoparticle.

Ex. 1001(-1358), Claim 1

-1358 Reply (Paper 59), 3, 8; -1359 Reply (Paper 59), 3, 8

Geall Discloses the Claimed "betacoronavirus (BetaCoV) S protein" Immunogen

A "structural protein forming a spike" is simply what a "spike protein" or "spike polypeptide" is

Daniel Griffin, M.D., Ph.D.

- Therefore, a POSA would readily understand that Geall's disclosure of a spike polypeptide refers to the SARS-CoV structural protein forming a spike

> By the priority date of the challenged patents, it was well known "[t]he spikes of SARS-CoV are composed of trimers of S protein" and that an expressed S protein folds into the figurative "spike" for which these proteins are named.[46] Therefore, as I explained in my initial declaration, "[a] POSA would have understood [Geall's] disclosure of 'spike polypeptide' from a SARS coronavirus . . . as referring to a structural protein forming a spike."
>
> Ex. 1159 (-1359), ¶ 42

Patent Owner's contention that "proteins do not inherently form" (-1358 sur-reply (Paper 72), 7) is a red herring

Argument # 3 Is Meritless: No "Picking and Choosing" Is Required

Patent Owner

C. Petitioners Pick and Choose.

Petitioners do not deny Schrum/Geall contain ***at least 3,000*** combinations. POR, 23-24. There is no anticipation where "the number of [prior-art] categories and components…is so large that the [claimed] combination…would not be immediately apparent." *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 851 F.3d 1270, 1274 (Fed. Cir. 2017) (citation omitted).

-1359 Sur-Reply (Paper 72), 8

- That Schrum discloses more embodiments than just what is claimed in the '600 and '127 patents ***does not*** preclude a finding of anticipation

INCEPT LLC,
Appellant

v.

PALETTE LIFE SCIENCES, INC.,
Appellee

Incept cannot use the fact that Wallace describes multiple compositions to evade an anticipation finding where Wallace provides "as complete detail as is contained in the patent claim," such that a skilled artisan would have understood that Wallace's compositions had the same generic properties as those in the '723 patent claims.

Incept LLC v. Palette Life Scis., Inc., 77 F.4th 1366, 1372 (Fed. Cir. 2023)

-1358 Reply (Paper 59), 4-6, 9-10; -1359 Reply (Paper 59), 4-6, 9-10

Patent Owner's Allegation of "Picking-and-Choosing" Relies on Its Argument that Schrum Does Not Disclose an mRNA-LNP Vaccine

Patent Owner

1009, ¶¶ 346, 340-350. Schrum does not expressly contemplate using an "mRNA encoding an immunogen encapsulated in a lipid nanoparticle 'for use in a vaccine such as…against a pathogen,'" Paper 1, 24, as Petitioners allege. To support that

* * *

Absent guidance in Schrum on arrangement of vaccine and delivery technology, a POSA would have to look at other sections of Schrum, with no apparent connection to the vaccine section, for discussion of mRNA delivery systems. Ex. 1009, ¶¶378-435. That Petitioners must rely on disclosures from different sections of a reference not explicitly connected to each other confirms the elements are not arranged as claimed. *Otonomy, Inc. v. Aurius Med., AG*, 743 Fed.

-1359 POR (Paper 42), 21-22

Patent Owner misreads Schrum

-1358 Reply (Paper 59), 4-6, 9-10; -1359 Reply (Paper 59), 4-6, 9-10; -1358 Petition (Paper 3), 26-27; -1359 Petition (Paper 1), 24, 26-29

Schrum Expressly Discloses the Use of Lipid Nanoparticles to Deliver mRNA Vaccines

Activation of the Immune Response: Vaccines

[0340] In one embodiment of the present invention, mRNA molecules may be used to elicit or provoke an immune response in an organism. The mRNA molecules to be delivered may encode an immunogenic peptide or polypeptide and may encode more than one such peptide or polypeptide.

Liposomes, Lipoplexes, and Lipid Nanoparticles

[0378] The modified nucleic acid molecules and mmRNA of the invention can be formulated using one or more liposomes, lipoplexes, or lipid nanoparticles. In one embodiment,

[0397] In one embodiment, an immune response may be elicited by delivering a lipid nanoparticle which may include a nanospecies, a polymer and an immunogen. (U.S. Publication No. 20120189700 and International Publication No. WO2012099805; each of which is herein incorporated by reference in their entirety). The polymer may encapsulate the nanospecies or partially encapsulate the nanospecies. The immunogen may be a recombinant protein, a modified RNA described herein. In one embodiment, the lipid nanoparticle may be formulated for use in a vaccine such as, but not limited to, against a pathogen.

Ex. 1009, ¶¶ 340, 378, 397

Schrum's immunogen-encoding mRNA vaccines are an "mmRNA of the invention" delivered using lipid nanoparticles

Schrum Discloses the Use of Lipid Nanoparticles to Deliver mRNA Vaccines

United States
Patent Application Publication
de Fougerolles et al.

Pub. No.: US 2013/0266640 A1
Pub. Date: Oct. 10, 2013

MODIFIED NUCLEOSIDE, NUCLEOTIDE, AND NUCLEIC ACID COMPOSITIONS

Applicant: MODERNA THERAPEUTICS, CAMBRIDGE, MA (US)

Inventors: Antonin de Fougerolles, Brookline, MA (US); Kevin M. Wood, Cambridge, MA (US); Sayda M. Elkasabi, Cambridge, MA (US); Nantaw R. Abysan, Cambridge, MA (US); Pedro Valencia, Cambridge, MA (US); Jason P. Schrum, Philadelphia, PA (US)

Appl. No.: 13/907,720

Filed: Jun. 14, 2013

Related U.S. Application Data

Foreign Application Priority Data

Publication Classification

ABSTRACT

Page 1 of 202

BioNTech-Pfizer Exhibit 1009

[0397] In one embodiment, an immune response may be elicited by delivering a lipid nanoparticle which may include a nanospecies, a polymer and an immunogen. (U.S. Publication No. 20120189700 and International Publication No. WO2012099805; each of which is herein incorporated by reference in their entirety). The polymer may encapsulate the nanospecies or partially encapsulate the nanospecies. The immunogen may be a recombinant protein, a modified RNA described herein. In one embodiment, the lipid nanoparticle may be formulated for use in a vaccine such as, but not limited to, against a pathogen.

Ex. 1009, ¶ 397

Petitioner's Expert, Dr. Moon

35. A POSA would have readily understood that Schrum's disclosure that "***an immune response may be elicited*** by delivering a lipid nanoparticle" refers to a lipid nanoparticle-based vaccine composition. In fact, Schrum uses nearly identical language in its discussion of mRNA vaccines. Under the heading, "Activation of the Immune Response: ***Vaccines***," Schrum teaches that "[i]n one embodiment of the present invention, ***mRNA molecules may be used to elicit or provoke an immune response*** in an organism." (Ex. 1009 at ¶ 340 (emphasis added).) Moreover, under the same "Vaccines" heading, Schrum also explains that the mRNA vaccines can "encode an immunogen," consistent with paragraph 397's reference to a modified mRNA ***immunogen***.

Ex. 1161 (-1359), ¶ 35

Schrum Discloses Each Limitation as Arranged in the Claims

Patent Owner:

"[P]aragraph 397 refers to ***modified*** RNA (of which there are many types . . . (saRNA, RNAi, siRNA, etc.)), not ***messenger*** RNA"

-1359 Sur-Reply (Paper 72), 8 n.7 (emphasis in original)

Petitioner's Expert, Dr. Moon

41. With respect to the last sentence in paragraph 397, Dr. Chan also states in his declaration that "[the sentence] does not mention mRNA at all" and contends that "Schrum discloses many different nucleic acids that can be formulated in a lipid nanoparticle." (Ex. 2198 at ¶ 101.) Dr. Chan's opinion, however, ignores the fact that the *only* nucleic acid referenced in paragraph 397 is the "modified RNA described herein." Moreover, Schrum's vaccine disclosure itself refers to mRNA. (Ex. 1009 at ¶ 340 ("In one embodiment of the present

Ex. 1161 (-1359), ¶ 41

Activation of the Immune Response: Vaccines

[0340] In one embodiment of the present invention, mRNA molecules may be used to elicit or provoke an immune response in an organism. The mRNA molecules to be delivered may encode an immunogenic peptide or polypeptide and may encode more than one such peptide or polypeptide.

Ex. 1009, ¶ 340

POSA would have understood that "modified RNA" refers to modified mRNA based on Schrum

-1358 Reply (Paper 59), 5-6; -1359 Reply (Paper 59), 5-6; Ex. 1161 (-1359), ¶¶ 41-43; Ex. 1159 (-1359), ¶¶ 52-53

Agenda

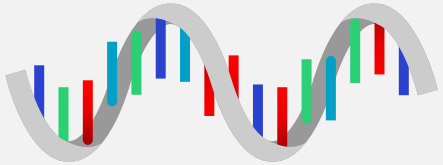
- Overview of the challenged patents, the prior art & the instituted grounds
- Anticipation by Schrum (Ground 1)
- Obviousness in view of Schrum and Geall, Yang, or Altmeyer (Grounds 2-4)
- The testimony of Patent Owner's declarants should be afforded little weight

Grounds 2-4 Each Combine Schrum With a Teaching of the S Protein

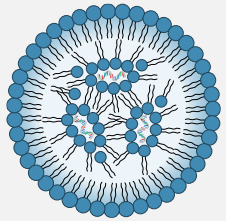
Schrum

- mRNA vaccine encoding for an immunogen used to induce an immune response
- Formulating mRNA, including mRNA vaccines, in lipid nanoparticles
- Standard mRNA components, include poly(A) tail, 5’ and 3’ UTRs, and 5’ cap

mRNA



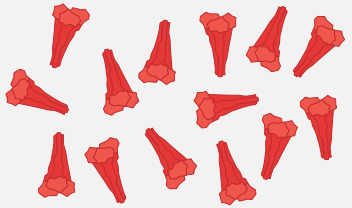
Lipid Nanoparticle



Geall/Yang/Altmeyer

- Well-known SARS-CoV S protein immunogen
- Type of immune response achieved by S protein vaccination

BetaCoV S Protein



Petitioner Has Carried Its Burden to Show Each Challenged Claim Is Unpatentable

Petitioner has shown:

1. Schrum in view of Geall/Yang/Altmeyer **teaches each claim limitation**
2. A POSA would have been **motivated to combine** Schrum and Geall/Yang/Altmeyer's teachings
3. A POSA would have had a **reasonable expectation of success** in combining Schrum and Geall/Yang/Altmeyer's teachings to arrive at the challenged claim

Schrum in View of Geall, Yang, or Altmeyer Teaches Every Limitation

- No dispute that **Schrum teaches every mRNA and LNP limitation** of the challenged claims
- **Geall, Yang, and Altmeyer all teach the claimed S protein** immunogen to be used in Schrum's vaccine and the use of an S protein-based vaccine to **induce an immune response**—indeed, a neutralizing antibody response

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(54) Title: IMMUNISATION OF LARGE MAMMALS WITH LOW DOSES OF RNA

(57) Abstract: RNA encoding an immunogen is delivered to a large mammal at a dose of between 2μg and 100μg. Thus the invention provides a method of raising an immune response in a large mammal, comprising administering to the mammal a dose of between 2μg and 100μg of immunogen-encoding RNA. Similarly, RNA encoding an immunogen can be delivered to a large mammal at a dose of 3ng/kg to 150ng/kg. The delivered RNA can elicit an immune response in the large mammal.

Geall Teaches SARS-CoV S Protein

Coronavirus: Viral immunogens include, but are not limited to, those derived from a SARS coronavirus, avian infectious bronchitis (IBV), Mouse hepatitis virus (MHV), and Porcine transmissible gastroenteritis virus (TGEV). The coronavirus immunogen may be a spike polypeptide.

RNA delivery according to the invention is for eliciting an immune response *in vivo* against an immunogen of interest. The immune response is preferably protective and preferably involves antibodies and/or cell-mediated immunity. The method may raise a booster response.

By raising an immune response the mammal can be protected against various diseases and/or infections *e.g.* against bacterial and/or viral diseases as discussed above. RNA-containing

Schrum in View of Geall, Yang, or Altmeyer Teaches Every Limitation

A DNA vaccine induces SARS coronavirus neutralization and protective immunity in mice

NATURE | VOL 428 | 1 APRIL 2004 | www.nature.com/nature

letters to nature

A DNA vaccine induces SARS coronavirus neutralization and protective immunity in mice

Zhi-yong Yang[1*], Wing-pui Kong[1*], Yue Huang[1], Anjeanette Roberts[2], Brian R. Murphy[3], Kanta Subbarao[3] & Gary J. Nabel[1]

Public health measures have successfully identified and contained outbreaks of the severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV)[1–3], but concerns remain over the possibility of future recurrences. Finding a vaccine for this virus therefore remains a high priority. Here, we show that a DNA vaccine encoding the spike (S) glycoprotein of the SARS-CoV induces T cell and neutralizing antibody responses, as well as protective immunity, in a mouse model. Alternative forms of S were analysed by DNA immunization. These expression vectors induced robust immune responses mediated by CD4 and CD8 cells, as well as significant antibody titres, measured by enzyme-linked immunosorbent assay. Moreover, antibody responses in mice vaccinated with an expression vector encoding a form of S that includes its transmembrane domain elicited neutralizing antibodies. Viral replication was reduced by more than six orders of magnitude in the lungs of mice vaccinated with these S plasmid DNA expression vectors, and protection was mediated by a humoral but not a T-cell-dependent immune mechanism. Gene-based vaccination for the SARS-CoV elicits effective immune responses that generate protective immunity in an animal model.

The SARS-CoV emerged in Asia as a highly aggressive pathogen that can be lethal in adults and the elderly[4–6]. Although its genetic organization is similar to other coronaviruses, recent phylogenetic studies suggest that it may be most closely related to type II coronaviruses[7–9]. Previously described coronaviruses have not usually induced lethal disease in humans, but their pathogenicity in domestic animal species has been well documented[10], and experimental vaccines developed for animals have provided insight into mechanisms of protective immunity[11,12]. Studies of the immune response to coronaviruses suggest that both cell-mediated and humoral immunity contribute to long-term protection[13,14].

To discover the gene products and mechanisms of protective immunity relevant to SARS-CoV, two sets of cDNAs encoding the SARS-CoV S glycoproteins were prepared using modified codons to optimize expression and to minimize recombination with endogenous coronaviruses. Because coronaviruses assemble in the compartment between the endoplasmic reticulum (ER) and Golgi apparatus[15], and the S leader may direct it to the ER, the native leader sequence was retained in one set of vectors (Fig. 1a) and replaced in another set with a leader sequence derived from the interleukin-2 gene. Expression was not significantly altered by this leader sequence substitution (data not shown), and it was not studied further. Two S carboxy-terminal mutants, one that truncated the cytoplasmic domain (SΔCD) and another that deleted the transmembrane and cytoplasmic regions (SΔTM), were prepared, and expression of these cDNAs by a mammalian expression vector suitable for human vaccination was confirmed (Fig. 1b).

