UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BIONTECH SE AND PFIZER INC.,
Petitioners,

v.

MODERNA TX, INC.,
Patent Owner.

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

Patent Owner's Demonstratives

United States Patent & Trademark Office

Before the Patent Trial & Appeal Board

Patent Owner Moderna TX, Inc.'s Demonstratives

Pfizer Inc. et al. v. Moderna TX, Inc.

Case IPR2023-01358, U.S. Patent No. 10,702,600

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

December 10, 2024

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DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Exemplary Challenged Claims

US 10,702,600

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.

'600 Patent (Ex. 1001), Cl. 1

US 10,933,127

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.

'127 Patent (Ex. 1001), Cl. 1

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

'127 Patent (Ex. 1001), Cl. 3

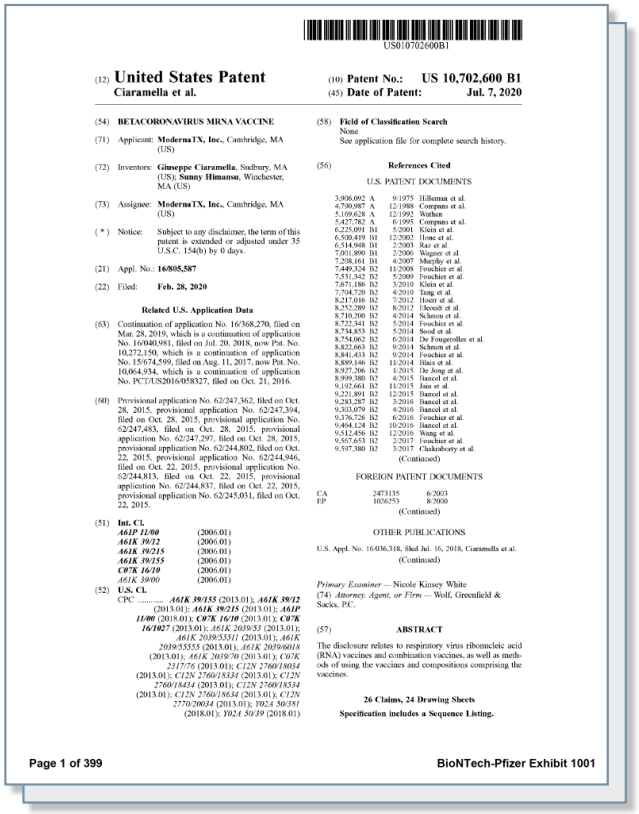
01359 POR, 15, 18, 26-28, 53-54, 57-58; 01359 Sur-Reply, 6-8, 11, 19-20
01358 POR, 15, 18-19, 25-28, 52-53, 56-58; 01358 Sur-Reply, 6-7, 10

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Exemplary Challenged Claims

'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. 62/247,304, 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 2039/53531* (2013.01); *A61K 2039/55555* (2013.01); *A61K 2039/60* (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); *Y02A 50/39* (2018.01)

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

(56) **References Cited**

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7,531,342	B2	5/2009	Fouchier et al.
7,671,186	B2	3/2010	Klein et al.
7,704,720	B2	4/2010	Jiang et al.
8,217,036	B2	7/2012	Hoerr et al.
8,252,289	B2	8/2012	Ekeruit et al.
8,710,200	B2	4/2014	Schmaus et al.
8,722,341	B2	5/2014	Fouchier et al.
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8,889,146	B2	11/2014	Blais et al.
8,927,206	B2	1/2015	De Jong et al.
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EP	1026253	8/2000

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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.

BioNTech-Pfizer Exhibit 1001

> 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.