The plasmids encoding these modified S glycoproteins were analysed for their ability to elicit antiviral immunity after intramuscular injection in BALB/c mice. Injection of S, SΔTM and SΔCD expression vectors induced a substantial immune response. A marked increase was observed in the number of SARS-CoV S-specific CD4 T-cell immune responses (Fig. 2a), as measured by intracellular cytokine staining for interferon-γ (IFN-γ) and tumour necrosis factor-α (TNF-α). In addition, substantial SARS-CoV S-specific CD8 cellular immunity was detected at levels at least sevenfold above the background response. Humoral immunity was initially

Figure 1 Schematic representation of SARS-CoV glycoprotein cDNAs and expression of recombinant proteins. a, The structure of the cDNAs used. b, Expression of these constructs, determined by western blot analysis with antisera reactive with SARS-CoV S, was evaluated after transfection of the indicated plasmid expression vectors in 293T cells. Arrows indicate specific SΔCD (upper) and SΔTM (lower) bands.

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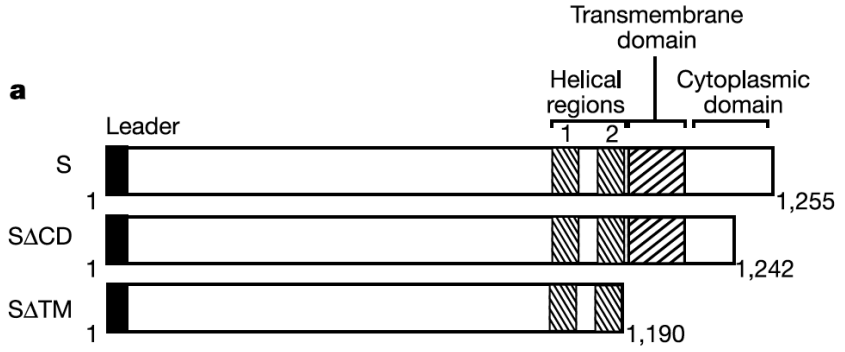
Page 1 of 4

BioNTech-Pfizer Exhibit 1011

Yang Teaches SARS-CoV S Protein

virus therefore remains a high priority. **Here, we show that a DNA vaccine encoding the spike (S) glycoprotein of the SARS-CoV induces T cell and neutralizing antibody responses, as well as protective immunity, in a mouse model.** Alternative forms of S

cular injection in BALB/c mice. Injection of S, SΔTM and SΔCD expression vectors induced a substantial immune response. A marked increase was observed in the number of SARS-CoV S-specific CD4 T-cell immune responses (Fig. 2a), as measured by intracellular cytokine staining for interferon-γ (IFN-γ) and tumour necrosis factor-α (TNF-α). In addition, substantial SARS-CoV S-specific



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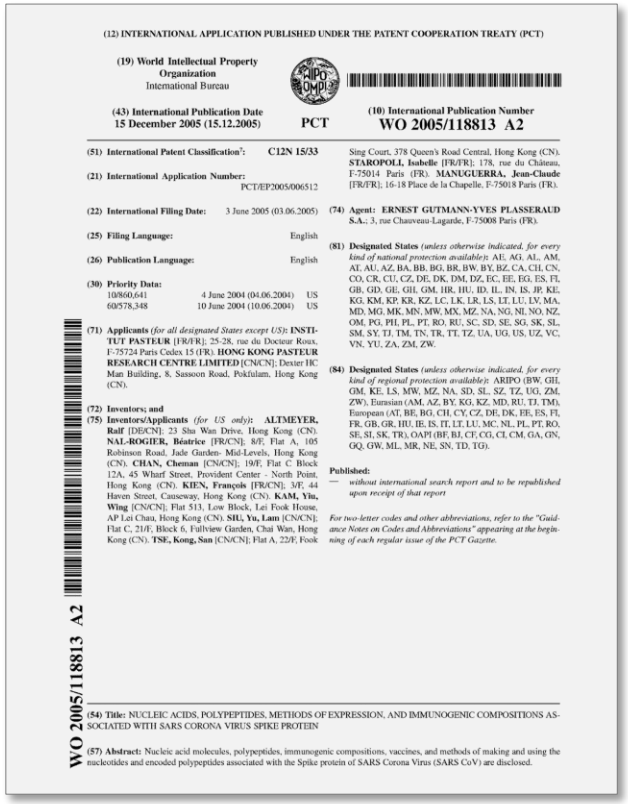

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(54) Title: NUCLEIC ACIDS, POLYPEPTIDES, METHODS OF EXPRESSION, AND IMMUNOGENIC COMPOSITIONS ASSOCIATED WITH SARS CORONA VIRUS SPIKE PROTEIN

(57) Abstract: Nucleic acid molecules, polypeptides, immunogenic compositions, vaccines, and methods of making and using the nucleotides and encoded polypeptides associated with the Spike protein of SARS Corona Virus (SARS CoV) are disclosed.

WO 2005/118813 A2

Altmeyer Teaches SARS-CoV S Protein

[097] Another aspect of the invention provides a method of RNA and/or DNA vaccination. The method also includes administering any combination of the nucleic acids encoding Spike polypeptides, the proteins and polypeptides *per se*, with or without carrier molecules, to an individual. In embodiments, the individual is an animal, and is preferably a

[0111] The Spike protein was tagged with a C-terminal Flag peptide, as shown in Figure 2. The Spike protein was expressed as a full-length protein, including the C-terminal and transmembrane domains as well as a C-terminal Flag tag, in the SFV vector system previously described (See Staropoli et al., Lozach et al., and Chanel et al., all of which are herein incorporated by reference.)

[0116] Mice were immunized intramuscularly with SFV Spike RNA, followed by intraperitoneal (IP) injection of Spike protein at day 14 and at day 35. Serum taken at day 34, day 42, and day 55 from immunized mice showed the presence of recombinant Spike-specific antibodies by Western Blot (Figure 6), FACS (Figure 7), and SARS CoV-specific antibodies by immunofluorescence on SARS CoV infected FRHK4 cells (Figure 8.) These

Ex. 1012 at [097], [0111], [0116]; -1358 Petition, 58-60; -1358 Reply, 11; -1359 Petition, 61-62; -1359 Reply at 12

A POSA Would Have Been Motivated to Combine the Prior Art's Teachings

1. POSA would have had good reason to create an mRNA+LNP vaccine to deliver an immunogen

2. POSA would have had good reason to use a betacoronavirus S protein as the immunogen in that vaccine

A POSA Would Have Been Motivated to Combine the Prior Art's Teachings

Schrum teaches using an mRNA+LNP vaccine encoding for an immunogen to induce an immune response

Activation of the Immune Response: Vaccines

[0340] In one embodiment of the present invention, mRNA molecules may be used to elicit or provoke an immune response in an organism. The mRNA molecules to be delivered may encode an immunogenic peptide or polypeptide and may encode more than one such peptide or polypeptide.

[0397] In one embodiment, an immune response may be elicited by delivering a lipid nanoparticle which may include a nanospecies, a polymer and an immunogen. (U.S. Publication No. 20120189700 and International Publication No. WO2012099805; each of which is herein incorporated by reference in their entirety). The polymer may encapsulate the nanospecies or partially encapsulate the nanospecies. The immunogen may be a recombinant protein, a modified RNA described herein. In one embodiment, the lipid nanoparticle may be formulated for use in a vaccine such as, but not limited to, against a pathogen.

The motivation to combine prior art references can come . . . from the prior art reference, itself.

Incept LLC v. Palette Life Scis., Inc., 77 F.4th 1366, 1372 (Fed. Cir. 2023)

Ex. 1009, ¶¶ 340, 397; -1358 Petition (Paper 3), 40; -1359 Petition (Paper 1), 41-42

A POSA Would Have Been Motivated to Combine the Prior Art's Teachings

Kallen 2014

Abstract: Recent advances strongly suggest that mRNA rather than DNA will be the nucleotide basis for a new class of vaccines and drugs. Therapeutic cancer vaccines against

* * *

transcription factors. The production of mRNA-based vaccines and drugs is highly flexible, scalable and cost competitive, and eliminates the requirement of a cold chain. mRNA-based drugs and vaccines offer all the advantages of a nucleotide-based approach at reduced costs and represent a truly disruptive technology that may start a revolution in medicine.

Schlake 2012

mRNA vaccines combine desirable immunological properties with an outstanding safety profile and the unmet flexibility of genetic vaccines. Based on in situ protein expression, mRNA vaccines are capable of inducing a balanced immune response comprising both cellular and humoral immunity while not subject to MHC haplotype restriction. In addition, mRNA is an intrinsically safe vector as it is a minimal and only transient carrier of information that does not interact with the genome. Because any protein can be expressed from mRNA without the need to adjust the production process, mRNA vaccines also offer maximum flexibility with respect to development. Taken together, mRNA presents a promising vector that may well become the basis of a game-changing vaccine technology platform. Here, we outline the current knowledge regarding different aspects that should be considered when developing an mRNA-based vaccine technology.

Ex. 1020 at 1; Ex. 1019 at 1319; -1358 Petition (Paper 3), 11-12; -1359 Petition (Paper 1), 11

A POSA Would Have Been Motivated to Combine the Prior Art's Teachings

Schrum expressly points to Geall to identify the immunogen for the mRNA to encode

Schrum

[0342] In one embodiment, the modified nucleic acid molecules and/or mmRNA of the invention may encode an immunogen. The delivery of modified nucleic acid molecules and/or mmRNA encoding an immunogen may activate the immune response. As a non-limiting example, the modified nucleic acid molecules and/or mmRNA encoding an immunogen may be delivered to cells to trigger multiple innate response pathways (see International Pub. No. WO2012006377; herein incorporated by reference in its entirety). As another non-limiting example, the modified nucleic acid molecules and mmRNA of the present invention encoding an immunogen may be delivered to a vertebrate in a dose amount large enough to be immunogenic to the vertebrate (see International Pub. No. WO2012006372 and WO2012006369; each of which is herein incorporated by reference in their entirety).

Geall

Coronavirus: Viral immunogens include, but are not limited to, those derived from a SARS coronavirus, avian infectious bronchitis (IBV), Mouse hepatitis virus (MHV), and Porcine transmissible gastroenteritis virus (TGEV). The coronavirus immunogen may be a spike polypeptide.

Ex. 1009, ¶ 342; Ex. 1010 at 19:26-29; -1358 Petition (Paper 3), 41; -1359 Petition (Paper 1), 41

A POSA Would Have Been Motivated to Combine the Prior Art's Teachings

A POSA would have good reason to select the S protein as the immunogen to be encoded in a SARS-CoV mRNA vaccine

Yang

virus therefore remains a high priority. **Here, we show that a DNA vaccine encoding the spike (S) glycoprotein of the SARS-CoV induces T cell and neutralizing antibody responses, as well as protective immunity, in a mouse model.** Alternative forms of S

Altmeyer

[097] Another aspect of the invention provides a method of RNA and/or DNA vaccination. The method also includes administering any combination of the nucleic acids encoding Spike polypeptides, the proteins and polypeptides *per se*, with or without carrier molecules, to an individual. In embodiments, the individual is an animal, and is preferably a

[0116] Mice were immunized intramuscularly with SFV Spike RNA, followed by intraperitoneal (IP) injection of Spike protein at day 14 and at day 35. Serum taken at day 34, day 42, and day 55 from immunized mice showed the presence of recombinant Spike-specific antibodies by Western Blot (Figure 6), FACS (Figure 7), and SARS CoV-specific antibodies by immunofluorescence on SARS CoV infected FRHK4 cells (Figure 8.) These

Yang and Altmeyer also disclose nucleic acid vaccines encoding for the SARS-CoV S protein

Ex. 1011 at 561; Ex. 1012 at [97], [0116]; -1358 Petition (Paper 3) 49, 60; -1359 Petition (Paper 1) 19, 50-51, 54, 62, 64

A POSA Would Have Been Motivated to Combine the Prior Art's Teachings

Both sides' experts agree: A POSA would be motivated to develop a SARS-CoV vaccine using the S protein

Patent Owner's Declarant, Dr. Krause

170. That latent need for a betacoronavirus vaccine to be ready in the event of a future pandemic existed even though the SARS and MERS outbreaks had been controlled with public health measures such that there was no immediate, pressing need for a specific vaccine as of 2015.

Patent Owner's Declarant, Dr. Fuller

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

Petitioner's Declarant, Dr. Griffin

Geall gives us a list of pathogens that we might want to make a vaccine for. . . . . [I]n that list are the top ten emerging -- some of the top ten emerging pathogens of pandemic potential, including at the very bottom of page 19, Coronavirus in the very last sentence, the spike protein.

Ex. 2200 (-1359), ¶ 170; Ex. 1104 at 41:20-42:3; Ex. 2114, 68:11-20; -1358 Reply (Paper 59), 12-13; -1359 Reply (Paper 59), 13-14

A POSA Would Have Been Motivated to Combine the Prior Art's Teachings

SARS-CoV S protein was known to be "one of the most important targets for the development of SARS vaccines and therapeutics"

Du 2009

Neutralizing antibodies and/or T-cell immune responses can be raised directly against several SARS-CoV proteins[21–23], but mainly target the S protein[20,24–26], suggesting that S protein-induced specific immune responses play important parts in the fight against SARS-CoV infection[18]. SARS-CoV S protein also has a key role in the ability of SARS-CoV to overcome the species barrier, as adaptive evolution of S protein can contribute to the animal-to-human transmission of SARS-CoV[27]. Because the S protein of SARS-CoV is involved in receptor recognition, as well as virus attachment and entry, it represents one of the most important targets for the development of SARS vaccines and therapeutics.

Vaccines based on the SARS-CoV S protein

The roles of S protein in receptor binding and membrane fusion indicate that vaccines based on the S protein could induce antibodies to block virus binding and fusion or neutralize virus infection. 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. S protein has therefore been selected as an important target for vaccine and antiviral development. A comparison of these approaches is provided in TABLE 1.

A POSA Would Have Been Motivated to Combine the Prior Art's Teachings

Patent Owner confirmed to the FDA that a POSA would have been motivated to select S-Protein

Patent Owner's FDA Submission

based vaccine against SARS-CoV-2(mRNA-1273). Prior preclinical studies have demonstrated that coronavirus spike proteins (S protein) are immunogenic and S protein-based vaccines, including deoxyribonucleic acid (DNA) and mRNA delivery platforms, are protective in animals. Prior clinical trials of vaccines targeting related coronaviruses and other viruses have demonstrated that DNA and mRNA-based vaccines are safe and immunogenic. It is therefore anticipated that mRNA-1273 will generate robust immune responses to the SARS-CoV-2S protein.