'600 Patent (Ex. 1001), Cl. 1

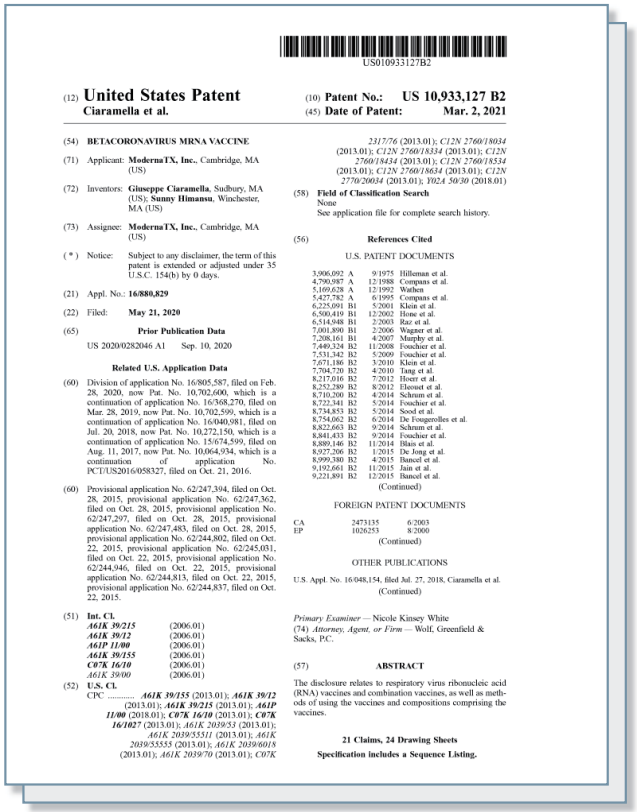
01358 POR, 15, 18-19, 25-28, 52-53, 56-58;
01358 Sur-Reply, 6-7, 10

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Exemplary Challenged Claims

'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.

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(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 2039/55531* (2013.01); *A61K 2039/55555* (2013.01); *A61K 2039/6018* (2013.01); *A61K 2039/70* (2013.01); *C07K 231/76* (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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5,427,782	A	6/1995	Compans et al.
6,225,091	B1	5/2001	Klein et al.
6,500,419	B1	12/2002	Hone et al.
6,514,948	B1	2/2003	Raz et al.
7,001,890	B1	2/2006	Wagner et al.
7,208,161	B1	4/2007	Murphy et al.
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8,841,433	B2	9/2014	Fouchier et al.
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8,999,380	B2	4/2015	Banoel et al.
9,192,661	B2	11/2015	Jain et al.
9,221,891	B2	12/2015	Banoel et al.

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EP	1026253	8/2000

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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.

'127 Patent (Ex. 1001), Cl. 1

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

'127 Patent (Ex. 1001), Cl. 3

01359 POR, 15, 18, 26-28, 53-54, 57-58;
01359 Sur-Reply, 6-8, 11, 19-20

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Exemplary Challenged 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.

'600 Patent (Ex. 1001), Cl. 1

01358 POR, 15, 18-19, 25-28, 52-53, 56-58;
01358 Sur-Reply, 6-7, 10

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Exemplary Challenged Claims

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.

'127 Patent (Ex. 1001), Cl. 1

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

'127 Patent (Ex. 1001), Cl. 3

01359 POR, 15, 18, 26-28, 53-54, 57-58; 01359 Sur-Reply, 6-8, 11, 19-20

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Immunogen References in Grounds Teach Different Vaccine Technologies and/or Delivery Methods

Reference	Vaccine Technology	Delivery Method
Geall	saRNA	Liposomes, CNE, Polymeric Nanoparticles, Virions, Naked
Yang	DNA	Naked
Altmeyer	Protein & Non-mRNA Nucleic Acid	Naked, Alum

Geall (Ex. 1010), 12:6-27, 29:29-38:6, 40:14-16; Yang (Ex. 1011), 561-562, 564; Altmeyer (Ex. 1012), ¶¶9-36, 114-131; Chan '127 Patent Decl. (Ex. 2198), ¶¶146-153, 208, 211; Fuller '127 Patent Decl. (Ex. 2199), ¶¶197-223; *see also* Chan '600 Patent Decl. (Ex. 2198), ¶¶146-153, 208, 211; Fuller '600 Patent Decl. (Ex. 2199), ¶¶197-223

01359 POR, 9-11, 30-33, 54-55, 59; 01359 Sur-Reply, 10
01358 POR, 9-11, 29-33, 53-54, 58; 01358 Sur-Reply, 10

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Dr. Fuller's Credentials and Experience



Dr. Deborah H. Fuller

Moderna's Expert

- **Professor of Microbiology, University of Washington**
- **Ph.D. in Cellular & Molecular Pathology in 2001, University of Wisconsin**
- **Interim Director of the Washington National Primate Research Center**
- **Hands-on Experience with Developing Nucleic Acid Vaccines, Including mRNA, Since 1990s**
- **Direct Experience Testing Nucleic Acid Technologies Head-to-Head**

Fuller '127 Patent Decl. (Ex. 2199), ¶¶4-15, 837; Fuller '600 Patent Decl. (Ex. 2199), ¶¶4-15, 843
Fuller Dep. (Ex. 1104), 7:20-8:2, 266:2-275:17; *see also id.*, 24:19-25:15, 26:2-16, 27:2-22

01359 POR, 4; 01359 Sur-Reply, 3, 13, 15
01358 POR, 4; 01358 Sur-Reply, 3, 13-15

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Dr. Fuller's Testimony



Dr. Deborah H. Fuller

Moderna's Expert

Q. And as of October 2015, what was your experience with mRNA vaccines?

A. **October 2015?**

Q. Correct.

A. **So I had started nucleic acid vaccine research in 1990 using different technologies, developing technology for delivery.**

* * *

So between 1990 and 1998, I did experiments with both DNA and mRNA. mRNA consistently failed in those experiments, but DNA was successful. And for the next two decades after that, my primary focus was on DNA. …

Fuller Dep. (Ex. 1104), 32:3-33:2

01359 POR, 4; 01359 Sur-Reply, 3, 14-15, 18
01358 POR, 4; 01358 Sur-Reply, 3, 14-15, 18

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Dr. Fuller Has Experience with Head-to-Head Modality Experiments



Dr. Deborah H. Fuller

Moderna's Expert

Q. So you have direct firsthand experience testing whether one nucleic acid system is interchangeable or predictive of another. Right?

A. **That's right.**

* * *

Q. … [I]f you took an saRNA vaccine with a particular protein choice and took that same protein choice and made an mRNA vaccine, would you expect the same results?

A. **No.**

* * *

Q. Is the same true between DNA and mRNA? Are those two nucleic acid modalities interchangeable?

A. **They are not. They are not interchangeable.**

Fuller Dep. (Ex. 1104), 266:16-19, 272:11-275:17, 273:16-22 (objections omitted); *see also id.*, 266:2-275:17

01359 Sur-Reply, 3, 13, 16; 01358 Sur-Reply, 3, 13, 16

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Claim Construction

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

"mRNA" Does Not Include saRNA or Replicase Machinery

Although attempts have been made to produce functional RNA vaccines, including mRNA vaccines and self-replicating RNA vaccines, the therapeutic efficacy of these RNA vaccines have not yet been fully established. Quite surprisingly, the inventors have discovered, according to aspects of the invention a class of formulations for delivering mRNA vaccines in vivo that results in significantly enhanced, and in many respects synergistic, immune responses including enhanced antigen generation and functional antibody production with neutralization capability. These results can be achieved even when significantly lower doses of the mRNA are administered in comparison with mRNA doses used in other classes of lipid based formulations. The formulations of the invention have demonstrated significant unexpected in vivo immune responses sufficient to establish the efficacy of functional mRNA vaccines as prophylactic and therapeutic agents. Additionally, self-replicating RNA vaccines rely on viral replication pathways to deliver enough RNA to a cell to produce an immunogenic response. The formulations of the invention do not require viral replication to produce enough protein to result in a strong immune response. Thus, the mRNA of the invention are not self-replicating RNA and do not include components necessary for viral replication.