Ex. 2056 at 6; Paper 20 (-1359), 69; -1358 Reply (Paper 59), 25; -1359 Reply (Paper 59), 25-26

A POSA Would Have a Reasonable Expectation of Success

Reasonable expectation of success is defined by the claim scope, not by any alleged commercial embodiment

Allergan, Inc. v. Sandoz Inc.

726 F.3d 1286 (Fed. Cir. 2013)
Decided Sep 9, 2013

There is no requirement that one of ordinary skill have a reasonable expectation of success in developing Combigan®. Rather, the person of ordinary skill need only have a reasonable expectation of success of developing the claimed invention.

Allergan, Inc v. Sandoz Inc., 726 F.3d 1286, 1292 (Fed. Cir. 2013)

A POSA Would Have Had a Reasonable Expectation of Making SARS-CoV S Protein-Encoding mRNA in an LNP

Schrum Teaches mRNA in an LNP

Synthesis of Modified Nucleic Acid Molecules

[0320] Modified nucleic acid molecules for use in accordance with the present disclosure may be prepared according to any available technique including, but not limited to, in vitro transcription such as chemical synthesis and enzymatic synthesis, or enzymatic and chemical cleavage of a longer precursor, etc. Methods of synthesizing RNA are known in the art (see, e.g., Gait, M. J. (ed.) *Oligonucleotide synthesis: a practical approach*, Oxford [Oxfordshire], Washington, D.C.: IRL Press, 1984; and Herdewijn, P. (ed.) *Oligonucleotide synthesis: methods and applications*, Methods in Molecular Biology, v. 288 (Clifton, N.J.) Totowa, N.J.: Humana Press, 2005; both of which are incorporated herein by reference).

Lipid Nanoparticle In Vivo Studies

[0995] G-CSF (cDNA with the T7 promoter, 5' Untranslated region (UTR) and 3'UTR used in in vitro transcription is given in SEQ ID NO: 5. mRNA sequence shown in SEQ ID NO: 6; polyA tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap 1; fully modified with 5-methylcytosine and pseudouridine) and Factor IX (cDNA with the T7 promoter, 5' UTR and 3'UTR used in in vitro transcription is given in SEQ ID NO: 13. mRNA sequence shown in SEQ ID NO:10; polyA tail of approximately 160 nucleotides not shown in sequence; 5' cap, Cap 1; fully modified with 5-methylcytosine and pseudouridine) modified mRNA were formulated as lipid nanoparticles (LNPs) using the syringe pump method. The 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). Formulations, listed in Table 27, were characterized by particle size, zeta potential, and encapsulation.

Ex. 1009, ¶¶ 320, 995; -1358 Petition (Paper 3), 26-27, 40-42; -1359 Petition (Paper 1), 24, 41-43

A POSA Would Have Reasonably Expected to Express the S-Protein with mRNA-LNP

Dr. Fuller conceded, and the art teaches, that a POSA reasonably would expect to achieve protein expression

Schlake 2012

mRNA as the technological basis of therapeutics and vaccines is characterized by a great flexibility with respect to production and application. Any protein can be encoded and expressed by mRNA, in principle enabling the development of prophylactic and therapeutic vaccines fighting diseases as diverse as infections and cancer as well as protein replacement therapies. Since changes of the encoded protein just alter the sequence of the RNA molecule, leaving its physico-chemical characteristics largely unaffected, diverse products can be manufactured using the same

Q. And your article proceeds, "For any given protein, once we know the genetic sequence or code, we can design an mRNA or DNA molecule that prompts a person's cells to start making it." Right?

A. That's right.

Patent Owner's Declarant, Dr. Fuller

Ex. 1019 at 1; Ex. 1104 at 78:11-16; -1358 Reply (Paper 59), 16, 19; -1359 Reply (Paper 59), 17, 20

A POSA Would Have Reasonably Expected mRNA to Elicit an Immune Response

mRNA vaccines were known to be effective at expressing antigens and eliciting immune responses to them

Geall 2013

3. Proof of concept

RNA vaccines (both mRNA and replicons) are effective at eliciting antigen-specific humoral and cellular immune responses in animal models of infectious and non-infectious diseases. Various RNA vaccine candidates targeting viral [22,28,32–38], and cancer [39–43] antigens, as well as allergens [44,45], have been evaluated. In many cases, functional, protective immunity was afforded by RNA vaccination [30,33,35,36,38]. Like DNA vaccines and viral vectors, RNA vaccine candidates induce both CD4+ and CD8+ T cell responses, as transfection of host cells can facilitate antigen presentation by major histocompatibility complex molecules and priming of naive T lymphocytes. *In situ* production of genic in CMV sero-negative individuals [29]. This growing body of preclinical and clinical evidence demonstrates proof of concept that vaccines based on RNA, whether conventional mRNA or self-amplifying replicons, are effective at eliciting functional immunity and should be rigorously tested.

A POSA Would Have Reasonably Expected mRNA to Elicit an Immune Response

Dr. Fuller also conceded that a POSA reasonably would expect an immune response once the spike protein is expressed

Patent Owner's Declarant, Dr. Fuller

Q. Once you know that the spike protein is expressing, you would expect that the vaccine candidate would induce an immune response.

. . . That was your expectation?

A. Yes.

Ex. 1104, 50:21-51:6; -1358 Reply (Paper 59), 20; -1359 Reply (Paper 59), 20-21

A POSA Would Have Reasonably Expected to Induce an Immune Response and Neutralizing Antibodies

A POSA would have had a reasonable expectation of using mRNA encoding for SARS-CoV S protein to induce <u>some</u> level of immune response, including <u>some</u> level of neutralizing antibodies

Daniel Griffin, M.D., Ph.D.

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

<u>*Every*</u> SARS-CoV S protein vaccine of record induced an immune response

Ex. 1159 (-1359), ¶ 197; Ex. 1132, 9804; -1358 Reply (Paper 59), 12-13, 20; -1359 Reply (Paper 59), 13-14, 20.

A POSA Would Have Reasonably Expected to Induce an Immune Response and Neutralizing Antibodies

Prior art reports use of S protein vaccines to induce an immune response

REVIEWS

The spike protein of SARS-CoV — a target for vaccine and therapeutic development

MARCH 2009 | VOLUME 7

Du 2009

The spike protein of SARS-CoV — a target for vaccine and therapeutic development

Lanying Du, Yuxian He*, Yusen Zhou‡, Shuwen Liu§, Bo-Jian Zheng‖ and Shibo Jiang**

Vaccines based on the full-length S protein. Several vaccines that are based on the full-length S protein of SARS-CoV have been reported. Yang *et al.*[59] showed that a DNA vaccine encoding the full-length S protein SARS-CoV Urbani strain could induce both T-cell and neutralizing-antibody responses, as well as protective immunity, in a mouse model. Other groups have also shown that vaccination of mice or monkeys with highly attenuated modified vaccinia virus Ankara (MVA), which encodes the full-length S protein of the SARS-CoV Urbani strain or HKU39849 strain, elicited S-specific neutralizing antibodies and protective immunity, as evidenced by decreased virus titres in the respiratory tracts of animals after homologous SARS-CoV challenge[60,61]. Passive transfer of murine serum to naive mice also protected these mice from the challenge of homologous SARS-CoV[60,61]. In addition, vaccination of mice or hamsters with a full-length S protein trimer protected these animals from infection by homologous SARS-CoV (HKU39849 strain)[62]. Furthermore, a recombinant baculovirus-expressed full-length S protein of the Urbani strain and its trimer could induce sufficient neutralizing antibodies against human and palm civet SARS pseudoviruses that bore S proteins of homologous and heterologous SARS-CoV variants (for example, Tor2, GD03T13 and SZ3 strains) in vaccinated mice[63]. These reports suggest that the full-length S protein is highly immunogenic and induces protection against SARS-CoV challenge and that neutralizing antibodies alone may be able to suppress virus proliferation, further justifying the rationale that vaccines can be developed based on the S protein.

Contributions of the structural proteins of severe acute respiratory syndrome coronavirus to protective immunity

Buchholz 2004

Contributions of the structural proteins of severe acute respiratory syndrome coronavirus to protective immunity

Ursula J. Buchholz*, Alexander Bukreyev, Lijuan Yang, Elaine W. Lamirande, Brian R. Murphy, Kanta Subbarao, and Peter L. Collins

homogenates. Thus, a single intranasal immunization with a recombinant vector expressing the S protein was highly immunogenic and protective against SARS-CoV challenge. In contrast, the N, M, and E proteins, singly or in two combinations, did not make a significant contribution to a neutralizing antibody response or protective immunity. Finally, there was no evidence that immunization with any of the SARS-CoV antigens, involving the induction of either neutralizing or nonneutralizing antibodies, led to antibody-mediated enhancement of infection, as described for feline infectious peritonitis virus (30–32).

Ex. 1031 at 229; Ex. 1132 at 9809; -1358 Reply (Paper 59), 13-14; -1359 Reply (Paper 59), 14-15

A POSA Would Have Reasonably Expected to Induce an Immune Response and Neutralizing Antibodies

Prior art reports use of S protein DNA vaccines to induce an immune response

Yang 2004

the possibility of future recurrences. **Finding a vaccine for this virus therefore remains a high priority. Here, we show that a DNA vaccine encoding the spike (S) glycoprotein of the SARS-CoV induces T cell and neutralizing antibody responses, as well as protective immunity, in a mouse model.** Alternative forms of S

cular injection in BALB/c mice. Injection of S, SΔTM and SΔCD expression vectors induced a substantial immune response. A marked increase was observed in the number of SARS-CoV S-specific CD4 T-cell immune responses (Fig. 2a), as measured by intracellular cytokine staining for interferon-γ (IFN-γ) and tumour necrosis factor-α (TNF-α). In addition, substantial SARS-CoV S-specific CD8 cellular immunity was detected at levels at least sevenfold above the background response. Humoral immunity was initially

Wang 2015

neutralization through fusion inhibition. We developed an alternative vaccine regimen, based on full-length S DNA and a truncated S1 subunit glycoprotein, to elicit a broad repertoire of antibodies with diverse mechanisms of viral neutralization, and found that immunization with these constructs protected non-human primates (NHPs) from severe lung disease after intratracheal challenge with MERS-CoV.

Full-length S DNA and S1 protein elicit high titers of NAb in mice. Mice primed either once with S1 protein or twice with S DNA and then boosted once with S1 protein generated the highest neutralizing antibody (NAb) titres among all groups (Fig. 1b). The full-length S DNA regimen induced a significantly higher antibody response than the truncated S-ΔTM or S1 DNA regimens. Antibody titres tended to be either low or undetectable

Ex. 1011 at 561; Ex. 1101 at 2; -1358 Petition, 48-49; -1358 Reply, 13-15; -1359 Petition, 50-51; -1359 Reply, 14-16

A POSA Would Have Reasonably Expected to Combine the Prior Art's Teachings and Arrive at the Challenged Claims

1	A POSA would have reasonably expected to **synthesize** SARS-CoV S protein-encoding mRNA and **formulate** that mRNA in lipid nanoparticles
2	A POSA would have reasonably expected that administration of S protein-encoding mRNA would lead to **expressing the S protein**
3	A POSA would have reasonably expected that expression of SARS-CoV S protein in the body would **induce some level of immune response**—indeed a neutralizing antibody response

Petitioner has demonstrated that each challenged claim would have been obvious to a POSA as of October 2015, and each challenged claim is therefore unpatentable

Agenda

- Overview of the challenged patents, the prior art & the instituted grounds
- Anticipation by Schrum (Ground 1)
- Obviousness in view of Schrum and Geall, Yang, or Altmeyer (Grounds 2-4)
  - Petitioner has demonstrated unpatentability
  - Patent Owner's arguments are defeated by the literature, the law, and its own experts' testimony
  - No secondary considerations support non-obviousness
- The testimony of Patent Owner's declarants should be afforded little weight

Patent Owner's Scattershot Arguments Fail to Rebut Obviousness

Patent Owner makes a series of contentions to move the goalposts of obviousness:

1. Alleged skepticism of mRNA vaccines
2. Alleged failure in the prior art
3. Alleged concerns with ADE
4. Alleged reasons not to use lipid nanoparticles
5. Alleged irrelevance of data using other vaccine modalities
6. Alleged lack of data using the claimed composition

None withstands scrutiny

Patent Owner's Scattershot Arguments Fail to Rebut Obviousness

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6. Alleged lack of data using the claimed composition

None withstands scrutiny

The Field Was Optimistic about mRNA Vaccines

Patent Owner's selective quotations ignore that its cited reference evidence optimism, not skepticism

Patent Owner:

"The literature was replete with reasons for skepticism. For example, a 2013 article from Dr. Geall explains mRNA was considered unstable and likely to trigger the body's innate immune response."

-1359 POR (Paper 42), 41

Geall 2013

3. Proof of concept

RNA vaccines (both mRNA and replicons) are effective at eliciting antigen-specific humoral and cellular immune responses in animal models of infectious and non-infectious diseases. Various RNA vaccine candidates targeting viral [22,28,32–38], and cancer [39–43] antigens, as well as allergens [44,45], have been evaluated. In many cases, functional, protective immunity was afforded by RNA vaccination [30,33,35,36,38]. Like DNA vaccines and viral vectors, RNA vaccine candidates induce both CD4+ and CD8+ T cell responses, as transfection of host cells can facilitate antigen presentation by major histocompatibility complex molecules and priming of naive T lymphocytes. *In situ* production of genic in CMV sero-negative individuals [29]. This growing body of preclinical and clinical evidence demonstrates proof of concept that vaccines based on RNA, whether conventional mRNA or self-amplifying replicons, are effective at eliciting functional immunity and should be rigorously tested.

Ex. 1016 at 154; -1358 Reply (Paper 59), 16-17; -1359 Reply (Paper 59), 17-18

The Field Was Optimistic about mRNA Vaccines

Patent Owner:

"For example, Petsch (2012) states 'mRNA-based Immunotherapeutics are currently undergoing clinical testing in ***oncological indications***, and they exhibit promising immunogenicity. However, ***whether mRNA vaccines*** induce protective antibody' responses and ***are efficacious in infectious disease is not clear***."

-1359 POR (Paper 42), 42

Petsch 2012

Quoted by Patent Owner:

Omitted by Patent Owner:

However, whether mRNA vaccines induce protective antibody responses and are efficacious in infectious disease is not clear. Here we validated the mRNA vaccine approach for a B cell–dependent mode of protection against an infectious disease, influenza. We designed optimized mRNA vaccines for prophylactic vaccination against influenza A H1N1, H3N2 and H5N1 viruses, administered these mRNA vaccines by intradermal injection in mice, ferrets and domestic pigs, and analyzed immunogenicity and/or protective efficacy in these animal models.