'127 Patent (Ex. 1001), 40:22-44;
see also '600 Patent (Ex. 1001), 40:27-49

01359 POR, 7; 01359 Sur-Reply, 3
01358 POR, 7; 01358 Sur-Reply, 3

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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"S Protein" Is a Full-Length Spike Protein

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.

'127 Patent (Ex. 1001), Cl. 1; *see also* '600 Patent (Ex. 1001), Cl. 1

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.

'127 Patent (Ex. 1001), Cls. 2 & 3; *see also* '600 Patent (Ex. 1001), Cl. 2

4. The method of claim **1**, wherein the open reading frame encodes a BetaCoV S protein subunit selected from an S1 subunit and an S2 subunit.

5. The method of claim **4**, wherein the immune response is a neutralizing antibody response specific to the BetaCoV S protein subunit.

'127 Patent (Ex. 1001), Cls. 4 & 5; *see also* '600 Patent (Ex. 1001), Cl. 3

01359 POR, 8-9; 01359 Sur-Reply, 4-5; Fuller '127 Patent Decl. (Ex. 2199), ¶¶163, 172-173
01358 POR, 8-9; 01358 Sur-Reply, 4-5; Fuller '600 Patent Decl. (Ex. 2199), ¶¶164, 173-174

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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"S Protein" Is a Full-Length Spike Protein

Specification Shows "S Protein" Is Full-Length

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

'127 Patent (Ex. 1001), 7:30-34; *see also* '600 Patent (Ex. 1001), 7:28-33

FIG. **18** is a graph showing the reciprocal MERS-CoV neutralizing antibody titers in mice immunized with *Betacoronavirus* mRNA vaccine encoding either the MERS-CoV full-length Spike protein, or the S2 subunit of the Spike protein. The full length spike protein induced a stronger immune response compared to the S2 subunit alone.

'127 Patent (Ex. 1001), 24:57-62; *see also* '600 Patent (Ex. 1001), 24:56-61

01359 POR, 8-9; 01359 Sur-Reply, 4-5; Fuller '127 Patent Decl. (Ex. 2199), ¶¶160, 169, 174, 183
01358 POR, 8-9; 01358 Sur-Reply, 4-5; Fuller '600 Patent Decl. (Ex. 2199), ¶¶161, 170, 175, 184

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

"S Protein" Is a Full-Length Spike Protein

Specification Shows "S Protein" Is Full-Length

Example 23: MERS CoV Vaccine Immunogenicity Study in Mice

The instant study was designed to test the immunogenicity in mice of candidate MERS-CoV vaccines comprising a mRNA polynucleotide encoding the full-length Spike (S) protein, or the S2 subunit (S2) of the Spike protein obtained from MERS-CoV.

Mice were vaccinated with a 10 μg dose of MERS-CoV mRNA vaccine encoding either the full-length MERS-CoV Spike (S) protein, or the S2 subunit (S2) of the Spike protein on days 0 and 21. Sera were collected from each mice on days 0, 21, 42, and 56. Individual bleeds were tested for anti-S, anti-S2 activity via a virus neutralization assay from all four time points.

'127 Patent (Ex. 1001), 217:41-60; *see also* '600 Patent (Ex. 1001), 213:56-214:9

Example 24: MERS CoV Vaccine Immunogenicity Study in New Zealand White Rabbits

The instant study was designed to test the immunogenicity of candidate MERS-CoV mRNA vaccines encoding the full-length Spike (S) protein. The New Zealand white rabbits used in this study weighed about 4-5 kg. The rabbits were divided into three groups (Group 1a, Group 1b, and Group 2, n=8). Rabbits in Group 1a were immunized intramuscularly (IM) with one 20 μg dose of the MERS-CoV mRNA vaccine encoding the full-length Spike protein on day 0. Rabbits in Group 1b were immunized intramuscularly (IM) with one 20 μg dose of the MERS-CoV mRNA vaccine encoding the full-length Spike protein on day 0, and again on day 21 (booster dose). Group 2 received placebo (PBS).

'127 Patent (Ex. 1001), 217:61-218:39; *see also* '600 Patent (Ex. 1001), 214:11-56

01359 POR, 8-9; 01359 Sur-Reply, 4-5; Fuller '127 Patent Decl. (Ex. 2199), ¶¶169, 183
01358 POR, 8-9; 01358 Sur-Reply, 4-5; Fuller '600 Patent Decl. (Ex. 2199), ¶¶170, 184

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

moderna

"S Protein" Is a Full-Length Spike Protein

Petitioners' Cited Passages Are Consistent with Patent Owner's Construction

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

'127 Patent (Ex. 1001), 35:19-22; *see also* '600 Patent (Ex. 1001), 35:23-26

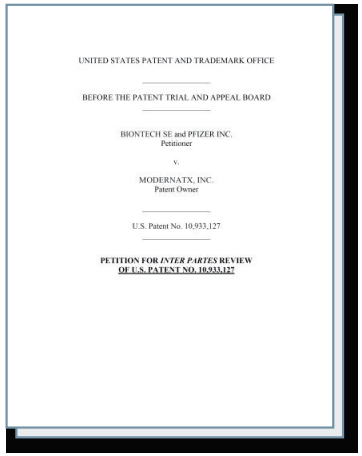
> (M) or an immunogenic fragment thereof. In some embodiments, a *Betacoronavirus* structural protein is a spike protein (S). In some embodiments, a *Betacoronavirus* structural protein is a S1 subunit or a S2 subunit of spike protein (S) or an immunogenic fragment thereof.

'127 Patent (Ex. 1001), 7:30-34; *see also* '600 Patent (Ex. 1001), 7:28-32

01359 POR, 8-9; 01359 Sur-Reply, 4-5; Fuller '127 Patent Decl. (Ex. 2199), ¶¶160, 162, 174, 176
01358 POR, 8-9; 01358 Sur-Reply, 4-5; Fuller '600 Patent Decl. (Ex. 2199), ¶¶161, 163, 175, 177

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

"S Protein" Requires "Forming a Spike"



UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BIONTECH SE and PFIZER INC.
Petitioner

v.

MODERNATX, INC.
Patent Owner

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

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

IX. **CLAIM CONSTRUCTION**

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

* * *

- **S protein**: a "spike protein," which is "a structural protein forming a spike."

01359 Petition, 19; *see also* 01358 Petition, 21

01359 POR, 7-8; 01359 Sur-Reply, 4
01358 POR, 8; 01358 Sur-Reply, 4

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Challenged Claims Are Not Anticipated

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

No Anticipation

1

Geall is incorporated only for its dose amounts

2

Geall does not disclose immune response to BetaCoV S protein

- No evidence reference to "spike polypeptide" is claimed full-length S protein
- No evidence that spike forms
- No immune response data to BetaCoV S protein

3

Not arranged as in claims because Schrum and Geall collectively disclose 3,000+ potential combinations

01359 POR, 9-10, 12, 14-25; 01359 Sur-Reply, 5-9; *e.g.*, Fuller '127 Patent Decl. (Ex. 2199), ¶¶235-322, 333-345
01358 POR, 9-10, 12, 14-25; 01358 Sur-Reply, 5-9; *e.g.*, Fuller '600 Patent Decl. (Ex. 2199), ¶¶236-308

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Schrum: Geall Not Incorporated for Immunogens

[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).

Schrum (Ex. 1009), ¶342

01359 POR, 15-17; 01359 Sur-Reply, 6 n.6
01358 POR, 15-17; 01358 Sur-Reply, 6 n.6

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Schrum & Geall: Do Not Disclose Full-Length BetaCoV 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.