* * *

adaptation and administration of vaccines. Here we show that mRNA vaccines can, in principle, address both requirements. We also argue that mRNA vaccines exhibit additional advantages. (i) As a synthetic format, mRNA avoids the complications of cell- or egg-based vaccine production, including inadvertent selective pressures on virus growth and isolation and handling of infectious virus. mRNA vaccine production requires only a relevant nucleic acid sequence that can be made accessible safely and rapidly. (ii) Unlike plasmid DNA, mRNA poses no danger of genomic integration and there remain no selective markers (e.g., antibiotic resistance genes) in the final vaccine product. (iii) Unlike recombinant viruses, mRNA is a minimal, nonreplicating and fully defined genetic vector. (iv) mRNA is short-lived, limiting vector persistence and antigen expression, and thereby giving precise control over pharmacokinetics and dosing. (v) mRNA is naturally recognized by innate pattern-recognition receptors, thereby inducing an effective, adaptive, immune response and potentially reducing the need for adjuvants. (vi) As a genetic format mRNA allows the production of complex antigens *in situ*, enabling state of the art rational vaccine design[37], and efficient access to the MHC class I compartment of antigen-expressing cells[8,12]; both are major limitations of traditional, protein-based vaccine formats.

Every **reference cited by Patent Owner demonstrates optimism, not skepticism**

Patent Owner's Scattershot Arguments Fail to Rebut Obviousness

Patent Owner makes a series of contentions to move the goalposts of obviousness:

1. Alleged skepticism of mRNA vaccines
2. Alleged failure in the prior art
3. Alleged concerns with ADE
4. Alleged reasons not to use lipid nanoparticles
5. Alleged irrelevance of data using other vaccine modalities
6. Alleged lack of data using the claimed composition

None withstands scrutiny

No Relevant Failure in the Prior Art

Filed: October 16, 2024

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BIONTECH SE AND PFIZER INC.,
Petitioner,

v.

MODERNA TX, INC.,
Patent Owner.

Case IPR2023-01359
Patent No. 10,933,127

PATENT OWNER'S SUR-REPLY

Prior-art failures would have made a POSA skeptical of using mRNA-LNP for an infectious disease vaccine or using betacoronavirus S-protein. Contrary to Petitioners' suggestion (Reply, 14-15), Moderna does not and need not argue teaching away. *Rembrandt Wireless Techs., LP v. Samsung Elecs. Co., Ltd.*, 853 F.3d 1370, 1379-1380 (Fed. Cir. 2017). Failures "undermine a finding of a reasonable expectation of success." *Univ. of Strathclyde v. Clear-Vu Lighting LLC*, 17 F.4th 155, 164-165 (Fed. Cir. 2021).

Patent Owner does not rely on teaching away—only on purported "failures" regarding reasonable expectation of success

Patent Owner's Reliance on Alleged "Failure" in the Prior Art Is Irrelevant and Unsupported

- Patent Owner's "failure" arguments rest on ***failure to commercialize*** clinical vaccine candidates
  - But "reasonable expectation of success" is defined by claim scope, not FDA licensure
- No evidence of any failure to achieve challenged claims
- No evidence of ***any*** betacoronavirus S protein-based vaccine that failed to induce an immune response

Patent Owner's Declarant, Dr. Fuller

Q. Are you aware of any SARS-CoV vaccines using spike proteins that induced an immune response?

A. Yes. . . Pretty much every vaccine type out there. There was primarily inactivated recombinant protein, there was DNA vaccine. There were others, various ones using different antigens formulated with different vaccines.

Ex. 1104, 65:15-66:2; -1358 Reply (Paper 59), 13, 20, 22; -1359 Reply (Paper 59), 14, 20-21, 23

No Relevant Failure in the Prior Art

Patent Owner:

"By 2015, no mRNA vaccine was approved for infectious disease. Ex. 2027, 268. Of thousands of infectious disease vaccine clinical trials, only seven were testing mRNA vaccines. Ex. 2084, Table 6; Ex. 2027, 268, Table 2. None tested betacoronavirus, none was formulated in LNP, and all ultimately ***failed*** . . ."

-1359 Sur-Reply (Paper 72), 18

ALLERGAN, INC., Plaintiff–Appellee,

v.

SANDOZ INC., Alcon Laboratories, Inc., Alcon Research, Ltd., Alcon, Inc., and Falcon Pharmaceuticals, Ltd., Defendants–Appellants,

For example, the claims are not drawn to the Combigan® formulation with any specificity given that Combigan® contains many elements in addition to those embodied in the claims. There is no requirement that one of ordinary skill have a reasonable expectation of success in developing Combigan®. Rather, the person of ordinary skill need only have a reasonable expectation of success of developing the claimed invention.

Allergan, Inc v. Sandoz Inc., 726 F.3d 1286, 1292 (Fed. Cir. 2013)

Failure of other vaccines to achieve licensure is not probative as to reasonable expectation of success in *developing the claimed invention*

See -1358 Reply (Paper 59), 19-22; -1359 Reply (Paper 59), 20-23

No Relevant Failure in the Prior Art

Patent Owner ignores that S protein vaccines showed only success, not failure:

"The skepticism in the art (with corresponding failures) and absence of any indicator of success defeat reasonable expectation of success. *See Eli Lilly*, 8 F.4th at 1356 (unpredictability "'equates . . . with nonobviousness'").

-1359 Sur-Reply (Paper 72), 19

Patent Owner's Declarant, Dr. Fuller

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

Ex. 1104 at 41:20-42:3

Daniel Griffin, M.D., Ph.D.

"Moreover, the fact that S-protein was the most obvious antigen for a betacoronavirus vaccine is further confirmed by the fact that multiple groups found it to be [the] effective antigen choice across a wide variety of vaccine approaches."

Ex. 1159 (-1359), ¶ 197

Patent Owner has not cited a *single* S protein vaccine that failed to induce an immune response

-1358 Reply (Paper 59), 13, 20-22; -1359 Reply (Paper 59), 13, 20-23

No Relevant Failure in the Prior Art

Patent Owner:

"None tested betacoronavirus, none was formulated in LNP, and all ultimately ***failed***, even those encoding for immunogens (**rabies, HIV**) on Geall's laundry list."

-1359 Sur-Reply (Paper 72), 18

Safety and immunogenicity of a mRNA rabies vaccine in healthy adults: an open-label, non-randomised, prospective, first-in-human phase 1 clinical trial

Martin Alberer, Ulrike Gnad-Vogt, Henoch Sangjoon Hong, Keyvan Tadjalli Mehr, Linus Backert, Greg Finak, Raphael Gottardo, Mihai Alexandru Bica, Aurelio Garofano, Sven Dominik Koch, Mariola Fotin-Mleczek, Ingmar Hoerr, Ralf Clemens, Frank von Sonnenburg

phase of the immune response. This finding was corroborated by SPICE analysis showing an increase of polyfunctional RABV-G-specific CD4+ T cells (figure 3C). There was a robust correlation between humoral and cellular immune responses (figure 3D). These data show that the mRNA vaccine can induce virus-specific cellular immune responses in previously naive participants.

Ex. 2046 at 8

Phase I clinical trial of an intranodally administered mRNA-based therapeutic vaccine against HIV-1 infection

In conclusion, this phase I exploratory dose-escalating trial showed that iHIVARNA vaccination was feasible, harmless and well tolerated, was able to induce moderate HIV-specific immune responses and transiently increased caHIV-RNA expression and ultrasensitive plasma viremia. These data support further exploration of iHIVARNA in the currently ongoing phase II clinical trial.

Ex. 1119 at 2542

The purported "failures" show that mRNA vaccines induced an immune response against rabies and HIV

See -1358 Reply (Paper 59), 19-22; -1359 Reply (Paper 59), 20-23; Ex. 1159 (-1359), ¶¶ 162-69

Patent Owner's Scattershot Arguments Fail to Rebut Obviousness

Patent Owner makes a series of contentions to move the goalposts of obviousness:

1. Alleged skepticism of mRNA vaccines
2. Alleged failure in the prior art
3. Alleged concerns with ADE
4. Alleged reasons not to use lipid nanoparticles
5. Alleged irrelevance of data using other vaccine modalities
6. Alleged lack of data using the claimed composition

None withstands scrutiny

Alleged "Concerns" with Enhanced Disease Support Obviousness, Not Non-Obviousness

Patent Owner relies on "enhanced disease" as teaching away from an S protein vaccine, but "enhanced disease" would direct a POSA towards—and not away—from the S protein immunogen

- Patent Owner relies on literature from ***other*** coronaviruses because prior art confirms ***no enhanced disease concerns with a betacoronavirus S protein vaccine***
- Patent Owner ignores that enhanced disease is a universal concern in vaccine development
- By October 2015, well-known that the S protein was the major target for neutralizing antibodies, which ***reduces*** the risk of enhanced disease

A POSA Would Not Have Been Dissuaded by Concerns about ADE

No evidence that immunization with SARS-CoV antigens would lead to antibody-mediated enhancement of infection

Bucholz 2004

Thus, a single intranasal immunization with a recombinant vector expressing the S protein was highly immunogenic and protective against SARS-CoV challenge. In contrast, the N, M, and E proteins, singly or in two combinations, did not make a significant contribution to a neutralizing antibody response or protective immunity. Finally, there was no evidence that immunization with any of the SARS-CoV antigens, involving the induction of either neutralizing or nonneutralizing antibodies, led to antibody-mediated enhancement of infection, as described for feline infectious peritonitis virus (30–32).

Du 2009

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. S protein has therefore been selected as an important target for vaccine and antiviral development

Ex. 1132 at 9809; Ex. 1031 at 229; -1358 Reply (Paper 59), 14-15; -1359 Reply (Paper 59), 15-16

A POSA Would Not Have Been Dissuaded by Concerns about ADE

Dr. Griffin has explained it is a **universal** concern in vaccine development that would not dissuade from an S protein vaccine

Daniel Griffin, M.D., Ph.D.

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

A POSA Would Not Have Been Dissuaded by Concerns about ADE

Experts agree that enhanced disease is a phenomenon resulting from a vaccine's inability to induce *neutralizing* antibodies

Daniel Griffin, M.D., Ph.D.

Second, to the extent a POSA was looking to minimize the risk of disease enhancement caused by a betacoronavirus vaccine, a POSA would be ***more*** motivated to use an S protein immunogen. Enhanced disease tends to arise where vaccines are unable to induce a neutralizing antibody response. As Dr. Fuller acknowledges, [a]ntibody-dependent enhancement of disease (ADE) . . . refers to a phenomenon in which a vaccine induces the production of antibodies that, when exposed to a real virus, enhance the ability of the virus to infect cells and cause disease, instead of neutralize the virus.

- Patent Owner's declarant, Dr. Krause: Enhanced disease "is more likely when the neutralizing antibody response is low compared to the total antibody response" Ex. 2200 (-1359), ¶ 145.

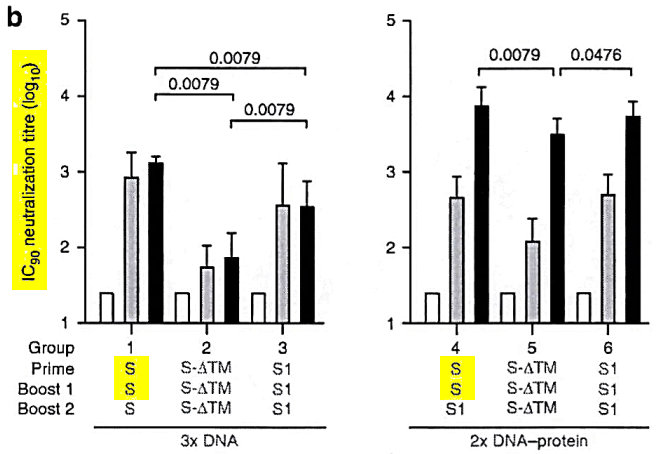
POSA would seek to *maximize* neutralizing antibody response to reduce risk of enhanced disease

Ex. 1159 (-1359), ¶ 211; -1358 Reply (Paper 59), 14; -1359 Reply (Paper 59), 15

A POSA Would Not Have Been Dissuaded by Concerns about ADE

Demonstrated by October 2015 that vaccination with "full-length" S protein increased neutralizing antibody response

Full-length S DNA and S1 protein elicit high titers of NAb in mice. Mice primed either once with S1 protein or twice with S DNA and then boosted once with S1 protein generated the highest neutralizing antibody (NAb) titres among all groups (Fig. 1b). The full-length S DNA regimen induced a significantly higher antibody response than the truncated S-ΔTM or S1 DNA regimens. Antibody titres tended to be either low or undetectable



Patent Owner's Declarant, Dr. Fuller

"In this figure, they ended up showing the full-length spike protein not surprisingly actually induced higher antibody titers than truncated version. And that's not surprising because it is going to – the full-length S protein will have more epitopes, neutralizing antibody epitopes to target."

POSA aiming to minimize risk of enhanced disease would have good reason to encode full-length S protein to *maximize* neutralizing antibody response

Ex. 1101 at 2, 3; Ex. 1104 at 260:9-15; -1358 Reply (Paper 59), 15-16; -1359 Reply (Paper 59), 16-17

A POSA Would Not Have Been Dissuaded by Concerns about ADE

Demonstrated by October 2015 that vaccination with "full-length" S protein increased neutralizing antibody response

Du 2009

It has been reported that antibodies raised to amino acids 485–625 in S1 or 1,029–1,192 in S2 neutralize infection by SARS-CoV strains (for example, Tor2 and Sin2774) in Vero E6 cells[56,57]. Vaccination of African green monkeys with an attenuated parainfluenza virus that encodes the full-length S protein of SARS-CoV Urbani strain resulted in the production of S protein-specific neutralizing antibodies, which protected vaccinated monkeys from subsequent homologous SARS-CoV challenge[58], suggesting that immunization with the S protein of SARS-CoV is highly effective in the prevention of SARS.

Vaccines based on the full-length S protein.

GD03T13 and SZ3 strains) in vaccinated mice[63]. These reports suggest that the full-length S protein is highly immunogenic and induces protection against SARS-CoV challenge and that neutralizing antibodies alone may be able to suppress virus proliferation, further justifying the rationale that vaccines can be developed based on the S protein.