Geall (Ex. 1010), 19:26-29

01359 POR, 17-18; 01359 Sur-Reply, 6-7
01358 POR, 18-19; 01358 Sur-Reply, 6-7

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Schrum & Geall: Do Not Disclose Full-Length BetaCoV S Protein

FIG. 2 shows an example electron micrograph of liposomes prepared by these methods. These liposomes contain encapsulated RNA encoding full-length RSV F antigen. Dynamic light scattering of one batch showed an average diameter of 141nm (by intensity) or 78nm (by number).

Geall (Ex. 1010), 32:17-18

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

Geall (Ex. 1010), 40:14-16

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.

Geall (Ex. 1010), 19:26-29

01359 POR, 10, 17; 01359 Sur-Reply, 7; *e.g.*, Fuller '127 Patent Decl. (Ex. 2199), ¶¶201, 247, 259
01358 POR, 10, 18; 01358 Sur-Reply, 6; *e.g.*, Fuller '600 Patent Decl. (Ex. 2199), ¶¶202, 247, 259

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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"S Protein" Requires "Structural Protein Forming a Spike"

Petitioners' Expert Testified Protein May Misfold in mRNA Vaccine



Dr. Daniel O. Griffin

Petitioners' Expert

Q. Are there situations where the protein can be expressed but doesn't properly form?

A. **I certainly can imagine examples where an RNA template is such that a produced protein does not form as one might expect.**

Q. Does misfolding occur just in nature?

A. **In nature proteins can misfold.**

Q. So misfolding can occur in the context of a synthetic mRNA vaccine?

A. **It seems rather hypothetical, but depending upon the construction of the mRNA technology, one could potentially end up with a misfolded protein.**

Griffin Reply Dep. (Ex. 2253), 48:4-16

01359 Sur-Reply, 7; 01358 Sur-Reply, 7

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Dr. Griffin's Testimony



Dr. Daniel O. Griffin

Petitioners' Expert

Q. … Is expression of the protein by itself sufficient to generate neutralizing antibodies?

A. **So expression of a protein by itself does not necessarily lead to production of neutralizing antibodies.**

Griffin Reply Dep. (Ex. 2253), 47:15-19

01359 Sur-Reply, 18; 01358 Sur-Reply, 18

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Schrum & Geall: Do Not Disclose BetaCoV S Protein Forming a Spike

To assess *in vivo* immunogenicity a replicon was constructed to express full-length F protein from respiratory syncytial virus (RSV). This was delivered naked (1µg), encapsulated in liposomes (0.1 or

Geall (Ex. 1010), 34:11-12

Three different RNAs were used for this study: (i) 'vA317' replicon that expresses RSV-F *i.e.* the surface fusion glycoprotein of RSV; (ii) 'vA17' replicon that expresses GFP; and (iii) 'vA336' that is replication-defective and encodes GFP.

Geall (Ex. 1010), 35:16-18

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

Geall (Ex. 1010), 40:14-16

01359 POR, 10, 17; 01359 Sur-Reply, 7; e.g., Fuller '127 Patent Decl. (Ex. 2199), ¶¶201, 247
01358 POR, 10, 18; 01358 Sur-Reply, 6; e.g., Fuller '600 Patent Decl. (Ex. 2199), ¶¶202, 247

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Schrum & Geall: Geall Does Not Teach the Claimed mRNA



Dr. Daniel O. Griffin

Petitioners' Expert

Q. … [Y]ou are not offering the opinion that Geall teaches non-amplifying mRNA; right?

A. **… So as I explained, I get the mRNA from Schrum, the LNPs from Schrum. I go to Geall for the antigen and I acknowledge that all of the working examples in Geall use self-amplifying mRNA, and I am not able to point to a working example in Geall where non-amplifying mRNA vaccines are used to produce a protein.**

Griffin Reply Dep. (Ex. 2253), 29:4-15; *see also id.*, 13:3-11

122. All embodiments encapsulating an RNA in the '693 Patent disclose only self-replicating RNA molecules as the RNA, unlike the mRNA used in Comirnaty®.