POSA aiming to minimize risk of enhanced disease would have good reason to encode full-length S protein to *maximize* neutralizing antibody response

Ex. 1031 at 229; -1358 Reply (Paper 59), 13-15; -1359 Reply (Paper 59), 14-16

A POSA Would Not Have Been Dissuaded by Concerns about ADE

Patent Owner's own statements likewise confirm no teaching away from S protein vaccines

Patent Owner's FDA Submission

based vaccine against SARS-CoV-2(mRNA-1273). Prior preclinical studies have demonstrated that coronavirus spike proteins (S protein) are immunogenic and S protein-based vaccines, including deoxyribonucleic acid (DNA) and mRNA delivery platforms, are protective in animals. Prior clinical trials of vaccines targeting related coronaviruses and other viruses have demonstrated that DNA and mRNA-based vaccines are safe and immunogenic. It is therefore anticipated that mRNA-1273 will generate robust immune responses to the SARS-CoV-2S protein.

Ex. 2056 at 6; Paper 20 (-1359), 69; -1358 Reply (Paper 59), 25; -1359 Reply (Paper 59), 25-26

A POSA Would Not Have Been Dissuaded by Concerns about ADE

Vennema (Ex. 2029) does not show disease enhancement by betacoronavirus vaccines

Vennema 1990

Feline infectious peritonitis (FIP) is a progressive, debilitating, highly fatal disease in wild and domestic *Felidae*. In the pathogenesis of FIP the infection of cells of the monocyte-macrophage lineage appears to be of central importance. The causative agent, FIP virus (FIPV), has been identified as a member of the family *Coronaviridae*. Based on circumstantial evidence, FIPV immunity is thought to be largely cell mediated. Thus far, attempts to vaccinate against FIPV have failed.

Yang 2004

The **feline infectious peritonitis virus** is a coronavirus that causes significant morbidity and mortality in **domestic animals** for which vaccines have been investigated, but the development of these vaccines has been complicated by possible immune potentiation of the disease and by viral evolution. In the present study, T-cell depletion and immune IgG passive transfer were used to assess the importance of humoral responses in protection against SARS-CoV challenge. **These results suggest that antibodies against SARS-CoV S glycoprotein protect against SARS-CoV challenge** and **do not enhance infection in this animal model**.

Bucholz 2004

Thus, a single intranasal immunization with a recombinant vector expressing the S protein was **highly immunogenic and protective against SARS-CoV challenge.** In contrast, the N, M, and E proteins, singly or in two combinations, did not make a significant contribution to a neutralizing antibody response or protective immunity. Finally, there was **no evidence that immunization with any of the SARS-CoV antigens**, involving the induction of either neutralizing or nonneutralizing antibodies, **led to antibody-mediated enhancement of infection**, as described for **feline infectious peritonitis virus**.

Patent Owner's principal evidence of enhanced disease is Vennema 1990 (Ex. 2029), which studied feline infectious peritonitis ("FIP") virus – *not* a betacoronavirus

Ex. 2029 at 1407; Ex. 1011 at 563; Ex. 1132 at 9809; -1358 Reply (Paper 59), 14; -1359 Reply (Paper 59), 15: Ex. 1159 (-1359), ¶¶ 223-25

A POSA Would Not Have Been Dissuaded by Concerns about ADE

Jaume (Ex. 2030) would not have dissuaded a POSA from using S-protein

Daniel Griffin, M.D., Ph.D.

[I]nfection of cells does not necessarily lead to increased disease severity. A POSA reading Jaume would have been acutely aware of this fact because **the virus that infected the human immune cells were unable to replicate and therefore could not produce infectious virus.**

Jaume

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

Jaume Reported that "No Evidence of Productive Virus Replication and Spread"

A POSA Would Not Have Been Dissuaded by Concerns about ADE

Jaume's (Ex. 2030) antibody administration would not have dissuaded a POSA from using S-protein

Daniel Griffin, M.D., Ph.D.

The mice [in Jaume] were never challenged with a SARS-CoV infection after immunization with the vaccine candidate. There was never any observation in Jaume, then, of enhanced disease in the mice in response to the vaccine itself . . . . [Instead], Jaume measured antibody-dependent enhancement of infection by **infecting human immune cells *in vitro* with SARS-CoV virus in the presence of the antibody sera collected from the mice.**

Patent Owner's Declarant, Dr. Krause

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

Moderna's Own Expert Testified that "Administration of an Antibody is Very Different From Administering an Antigen"

Ex. 1159 (-1359), ¶¶ 218-219; Ex. 2200 ¶ 161; -1358 Reply (Paper 59), 14; -1359 Reply (Paper 59), 15

A POSA Would Not Have Been Dissuaded by Concerns about ADE

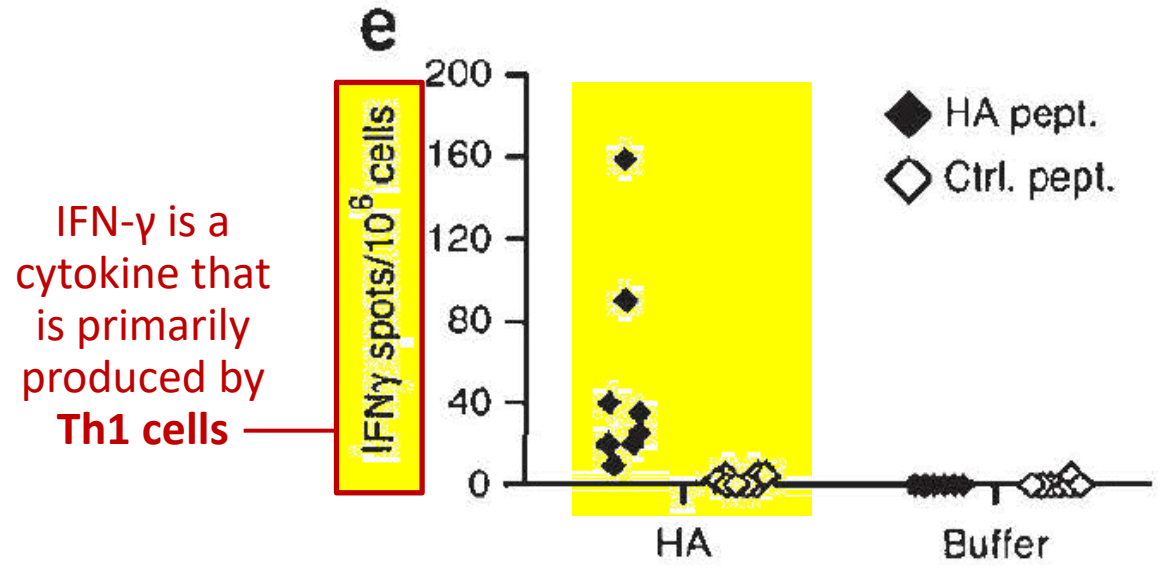
Dr. Fuller's testimony further confirms that ADE would not have dissuaded a POSA from pursuing a mRNA vaccine encoding the S-protein

Patent Owner's Declarant, Dr. Fuller

"Th2 type immune responses had been associated with enhanced infection when used with the S protein. And we knew that Th1 type of responses were associated with lack of enhanced disease."

Protective efficacy of *in vitro* synthesized, specific mRNA vaccines against influenza A virus infection

Benjamin Petsch[1,5,6], Margit Schnee[2,6], Annette B Vogel[1,5], Elke Lange[3], Bernd Hoffmann[4], Daniel Voss[2], Thomas Schlake[2], Andreas Thess[2], Karl-Josef Kallen[2], Lothar Stitz[1,5] & Thomas Kramps[2]



IFN-γ is a cytokine that is primarily produced by **Th1 cells**

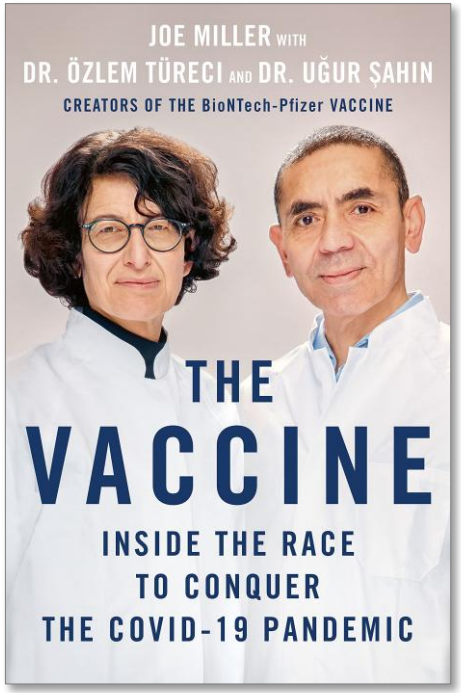
Ex. 1159 (-1359), ¶ 214; Ex. 2025 at 1210-11; *contra* -1358 Sur-Reply (Paper 72), 22, -1359 Sur-Reply (Paper 72), 22

A POSA Would Not Have Been Dissuaded by Concerns about ADE

Patent Owner:

"This skepticism was confirmed by BioNTech's CEO who explained his team remained concerned about avoiding 'an ADE disaster' and expressed concerns that using full-length spike protein in an mRNA-LNP vaccine could be catastrophic."

-1359 Sur-Reply (Paper 72), 22-23



There was little doubt among the leaders of BioNTech's team about the best way to build a coronavirus vaccine that was both effective and safe namely, to engineer an authentic copy of the spike protein. A 2009 study had found that the small bulges studded on the surfaces of coronaviruses were chiefly responsible for enabling the pathogens to infect humans. The paper also revealed that the body's *own* immune responses to the SARS coronavirus mainly targeted these proteins, recognizing them as the most efficient way of stopping the threat dead. "We were lucky," Özlem says. Unlike many other viruses, which unfold like a Swiss Army knife, and have a plethora of different-shaped tools for infiltrating healthy cells, "this virus was pretty unidimensional; it had a clear molecule with which it enters lung cells." The Lightspeed team simply had to ensure its vaccines replicated that molecule-in the form of a wanted poster-for the immune system's troops to scrutinize and learn to attack.

The S-Protein was the "clear molecule with which [the virus] enters lung cells" that was a "wanted poster" for the immune system

Ex. 2106 at 69; -1358 Reply (Paper 59), 14-15; -1359 Reply (Paper 59), 15

A POSA Would Not Have Been Dissuaded by Concerns about ADE

Patent Owner:

"Dr. Yang's group found DNA vaccines encoding full-length S-protein—but not truncated S-protein—caused enhanced disease."

-1359 Sur-Reply (Paper 72), 17, n. 14

Yang 2005

Evasion of antibody neutralization in emerging severe acute respiratory syndrome coronaviruses

Zhi-yong Yang*, Heidi C. Werner*, Wing-pui Kong*, Kwanyee Leung*, Elisabetta Traggiai†, Antonio Lanzavecchia†, and Gary J. Nabel*‡

*Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Building 40, Room 4502, MSC-3005, 40 Convent Drive, Bethesda, MD 20892-3005; and †Institute for Research in Biomedicine, Via Vincenzo Vela 6, CH-6500 Bellinzona, Switzerland

To date, Ab-dependent enhancement has not been observed with any human SARS-CoV strain, which may allay concerns that such vaccines might enhance viral infection; however, it will be important to assess such vaccines in relevant animal models as they become available. Because it is technically

was markedly resistant to Ab inhibition. Unexpectedly, Abs that neutralized most human S glycoproteins enhanced entry mediated by the civet virus S glycoproteins. The mechanism of enhancement involved the interaction of Abs with conformational epitopes in the hACE-2-binding domain. Finally, improved immunogens and mAbs that minimize this complication have been defined. These data show that the entry of severe acute respiratory syndrome coronaviruses can be enhanced by Abs, and they underscore the need to address the evolving diversity of this newly emerged virus for vaccines and immune therapies.

Yang 2005 found ADE in a civet virus, but emphasizes that no ADE has ever been observed in human SARS-CoV

Patent Owner's Scattershot Arguments Fail to Rebut Obviousness

Patent Owner makes a series of contentions to move the goalposts of obviousness:

1. Alleged skepticism of mRNA vaccines
2. Alleged failure in the prior art
3. Alleged concerns with ADE
4. Alleged reasons not to use lipid nanoparticles
5. Alleged irrelevance of data using other vaccine modalities
6. Alleged lack of data using the claimed composition

None withstands scrutiny

No Teaching Away from Lipid Nanoparticles

- Patent Owner alleges teaching away from LNPs, but by October 2015, prior art provided good reason to use LNPs to deliver immunogen-encoding mRNA
- Schrum teaches ***towards*** lipid nanoparticle vaccines, and demonstrates efficient expression of mRNA using LNPs
- Prior art had already used lipid nanoparticles to improve mRNA vaccine performance

Petitioner's Expert, Dr. Moon

It is Dr. Chan's declaration, however, that does not address the decades of experience using lipid nanoparticle systems, including for the delivery of mRNA. Instead, the true "state of the art" provides further motivation, in addition to Schrum's teachings, to use such systems for the delivery of immunogen-encoding mRNA.

Ex. 1161 (1359), ¶ 74

-1358 Reply (Paper 59), 17-19; -1359 Reply (Paper 59), 18-19

A POSA Had Good Reason to Use Lipid Nanoparticle Formulations

Patent Owner alleges that the prior art teaches away from use of LNPs due to other available delivery approaches; it does not

> **c. A POSA Would Have Had Reason Not to Use LNPs.**
>
> The Reply does not address Moderna's evidence that different delivery methods were known to have different benefits, such as adjuvant effects, sustained release, and manufacturing benefits (POR, 39-40; Ex. 2198, ¶¶37-66, 164-179, 208-212), or that protamine was thought necessary for mRNA vaccine immune response (Ex. 2024, 2264; Ex. 2025, 1210-1216; Ex. 2198, ¶¶46-50). *Virtek Vision*

-1359 Sur-Reply (Paper 72), 25

ACCO BRANDS CORPORATION,
Appellant

v.

FELLOWES, INC., Appellee.

No. 2015–1045.

United States Court of Appeals,
Federal Circuit.

Feb. 22, 2016.

But even if one possible obvious combination falls outside of the claims, it fails to undercut the fact that the other possible obvious combination lies within their scope. The examiner therefore successfully set out a prima facie case that claims 9 and 11 would have been obvious.

ACCO Brands Corp. v. Fellowes, Inc., 813 F.3d 1361, 1367 (Fed. Cir. 2016)

-1358 Reply (Paper 59), 13-14, 17-19; -1359 Reply (Paper 59), 14, 18-19

A POSA Had Good Reason to Use Lipid Nanoparticle Formulations

Schrum provides good reason to utilize lipid nanoparticles to deliver mRNA vaccine encoding SARS-CoV S protein

Schrum

[0998] As shown in Table 30, the LNP formulations described above have about a 10,000-100,000-fold increase in protein production compared to an administration of an intravenous (IV)-lipoplex formulation for the same dosage of modified mRNA and intramuscular (IM) or subcutaneous (SC) administration of the same dose of modified mRNA in saline. As used in Table 30, the symbol "~" means about.

TABLE 30

Protein Production

G-CSF	Dose (ug)	Serum Concentration (pg/ml) 8-12 hours after administration
IM	100	~20-80
SC	100	~10-40
IV (Lipoplex)	100	~30
IV (LNP)	100	~5,000,000
IV (LNP)	10	~1,000,000
IV (LNP)	1	~20,000

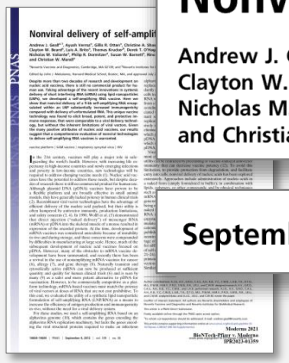
[0397] In one embodiment, an immune response may be elicited by delivering a lipid nanoparticle which may include a nanospecies, a polymer and an immunogen. (U.S. Publication No. 20120189700 and International Publication No. WO2012099805; each of which is herein incorporated by reference in their entirety). The polymer may encapsulate the nanospecies or partially encapsulate the nanospecies. The immunogen may be a recombinant protein, a modified RNA described herein. In one embodiment, the lipid nanoparticle may be formulated for use in a vaccine such as, but not limited to, against a pathogen.

mRNA vaccines, like any mRNA, require efficient delivery to the cell in order to achieve translation of the encoded immunogen

Ex. 1009, ¶¶ 998, 397; -1358 Petition (Paper 3), 16, 40; -1359 Petition (Paper 1), 15, 41

A POSA Had Good Reason to Use Lipid Nanoparticle Formulations

By 2015, prior art had *already* demonstrated that use of lipid nanoparticles to deliver immunogen-encoding mRNA "substantially increased" vaccine performance



Nonviral delivery of self-amplifying RNA vaccines

Andrew J. Geall[a,1], Ayush Verma[a], Gillis R. Otten[a], Christine A. Shaw[a], Armin Hekele[a], Kaustuv Banerjee[a], Yen Cu[a], Clayton W. Beard[a], Luis A. Brito[a], Thomas Krucker[b], Derek T. O'Hagan[a], Manmohan Singh[a], Peter W. Mason[a], Nicholas M. Valiante[a], Philip R. Dormitzer[a], Susan W. Barnett[a], Rino Rappuoli[a], Jeffrey B. Ulmer[a], and Christian W. Mandl[a]

September 4, 2012 | vol. 109 | no. 36

Geall 2012

man use. **Taking advantage of the recent innovations in systemic delivery of short interfering RNA (siRNA) using lipid nanoparticles (LNPs), we developed a self-amplifying RNA vaccine. Here we show that nonviral delivery of a 9-kb self-amplifying RNA encapsulated within an LNP substantially increased immunogenicity compared with delivery of unformulated RNA.** This unique vaccine

neutralizing antibodies after two vaccinations (Fig. 5 *A* and *B*). The LNP/RNA formulation boosted F-specific IgG titers approximately 8-fold (GMTs 4,355) and neutralization titers 10-fold (GMTs 1,493) relative to the same dose of naked RNA [GMTs of 526 (F-specific IgG) and 154 (neutralization)]. The LNP/RNA was statistically superior to naked RNA and equivalent to the 5×10^6 IU of VRPs [GMTs 5,861 (F-specific IgG) and 1,690 (neutralization)].

- Patent Owner's scientists described Ex. 2021 as the "first study that established amino lipid based LNPs . . . form stable particles with mRNA and effectively release the mRNA for protein translation in vivo."

A POSA Had Good Reason to Use Lipid Nanoparticle Formulations

- Patent Owner concedes that "Schrum discusses the same LNP formulation as the patent"
- Schrum demonstrates that use of LNPs to deliver mRNA achieves efficient protein production, which is required for any mRNA medicine, including mRNA vaccines

Schrum

[0998] As shown in Table 30, the LNP formulations described above have about a 10,000-100,000-fold increase in protein production compared to an administration of an intravenous (IV)-lipoplex formulation for the same dosage of modified mRNA and intramuscular (IM) or subcutaneous (SC) administration of the same dose of modified mRNA in saline. As used in Table 30, the symbol "~" means about.

TABLE 30

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G-CSF	Dose (ug)	Serum Concentration (pg/ml) 8-12 hours after administration
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IV (LNP)	100	~5,000,000
IV (LNP)	10	~1,000,000
IV (LNP)	1	~20,000

Patent Owner's Declarant, Dr. Fuller

Q. Once you know that the spike protein is expressing, you would expect that the vaccine candidate would induce an immune response. Is that fair . . . That was your expectation?

A. Yes.

Schrum expressly teaches the use of lipid nanoparticles for vaccine delivery (Ex. 1009, ¶ 397)

-1359 Sur-Reply (Paper 72), 25; Ex. 1009, ¶¶ 397, 998; -1358 Petition (Paper 3), 16, 40; -1359 Petition (Paper 1), 15, 41 Ex. 1104, 50:21-51:2; 1359 Reply (Paper 59), 20-21; 1358 Reply (Paper 59), 20

A POSA Had Good Reason to Use Lipid Nanoparticle Formulations

- Prior art introduced by Patent Owner confirms no teaching away from lipid nanoparticles—just the opposite

Nonviral delivery of self-amplifying RNA vaccines

September 4, 2012

man use. **Taking advantage of the recent innovations in systemic delivery of short interfering RNA (siRNA) using lipid nanoparticles (LNPs), we developed a self-amplifying RNA vaccine. Here we show that nonviral delivery of a 9-kb self-amplifying RNA encapsulated within an LNP substantially increased immunogenicity compared with delivery of unformulated RNA.** This unique vaccine

Mechanisms for increased immunogenicity

process produces consistent LNP/RNA particles. Agarose gel electrophoresis showed that RNA integrity was maintained during formulation (Fig. 1*C*, lane 4) and that the LNPs protected the RNA from degradation by RNase A (Fig. 1*C*, lane 5). In contrast, the naked control RNA was degraded by RNase A (Fig. 1*C*, lane 3 compared with lane 2). Encapsulation was also required for efficient delivery of functional RNA into muscle. Six days after in-

Patent Owner's Declarant, Dr. Fuller

"So, it's that RNA, mRNA, does require a vehicle to get efficient delivery. It can be delivered naked. It can be injected and you can still get an immune response. But to get – if you – to get levels of protein that you need to – for gene therapy or for an immune response, it's well known now that you need a delivery vehicle."

Dr. Fuller confirmed that the benefits described in Ex. 2021 were equally applicable to non-replicating mRNA (Ex. 1104 at 105:13-106:5)

Ex. 2021 at 14604-05; Ex. 1104 at 192:4-11; -1358 Reply (Paper 59), 17-19; -1359 Reply (Paper 59), 18-19; Ex. 1161 (1359) ¶ 77; Ex. 1159 (1359) ¶ 239.

Patent Owner's Scattershot Arguments Fail to Rebut Obviousness

Patent Owner makes a series of contentions to move the goalposts of obviousness:

1. Alleged skepticism of mRNA vaccines
2. Alleged failure in the prior art
3. Alleged concerns with ADE
4. Alleged reasons not to use lipid nanoparticles
5. Alleged irrelevance of data using other vaccine modalities
6. Alleged lack of data using the claimed composition

None withstands scrutiny

Record Refutes Patent Owner's Attempts to Evade the Teachings of Other Vaccine Modalities

- Patent Owner argues that data showing immunogenicity of other S protein vaccines—including DNA, self-amplifying, and traditional vaccines—is irrelevant
- Record, including the testimony of Patent Owner's own experts, demonstrates that a POSA would consider—and be informed by—all types of vaccines built upon the same immunogen

Daniel Griffin, M.D., Ph.D.

For any type of nucleic acid vaccine, the nucleic acid encoding the immunogen ultimately must be translated by the cell's host cell machinery. Thus, the use of a DNA vaccine or a viral vector to deliver the spike protein and include an immune response would have demonstrated that (1) a nucleic acid (including DNA and RNA) could be safely administered to patients, (2) the cellular machinery is capable of translating the protein, and that (3) the body can recognize the protein and generate an immune response. Those lessons would have been applicable across any nucleic acid vaccine.

Ex. 1159 (-1359), ¶ 207

-1358 Reply (Paper 59), 12-13; -1359 Reply (Paper 59), 13

The Record Confirms a POSA Would Have Considered Data from Other Vaccine Modalities

- Patent Owner ignores evidence that ***every*** S protein vaccine of record induced an immune response

> Petitioners' obviousness arguments rest on extrapolating results from non-mRNA vaccine technologies—like saRNA (Geall),[10] DNA (Yang), or protein and non-mRNA nucleic acid (Altmeyer)[11]—to make predictions about mRNA-LNP. But Petitioners, bearing the burden, adduce no evidence anyone did or would successfully make such extrapolation. The evidence establishes that jumping

The Record Confirms a POSA Would Have Considered Data from Other Vaccine Modalities

REVIEW

RNA Biology 9:11, 1319-1330; November 2012; © 2012 Landes Bioscience

Developing mRNA-vaccine technologies

Thomas Schlake,* Andreas Thess, Mariola Fotin-Mleczek and Karl-Josef Kallen

CureVac GmbH; Tübingen, Germany

Keywords: mRNA, adjuvant, vaccine, mRNA production, mRNA design, mRNA uptake, formulation, protein expression

Abbreviations: ARCA, anti-reverse cap analog; cDNA, complementary DNA; CTL, cytotoxic T cell; dsRNA, double-stranded RNA; EMCV, encephalomyocarditis virus; GMP, good manufacturing practice; HPLC, high performance liquid chromatography; IRES, internal ribosome entry site; mRNA, messenger RNA; MHC, major histocompatibility complex; miRNA, microRNA; ORF, open reading frame; pAPC, professional antigen presenting cell; pDNA, plasmid DNA; PEG, polyethylenglycol; siRNA, small interfering RNA; tRNA, transfer RNA; TLR, toll-like receptor; UTR, untranslated region

mRNA vaccines combine desirable immunological properties with an outstanding safety profile and the unmet flexibility of genetic vaccines. Based on in situ protein expression, mRNA vaccines are capable of inducing a balanced immune response comprising both cellular and humoral immunity while not subject to MHC haplotype restriction. In addition, mRNA is an intrinsically safe vector as it is a minimal and only transient carrier of information that does not interact with the genome. Because any protein can be expressed from mRNA without the need to adjust the production process, mRNA vaccines also offer maximum flexibility with respect to development. Taken together, mRNA presents a promising vector that may well become the basis of a game-changing vaccine technology platform. Here, we outline the current knowledge regarding different aspects that should be considered when developing an mRNA-based vaccine technology.

Introduction

RNA is considered as notoriously unstable making its therapeutic use a provocative idea. Despite the sensitivity of the molecule to the virtually omnipresent ribonucleases (RNases),[1] mRNA as a therapeutic was first promoted in 1989 after the development of a broadly applicable in vitro transfection technique.[2] Only a couple of years later, mRNA was advocated as a vaccine platform, perhaps being ideal in the sense that it brings together the immunological features of live attenuated vaccines such as endogenous antigen expression and T cell induction with those of killed or subunit vaccines like defined composition and safety.[3,4]

Particularly compared with DNA as a therapeutic or more specifically as a vaccine, mRNA offers strong safety advantages.[5] As the minimal genetic construct, it harbors only the elements directly required for expression of the encoded protein. Moreover, while recombination between single-stranded RNA molecules may occur in rare cases,[6,7] mRNA does not interact with the genome. Thus, potentially detrimental genomic integration is excluded. Finally, this lack of genomic integration in combination with mRNA being non-replicative as well as metabolically decaying within a few days[8] makes mRNA a merely transient carrier of information.

mRNA as the technological basis of therapeutics and vaccines is characterized by a great flexibility with respect to production and application. Any protein can be encoded and expressed by mRNA, in principle enabling the development of prophylactic and therapeutic vaccines fighting diseases as diverse as infections and cancer as well as protein replacement therapies. Since changes of the encoded protein just alter the sequence of the RNA molecule, leaving its physico-chemical characteristics largely unaffected, diverse products can be manufactured using the same established production process without any adjustment, saving time and reducing cost compared with other vaccine platforms. In terms of efficacy, mRNA-based therapeutics profit from the fact that they do not need to cross the nuclear envelope as opposed to DNA. In contrast to peptides, mRNA vaccines lack MHC haplotype restriction. In addition, mRNA binds to pattern recognition receptors and mRNA vaccines may be designed to be self-adjuvanting,[9] a property which peptide- and protein-based vaccines lack.

All in all, mRNA presents a promising, even if challenging, class of therapeutic molecules that has the potential to become the basis of a "disruptive technology."[10] In the following we are casting light on what has to be considered when developing an mRNA-vaccine technology touching important topics such as mRNA manufacturing and quality, mRNA format and formulation as well as antigen/protein expression and immunological properties of mRNA-vaccines.

mRNA Production

mRNA synthesis. Functional synthetic mRNA may be obtained by in vitro transcription of a cDNA template, typically plasmid DNA (pDNA), using a bacteriophage RNA polymerase.[11] Hence, the preparation of pDNA is the first step in the production of mRNA. Manufacture of mRNA might thus appear to require more effort than manufacture of pDNA. However, unpolished pDNA contains traces of bacterial genomic DNA and three forms of pDNA (supercoiled, relaxed circle or linear) in

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http://dx.doi.org/10.4161/rna.22269

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BioNTech-Pfizer Exhibit 1019

Schlake 2012

subject to MHC haplotype restriction. In addition, mRNA is an intrinsically safe vector as it is a minimal and only transient carrier of information that does not interact with the genome. Because any protein can be expressed from mRNA without the need to adjust the production process, mRNA vaccines also offer maximum flexibility with respect to development. Taken together, mRNA presents a promising vector that may well become the basis of a game-changing vaccine technology platform. Here, we outline the current knowledge regarding

By 2015, "any protein can be encoded and expressed by mRNA" and it was well established that the S-protein could be expressed using nucleic acid platforms

The Record Confirms a POSA Would Have Considered Data from Other Vaccine Modalities

- Dr. Fuller confirmed that, in designing her own betacoronavirus vaccine, she **reviewed results from other vaccine technologies**

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CORONAVIRUS

An *Alphavirus*-derived replicon RNA vaccine induces SARS-CoV-2 neutralizing antibody and T cell responses in mice and nonhuman primates

Deborah Heydenburg Fuller[1,4,6]*

*Corresponding author. Email: fullerdh@uw.edu

after one or two doses and would need to be manufactured using components suitable for scale up. **Here, we developed an *Alphavirus*-derived replicon RNA vaccine candidate, repRNA-CoV2S, encoding the SARS-CoV-2 spike (S) protein. The RNA replicons were formulated with lipid inorganic nanoparticles** (LIONs) that were de-signed to **enhance vaccine stability, delivery, and immunogenicity.** We show that a single intramuscular injection

Patent Owner's Declarant, Dr. Fuller

Q. Why didn't you just limit [your review] to self-amplifying vaccines?

A. …

The majority of the vaccine approaches that were favored in 2003 when the SARS-CoV-1 and then later for the MERS was relying on more traditional vaccine approaches. And that's what we looked at.