Petitioners' District Court Answer (Ex. 1312), 96 (¶122)

01359 Sur-Reply, 2 n.1; 01358 Sur-Reply, 2 n.1

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Testing Required to Determine Whether Spike Forms



Dr. Daniel O. Griffin

Petitioners' Expert

Q. … So earlier our discussion about circumstances where, for example, a protein may not express or not properly fold, are you saying that doesn't happen in the context of SARS or any betacoronavirus?

A. **Yeah, with reference to our earlier discussion, if one doesn't get the mRNA sequence correct or one fails to actually get the protein to express, well, then it wouldn't be able to, but if the mRNA sequence is correct and the protein is expressed, then the expressed S protein would fold into the figurative spike for which these proteins are named.**

Q. Okay. And how do you know if the mRNA expresses, how does one determine that?

A. **The most compelling evidence would be to assay the level of protein produced.**

Griffin Reply Dep. (Ex. 2253), 68:4-69:1 (objection omitted)

01359 Sur-Reply, 7; 01358 Sur-Reply, 7

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Challenged Patents' Data

Example 24: MERS CoV Vaccine Immunogenicity Study in New Zealand White Rabbits

The instant study was designed to test the immunogenicity of candidate MERS-CoV mRNA vaccines encoding the full-length Spike (S) protein. The New Zealand white rabbits used in this study weighed about 4-5 kg. The rabbits were divided into three groups (Group 1a, Group 1b, and Group 2, n=8). Rabbits in Group 1a were immunized intramuscularly (IM) with one 20 μg dose of the MERS-CoV mRNA vaccine encoding the full-length Spike protein on day 0. Rabbits in Group 1b were immunized intramuscularly (IM) with one 20 μg dose of the MERS-CoV mRNA vaccine encoding the full-length Spike protein on day 0, and again on day 21 (booster dose). Group 2 received placebo (PBS). The immunized rabbits were then challenged and samples were collected 4 days after challenge. The viral loads in the lungs, bronchoalveolar lavage (Bal), nose, and throat of the rabbits were determined, e.g., via quantitative PCR. Replicating virus in the lung tissues of the rabbits were also detected. Lung histopathology were evaluated and the neutralizing antibody titers in serum samples of the rabbits were determined.

Two 20 μg doses of MERS-CoV mRNA vaccine resulted in a 3 log reduction of viral load in the nose and led to complete protection in the throat of the New Zealand white rabbits (FIG. **19**A). Two 20 μg doses of MERS-CoV mRNA vaccine also resulted in a 4 log reduction of viral load in the BAL of the New Zealand white rabbits (FIG. **19**B). One 20 μg dose of MERS-CoV mRNA vaccine resulted in a 2 log reduction of viral load, while two 20 μg doses of MERS-CoV mRNA vaccine resulted in an over 4 log reduction of viral load in the lungs of the New Zealand white rabbits (FIG. **19**C).

Quantitative PCR results show that two 20 μg doses of MERS-CoV mRNA vaccine reduced over 99% (2 log) of viruses in the lungs of New Zealand white rabbits (FIG. **20**A). No replicating virus were detected in the lungs (FIG. **20**B).

Further, as shown in FIG. **21**, two 20 μg doses of MERS-CoV mRNA vaccine induced significant amount of neutralizing antibodies against MERS-CoV (EC_{50} between 500-1000). The MERS-CoV mRNA vaccine induced antibody titer is 3-5 fold better than any other vaccines tested in the same model.

'127 Patent (Ex. 1001), 217:61-218:39;
see also '600 Patent (Ex. 1001), 214:11-56

01359 POR, 2-3, 8-9; 01359 Sur-Reply, 4; *e.g.*, Fuller '127 Patent Decl. (Ex. 2199), ¶¶143-147, 169, 183
01358 POR, 2-3, 8-9; 01358 Sur-Reply, 4; *e.g.*, Fuller '600 Patent Decl. (Ex. 2199), ¶¶144-148, 170, 184

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

No Anticipation Where Picking and Choosing Is Required

***In re Arkley*, 455 F.2d 586 (CCPA 1972)**

> [R]ejections under 35 U.S.C. § 102 are proper only when the claimed subject matter is identically disclosed or described in "the prior art." Thus, for the instant rejection under 35 U.S.C. § 102(e) to have been proper, the Flynn reference **must clearly and unequivocally disclose the claimed compound** or direct those skilled in the art to the compound **without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference**. **Such picking and choosing … has no place in the making of a 102, anticipation rejection**.