Ex. 1099 at 1; Ex. 1104 at 43:15-44:4; -1358 Reply (Paper 59), 12-13; -1359 Reply (Paper 59), 13

The Record Confirms a POSA Would Have Considered Data from Other Vaccine Modalities

- Dr. Fuller explained that the S-protein elicited an immune reaction, regardless of the vaccine modality

Patent Owner's Declarant, Dr. Fuller

Q. Are you aware of any SARS-CoV vaccines using spike proteins that induced an immune response?

A. Yes.

Q. Which ones are you aware of?

A. Pretty much every vaccine type out there. There was primarily inactivated recombinant protein, there was DNA vaccine. There were others, various ones using different antigens formulated with different vaccines.

Ex. 1104 at 65:15-66:2; ; Ex. 1159 (-1358), ¶ 210; Ex. 1159 (-1359), ¶ 204; -1358 Reply (Paper 59), 12-13; -1359 Reply (Paper 59), 13

The Record Confirms a POSA Would Have Considered Data from Other Vaccine Modalities

- Patent Owner's ***own*** representations to FDA relied on extrapolation of results of other vaccine technologies to make predictions about its own mRNA-LNP vaccine

based vaccine against SARS-CoV-2(mRNA-1273). Prior preclinical studies have demonstrated that coronavirus spike proteins (S protein) are immunogenic and S protein-based vaccines, including deoxyribonucleic acid (DNA) and mRNA delivery platforms, are protective in animals. Prior clinical trials of vaccines targeting related coronaviruses and other viruses have demonstrated that DNA and mRNA-based vaccines are safe and immunogenic. It is therefore anticipated that mRNA-1273 will generate robust immune responses to the SARS-CoV-2S protein.

Ex. 2056 at 6; -1358 Reply (Paper 59), 25; -1359 Reply (Paper 59), 25-26

The Record Confirms a POSA Would Have Considered Data from Other Vaccine Modalities

Prior art reaffirms that experience with other vaccine modalities is relevant to mRNA vaccines encoding for the same immunogen

DNA Vaccines	Administration of antigen-encoding DNA	Transcription of DNA into antigen-encoding mRNA	Translation of mRNA into chosen antigen	Body mounts immune response to antigen
mRNA Vaccines	Administration of antigen-encoding DNA	Transcription of DNA into antigen-encoding mRNA	Translation of mRNA into chosen antigen	Body mounts immune response to antigen
Traditional Vaccines	Administration of antigen-encoding DNA	Transcription of DNA into antigen-encoding mRNA	Translation of mRNA into chosen antigen	Body mounts immune response to antigen

Ex. 1016 at 152; -1358 Petition (Paper 3), 7-9; -1358 Reply (Paper 59), 12; -1359 Petition (Paper 1), 7-9; -1359 Reply (Paper 59), 13

The Record Confirms a POSA Would Have Considered Data from Other Vaccine Modalities

- Patent Owner relies on Brito 2014 (Ex. 2005) as evidencing that "saRNA, mRNA, and DNA vaccines" induced "***different***" immune responses (-1359 Sur-Reply (Paper 72), 12-13)
- But obviousness does not require identical immune response levels

Daniel Griffin, M.D., Ph.D.

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

Ex. 1159, ¶ 256; -1358 Reply (Paper 59), 12; -1359 Reply (Paper 59), 13; *contra* -1359 Sur-Reply (Paper 72) at 13 n.12

The Record Confirms a POSA Would Have Considered Data from Other Vaccine Modalities

- Contrary to Dr. Fuller's Testimony, the record demonstrates that non-amplifying mRNA can generate an immune response

Patent Owner's Declarant, Dr. Fuller

A POSA would have understood that the mRNA dose of 15 µg administered in Brito's mouse study is past the upper limit at which a response, if any, would have been expected. Therefore, the difference in dose does not resolve the lack of interchangeability between mRNA and saRNA.

Brito 2014

A Cationic Nanoemulsion for the Delivery of Next-generation RNA Vaccines

Luis A Brito[1], Michelle Chan[1], Christine A Shaw[1], Armin Hekele[2], Thomas Carsillo[1], Mary Schaefer[1], Jacob Archer[1], Anja Seubert[3], Gillis R Otten[1], Clayton W Beard[2], Antu K Dey[2], Anders Lilja[1,4], Nicholas M Valiante[1], Peter W Mason[1], Christian W Mandl[1], Susan W Barnett[1], Philip R Dormitzer[1], Jeffrey B Ulmer[1], Manmohan Singh[2], Derek T O'Hagan[1] and Andrew J Geall[1]

[1]*Novartis Vaccines, Cambridge, Massachusetts, USA;* [2]*Novartis Vaccines, Holly Springs, North Carolina, USA;* [3]*Novartis Vaccines, Siena, Italy;* [4]*Current address: Hookipa Biotech AG, Helmut-Qualtinger-Gasse 2, Vienna, Austria*

delivery of self-amplifying mRNA and pDNA, highlight that the optimal delivery technologies for pDNA and RNA vaccines are different.[32] mRNA was unable to induce responses in our hands, perhaps due to the low dose being tested here. Previous reports with mRNA have shown that much higher doses (80 µg) of mRNA have been used to generate immune responses in mice.[6]

6. Petsch, B, Schnee, M, Vogel, AB, Lange, E, Hoffmann, B, Voss, D *et al.* (2012). Protective efficacy of *in vitro* synthesized, specific mRNA vaccines against influenza A virus infection. *Nat Biotechnol* **30**: 1210–1216.

Ex. 2199 (-1359), ¶ 557; Ex. 2005 at 2124; Ex. 1159 ¶ 351; *contra* -1359 Sur-Reply (Paper 72), 13 n.12; *see also* -1359 Reply (Paper 59), 20-21

The Record Confirms a POSA Would Have Considered Data from Other Vaccine Modalities

- Dr. Fuller's opinion based on her recollections are inaccurate and do not reflect what a POSA would have known by 2015

Patent Owner's Declarant, Dr. Fuller

Additionally, in my experience, a dose of 10 µg or higher of mRNA administered to mice is at the upper limit for detecting a response, at which point increasing the dose would have negligible, if any, effect.

A POSA would have understood that the mRNA dose of 15 µg administered in Brito's mouse study is past the upper limit at which a response, if any, would have been expected.

Petsch 2012

dependent mode of action. When given twice at an 80-µg dose, mRNA vaccines induced protective immunity in mice of all ages. In adult mice, protective humoral immunity induced by two injections of 20 µg mRNA lasted throughout their lifetimes. For the prophylaxis of

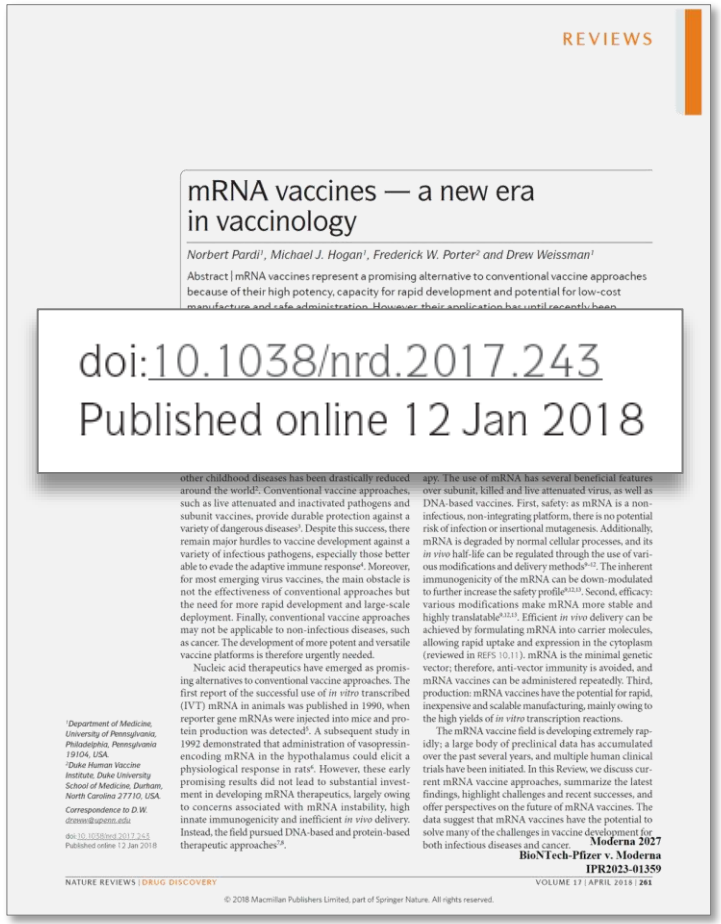
half-life on the order of days (ref. 15 and data not shown). In ferrets, the animal model of choice for preclinical proof-of-concept studies in influenza research[32], 80–250 µg doses of an H1 mRNA vaccine matched a licensed inactivated virus vaccine with regard to immunogenicity. In domestic pigs, 250 µg mRNA doses induced pronounced antibody responses that meet serological requirements for seasonal influenza vaccine licensure. Notably, naive pigs immunized with

Petsch 2012 demonstrates that mRNA vaccines induced an immune response at doses higher than in Brito

Ex. 2199 (-1359), ¶ 557; Ex. 2025 at 1215; *contra* -1359 Sur-Reply (Paper 72), 13 n.12; *see also* -1359 Reply (Paper 59), 20-21; Ex. 1159 (-1359), ¶ 152

The Record Confirms a POSA Would Have Considered Data from Other Vaccine Modalities

The literature confirms that developments in mRNA technology render Dr. Fuller's unsupported recollections of research between 1990-1998 of little probative value



REVIEWS

mRNA vaccines — a new era in vaccinology

Norbert Pardi[1], Michael J. Hogan[1], Frederick W. Porter[2] and Drew Weissman[1]

Abstract | mRNA vaccines represent a promising alternative to conventional vaccine approaches because of their high potency, capacity for rapid development and potential for low-cost

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Published online 12 Jan 2018

other childhood diseases has been drastically reduced around the world[2]. Conventional vaccine approaches, such as live attenuated and inactivated pathogens and subunit vaccines, provide durable protection against a variety of dangerous diseases[3]. Despite this success, there remain major hurdles to vaccine development against a variety of infectious pathogens, especially those better able to evade the adaptive immune response[4]. Moreover, for most emerging virus vaccines, the main obstacle is not the effectiveness of conventional approaches but the need for more rapid development and large-scale deployment. Finally, conventional vaccine approaches may not be applicable to non-infectious diseases, such as cancer. The development of more potent and versatile vaccine platforms is therefore urgently needed.

Nucleic acid therapeutics have emerged as promising alternatives to conventional vaccine approaches. The first report of the successful use of *in vitro* transcribed (IVT) mRNA in animals was published in 1990, when reporter gene mRNAs were injected into mice and protein production was detected[5]. A subsequent study in 1992 demonstrated that administration of vasopressin-encoding mRNA in the hypothalamus could elicit a physiological response in rats[6]. However, these early promising results did not lead to substantial investment in developing mRNA therapeutics, largely owing to concerns associated with mRNA instability, high innate immunogenicity and inefficient *in vivo* delivery. Instead, the field pursued DNA-based and protein-based therapeutic approaches[7,8].

apy. The use of mRNA has several beneficial features over subunit, killed and live attenuated virus, as well as DNA-based vaccines. First, safety: as mRNA is a non-infectious, non-integrating platform, there is no potential risk of infection or insertional mutagenesis. Additionally, mRNA is degraded by normal cellular processes, and its *in vivo* half-life can be regulated through the use of various modifications and delivery methods[9–12]. The inherent immunogenicity of the mRNA can be down-modulated to further increase the safety profile[9,12,13]. Second, efficacy: various modifications make mRNA more stable and highly translatable[9,12,13]. Efficient *in vivo* delivery can be achieved by formulating mRNA into carrier molecules, allowing rapid uptake and expression in the cytoplasm (reviewed in REFS 10,11). mRNA is the minimal genetic vector; therefore, anti-vector immunity is avoided, and mRNA vaccines can be administered repeatedly. Third, production: mRNA vaccines have the potential for rapid, inexpensive and scalable manufacturing, mainly owing to the high yields of *in vitro* transcription reactions.

The mRNA vaccine field is developing extremely rapidly; a large body of preclinical data has accumulated over the past several years, and multiple human clinical trials have been initiated. In this Review, we discuss current mRNA vaccine approaches, summarize the latest findings, highlight challenges and recent successes, and offer perspectives on the future of mRNA vaccines. The data suggest that mRNA vaccines have the potential to solve many of the challenges in vaccine development for both infectious diseases and cancer.

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Moderna 2027
BioNTech-Pfizer v. Moderna
IPR2023-01359

Over the past decade, major technological innovation and research investment have enabled mRNA to become a promising therapeutic tool in the fields of vaccine development and protein replacement therapy. The use of mRNA has several beneficial features over subunit, killed and live attenuated virus, as well as DNA-based vaccines. First, safety: as mRNA is a noninfectious, non-integrating platform, there is no potential risk of infection or insertional mutagenesis. Additionally, mRNA is degraded by normal cellular processes, and its in vivo half-life can be regulated through the use of various modifications and delivery methods. The inherent immunogenicity of the mRNA can be down-modulated to further increase the safety profile. Second, efficacy: various modifications make mRNA more stable and highly translatable. Efficient *in vivo* delivery can be achieved by formulating mRNA into carrier molecules, allowing rapid uptake and expression in the cytoplasm (reviewed in REFS 10,11). mRNA is the minimal genetic vector; therefore, anti-vector immunity is avoided, and mRNA vaccines can be administered repeatedly. Third, production: mRNA vaccines have the potential for rapid, inexpensive and scalable manufacturing, mainly owing to the high yields of *in vitro* transcription reactions.

Recent advances in mRNA vaccine technology

Various mRNA vaccine platforms have been developed in recent years and validated in studies of immunogenicity and efficacy. Engineering of the RNA sequence has rendered synthetic mRNA more translatable than ever before. Highly efficient and non-toxic RNA carriers have been developed that in some cases allow prolonged antigen expression *in vivo* (TABLE 1). Some vaccine formulations contain novel adjuvants, while others elicit potent responses in the absence of known adjuvants. The following section summarizes the key advances in these areas of mRNA engineering and their impact on vaccine efficacy.

Ex. 2027 at 261, 62; -1358 Reply (Paper 59), 17; -1359 Reply (Paper 59), 18

Patent Owner's Scattershot Arguments Fail to Rebut Obviousness

Patent Owner makes a series of contentions to move the goalposts of obviousness:

1. Alleged skepticism of mRNA vaccines
2. Alleged failure in the prior art
3. Alleged concerns with ADE
4. Alleged reasons not to use lipid nanoparticles
5. Alleged irrelevance of data using other vaccine modalities
6. Alleged lack of data using the claimed composition

None withstands scrutiny

Obviousness Does Not Require Data with the Exact Composition or Method Claimed

Contrary to governing law, Patent Owner argues that obviousness is defeated because the grounds do not expressly exemplify what was later claimed in the '600 and '127 patents

"There was no 'efficacy data or any other reliable indicator of success' for an mRNA vaccine encoding a betacoronavirus S-protein in an LNP, let alone one generating an immune response / neutralizing antibodies."

-1359 Sur-Reply (Paper 72), 9

ACORDA THERAPEUTICS, INC.,
Plaintiff-Appellant,

Alkermes Pharma Ireland Limited,
Plaintiff-Appellee,

v.

ROXANE LABORATORIES, INC., Mylan Pharmaceuticals Inc., Teva Pharmaceuticals USA, Inc., Defendants-Cross-Appellants

Acorda's core argument appears not to be that the evidence fails to support the finding of a motivation to combine. Rather, it appears to be that the evidence cannot support a finding of a reasonable expectation of success (in 2004) in the absence of publications showing a statistically significant difference in walking tests between the specific dose of 10 mg 4-AP taken twice daily versus placebo. . . . We reject this contention.

To the extent that Acorda's contention is a legal one, asserting a law-required minimum for what can support a "reasonable" expectation of success, Acorda has offered no support for the contention. This court has long rejected a requirement of "[c]onclusive proof of efficacy" for obviousness. *See, e.g.*, *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014); *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1364 (Fed. Cir. 2007); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364, 1367-68 (Fed. Cir. 2007) (reasoning that "the expectation of success need only be reasonable, not absolute").

Acorda Therapeutics, Inc. v. Roxane Labs., Inc., 903 F.3d 1310, 1333 (Fed. Cir. 2018)

-1359 Institution Decision (Paper 20), 58

Obviousness Does Not Require Data with the Exact Composition or Method Claimed

Patent Owner relies on *OSI* for its contention that a reasonable expectation of success requires data for precisely what is claimed; it does not

OSI PHARMACEUTICALS, LLC, Appellant

v.

APOTEX INC., Apotex Corp., Apotex Pharmaceuticals Holdings Inc., Apotex Holdings Inc., Appellees

But the asserted references do not disclose any data or other information about erlotinib's efficacy in treating NSCLC. The record does not contain any clinical (human) data or preclinical (animal) data. It does not even include *in vitro* (test tube) data regarding erlotinib's effect on NSCLC..

* * *

Turning first to Schnur in view of Gibbs, the asserted references do not disclose any information about erlotinib's efficacy in treating NSCLC in a mammal. Schnur broadly discloses at least 105 compounds for the treatment of twelve different types of cancer. There is no dispute that Schnur fails to disclose any *in vitro* or *in vivo* efficacy data for erlotinib or otherwise suggest the use of erlotinib to treat NSCLC.

OSI Pharm., LLC v. Apotex Inc., 939 F.3d 1375, 1383-84 (Fed. Cir. 2019)

Here, data of record *exclusively* shows that S protein vaccines induce an immune response—Patent Owner has not adduced any evidence of an S protein vaccine *failing* to induce an immune response

-1358 POR (Paper 41), 26, 29, 32, 44, 54; -1359 POR (Paper 42), 26, 29, 33, 44, 55; -1358 Sur-Reply (Paper 72), 9, 11, 19, 20; -1359 Sur-Reply (Paper 72), 9-10, 12, 19, 21

Agenda

- Overview of the challenged patents, the prior art & the instituted grounds
- Anticipation by Schrum (Ground 1)
- Obviousness in view of Schrum and Geall, Yang, or Altmeyer (Grounds 2-4)
  - Petitioner has demonstrated unpatentability
  - Patent Owner's arguments are defeated by the literature, the law, and its own experts' testimony
  - No secondary considerations support non-obviousness
- The testimony of Patent Owner's declarants should be afforded little weight

Alleged Secondary Considerations Evidence Is Not Reasonably Commensurate with the Scope of the Claims

1. A composition, comprising: a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit formulated in a lipid nanoparticle.

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

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

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

Claims cover:

- mRNA encoding for any betacoronavirus S protein
- Any mRNA sequence encoding for such protein
- Any lipid nanoparticle formulation
- ('127) Any level of immune response in any mammal

-1358 Reply (Paper 59), 25-26; -1359 Reply (Paper 59), 26-27; Ex. 1001 (-1358), Claim 1; Ex. 1001 (-1359), Claims 1-3

Alleged Secondary Considerations Evidence Is Not Reasonably Commensurate with the Scope of the Claims

No evidence of:

- S protein for a betacoronavirus other than SARS-CoV-2
- S protein subunit for any betacoronavirus
- Vaccines without the 1-methylpseudouridine modification
- Vaccines without the particular, optimized LNP formulations, mRNA sequences 5’ caps, 5’ and 3’ untranslated regions, [and] codon optimizations used in Comirnaty/Spikevax
- Vaccines not developed in response to an unprecedented global pandemic

Patent Owner Has Not Met Its Burden to Establish Nexus

ORMCO CORPORATION,
Appellant

v.

ALIGN TECHNOLOGY, INC.,
Appellees

2005–1426

Thus, if the [secondary consideration] is due to an unclaimed feature of the device, the [secondary consideration] is irrelevant. So too if the feature that creates the [secondary consideration] was known in the prior art, the [secondary consideration] is not pertinent.

Ormco Corp. v. Align Technology, Inc., 463 F.3d 1299, 1312 (Fed. Cir. 2006)

Prior art squarely discloses the concept of an mRNA-LNP formulation encoding a betacoronavirus S protein to induce an immune response

Activation of the Immune Response: Vaccines

[0340] In one embodiment of the present invention, mRNA molecules may be used to elicit or provoke an immune response in an organism. The mRNA molecules to be delivered may encode an immunogenic peptide or polypeptide and may encode more than one such peptide or polypeptide.

Liposomes, Lipoplexes, and Lipid Nanoparticles

[0378] The modified nucleic acid molecules and mmRNA of the invention can be formulated using one or more liposomes, lipoplexes, or lipid nanoparticles. In one embodiment,

[0397] In one embodiment, an immune response may be elicited by delivering a lipid nanoparticle which may include a nanospecies, a polymer and an immunogen. (U.S. Publication No. 20120189700 and International Publication No. WO2012099805; each of which is herein incorporated by reference in their entirety). The polymer may encapsulate the nanospecies or partially encapsulate the nanospecies. The immunogen may be a recombinant protein, a modified RNA described herein. In one embodiment, the lipid nanoparticle may be formulated for use in a vaccine such as, but not limited to, against a pathogen.

Ex. 1009, ¶¶ 340, 378, 397; -1358 Reply (Paper 59), 26 n.14, 26-27; -1359 Reply (Paper 59), 27 n.14, 27-28

Patent Owner Has Not Met Its Burden to Establish Nexus

Patent Owner does not dispute Schrum's disclosure, but repeats its flawed argument that—without testing data—Schrum cannot disprove novelty

> Finally, Petitioners are wrong that "the generic concept" of the patent was known. Reply, 28. Dr. Griffin confirmed he cited ***no reference*** before October 2015 testing an mRNA vaccine for a betacoronavirus, much less in LNPs. Ex. 2253, 142:19-143:19. In any event, objective indicia can apply to a unique combination

No. 00-1304
United States Court of Appeals, Federal Circuit

Bristol-Myers Squibb v. Ben Venue Labs

246 F.3d 1368 (Fed. Cir. 2001)
Decided Apr 20, 2001

Furthermore, although he did not actually premedicate the patients himself, 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)

-1359 Sur-Reply (Paper 72), 28; -1358 Petition (Paper 3), 26; -1359 Petition (Paper 1), 23-24

Evidence Fails to Show Satisfaction of Long-Felt Need or Failure of Others

Patent Owner's Declarant, Dr. Krause

170. That latent need for a betacoronavirus vaccine to be ready in the event of a future pandemic existed even though the SARS and MERS outbreaks had been controlled with public health measures such that there was no immediate, pressing need for a specific vaccine as of 2015. That latent need for a betacoronavirus

Ex. 2200, ¶ 170; -1358 Reply (Paper 59), 27; -1359 Reply (Paper 59), 28

Agenda

- Overview of the challenged patents, the prior art, & the instituted grounds
- Anticipation by Schrum (Ground 1)
- Obviousness in view of Schrum and Geall, Yang, or Altmeyer (Grounds 2-4)
- The testimony of Patent Owner's declarants should be afforded little weight

Dr. Fuller's Testimony Should Be Afforded Little Weight

Patent Owner's Declarant, Dr. Fuller

Dr. Fuller's opinions are entirely contrary to governing law

Q. What is your opinion with regard to whether Schrum anticipates any claims at issue in these proceedings?

A. My opinion on Schrum is that Schrum is a document that describes the use of mRNA for therapeutics, and it doesn't anticipate mRNA for vaccines. It offers examples on using mRNA for therapeutics . . . So my opinion is that Schrum is not anticipatory because it focuses on methods and technologies to – for mRNA as a therapeutic, not as a vaccine. So it's not anticipatory for vaccines. It has only examples that are specific towards production of protein and the amount of protein in vivo but not any examples that show vaccines that relate in any way to vaccines.

Ex. 1104 at 216:13-20, 218:17-219:3,

BRISTOL–MYERS SQUIBB COMPANY, Plaintiff–Appellant,

v.

BEN VENUE LABORATORIES, INC., Bedford Laboratories, and Boehringer Ingelheim Corporation, Defendants–Appellees,

Furthermore, although he did not actually premedicate the patients himself, 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)

-1358 Reply (Paper 59), 2 n.2, 4; -1359 Reply (Paper 59), 2 n.2, 4-5; Ex. 1159 (-1358, -1359), ¶¶ 29-32; -1358 Petition (Paper 3), 26; -1359 Petition (Paper 1), 23-24

Dr. Chan's Testimony Should Be Afforded Little Weight

Patent Owner's Expert, Dr. Chan

Despite offering opinions on vaccines in his submitted declaration, Dr. Chan professed that he is not qualified to opine on vaccine technology

Dr. Chan's Declaration:

180. Without testing, it was generally unclear whether any particular type of formulation would be useful in delivery of a specific mRNA vaccine and in leading to a meaningful immune response . . .

181. Importantly, a POSA understood that expression of the antigen is required for an immune response but other factors also impact the immune response . . . .

Ex. 2198 (-1359), ¶¶ 180-81

Q. Dr. Chan, do you know what a vaccine is?

A. I know what a vaccine does, but the specifics of the mechanism, the details, that is not my area of expertise, right. My area of expertise is focused on the delivery system. And that's one part. The second part of my expertise is to be able to – it's how the engineers do these things, which is you measure the outcome of it, right.

* * *

Q. So you don't know if a vaccine elicits or provokes an immune response; is that right?

A. Again, I'm focused on the delivery part. That is my expertise, right.

Ex. 1152 at 101:12-21, 116:11-14

-1358 Reply (Paper 59), 2 n.2; -1359 Reply (Paper 59), 2 n.2; Ex. 1161 (-1358, -1359), ¶¶ 14-17

Dr. Chan's Testimony Should Be Afforded Little Weight

Patent Owner's Expert, Dr. Chan

At deposition, Dr. Chan stated that he lacked the expertise to support—and contradicted—his own opinions

182. Indeed, beyond the antigenic protein translated from the mRNA, the immunogenicity of every component of the mRNA vaccine may contribute to the immunogenicity of the vaccine as a whole, as the innate immunity evoked by these

Ex. 2198 (-1359), ¶ 182

Q. Do you agree that beyond the antigen[]ic protein translated from the mRNA, the immunogenicity of every component of the mRNA vaccine may contribute to the immunogenicity of the vaccine as a whole?

A. Yes. It's – so what I mean by that is that the question you're asking is very general, right. The term "immunogenicity," it's very – every component is general, right. I can work on specificity. So if you provide more specific questions, then I can address that, right.

Q. So you're unable to answer that question, as phrased?

A. As you present it.

Ex. 1152 at 150:19-151:12 (objections omitted)

-1358 Reply (Paper 59), 2 n.2; -1359 Reply (Paper 59), 2 n.2; Ex. 1161 (-1358, -1359), ¶¶ 14-17

Dr. Chan Claimed that Schrum's Lipid Nanoparticle Teachings Were Only "little sprinkles" That He "would not look at"

Patent Owner's Expert, Dr. Chan

A. And my impression of [Schrum] is [that it is] actually a polymer PLGA nanoparticle, microparticle patent, right, that was focused on protein replacement therapy . . . I am – to me, it is a polymer – PLGA polymer patent with ***little sprinkles*** of different things inside. ***But I would not look at these other things***, right.

Ex. 1152 at 56:6-18

Dr. Chan's Testimony Is Incredible

- Dr. Moon explains that ***twenty-nine*** working examples and ***twenty-three*** claims of Schrum involve and are directed to delivering mRNA using the claimed four-component lipid nanoparticle systems
- At deposition, Dr. Chan testified that his analysis did "not consider" these teachings because he did not think they were the "focus" of Schrum, contrary to the maxim that prior art must be considered for all it teaches

See, e.g., Ex. 1161, ¶¶ 44-51

Ex. 1161 (-1358, -1359), ¶¶ 44-51; -1358 Reply (Paper 59), 4, 9 n.7. -1359 Reply (Paper 59), 4-5, 9 n.7.

Dr. Krause's Testimony Should Be Afforded Little Weight

Dr. Krause Opined on Secondary Considerations But Did Not Consider Any of the Prior Art

Ormco Corp. v. Align Technology, Inc.

463 F.3d 1299, 1312 (Fed. Cir. 2006)

[I]f the feature that creates the [secondary consideration] was known in the prior art, the [secondary consideration] is not pertinent.

Patent Owner's Declarant, Dr. Krause

I know that – and this is the **so-called Schrum patent** – that **the materials in the Schrum patent isn't directly germane to the major points that I make in the declaration.**

* * *

[T]his is a patent by Andrew Geall, and it's the World Intellectual Property Organization. And I think it's correct: I'm not – **my declaration doesn't directly address material in this patent**. But I can't rule out the possibility that it glancingly does.

Ex. 1105 at 11:21-13:8; -1358 Reply (Paper 59), 22 n.10, 26 n.14, 27; -1359 Reply (Paper 59), 22 n.10, 27 n. 14, 28

Petitioner's Demonstratives

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 Nos. 10,702,600 and 10,933,127

Cases: IPR2023-01358, IPR2023-01359

Oral Hearing: December 10, 2024