455 F.2d at 587-588

> [T]here is nothing in the teachings relied upon by the Patent Office which "clearly and unequivocally" directs those skilled in the art to make this selection nor any indication that Flynn ever made the selection himself.

455 F.2d at 588

01359 POR, 12-13, 19-20, 24; 01358 POR, 12-13, 19-20, 24

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

No Anticipation Where Categories Are So Large That Combination Is Not Immediately Apparent

***Nidec Motor Corp. v. Zongshan Broad Ocean Motor Co.*, 851 F.3d 1270 (Fed. Cir. 2017)**

As we explained, the relevant question [in *Kennametal*] was "whether **the number of categories and components disclosed in [the prior art reference] is so large** that the combination of ruthenium and PVD coatings **would not be immediately apparent** to one of ordinary skill in the art."

851 F.3d at 1274

01359 POR, 23; 01359 Sur-Reply, 8
01358 POR, 23; 01358 Sur-Reply, 7

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

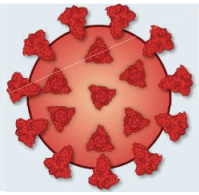
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Schrum: Not Arranged as in Claims



Vaccine Technology: 2+

×



Immunogens: 500+

×



Delivery Options: 3+

3,000+ Options

01359 POR, 14-25; 01359 Sur-Reply, 8-9; *e.g.*, Fuller '127 Patent Decl. (Ex. 2199), ¶¶276-316
01358 POR, 14-25; 01358 Sur-Reply, 7-9; *e.g.*, Fuller '600 Patent Decl. (Ex. 2199), ¶¶261-301

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Schrum: Working Examples in Therapeutics, Not Vaccines



Dr. Deborah H. Fuller

Moderna's Expert

> 282. Schrum's working examples are directed to therapeutic proteins. Ex. 1009, ¶¶904-1332. **None** of Schrum's examples use an infectious disease protein or viral immunogen. Ex. 1009, ¶¶904-1332.

Fuller '127 Patent Decl. (Ex. 2199), ¶282;
see also Fuller '600 Patent Decl. (Ex. 2199), ¶267

01359 POR, 9-10, 20; 01359 Sur-Reply, 25
01358 POR, 9-10, 20; 01358 Sur-Reply, 25

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Schrum: Does Not Exemplify mRNA-LNP Compositions Encoding Infectious Disease Proteins

[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.

Schrum (Ex. 1009), ¶397

[0022] In one embodiment, the present disclosure provides a formulation composition which comprises a modified nucleic acid molecule and a delivery agent. The modified nucleic acid molecule may be selected from the group consisting of DNA, complimentary DNA (cDNA), RNA, messenger RNA (mRNA), RNAi-inducing agents, RNAi agents, siRNA, shRNA, miRNA, antisense RNA, ribozymes, catalytic DNA, RNA that induce triple helix formation, aptamers, vectors and combinations thereof. If the modified nucleic acid molecule is mRNA the mRNA may be derived from cDNA.

Schrum (Ex. 1009), ¶22

01359 POR, 20-22; 01359 Sur-Reply, 8 n.7
01358 POR, 21-22; 01358 Sur-Reply, 8 n.7

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Geall: Discloses 500+ Immunogens

The immunogen

* * *

In some embodiments the immunogen elicits an immune response against one of these bacteria:

* * *

In some embodiments the immunogen elicits an immune response against one of these viruses:

* * *

Fungal immunogens may be derived from Dermatophytres, including: *Epidermophyton floccusum*

* * *

In some embodiments the immunogen elicits an immune response against a parasite

* * *

In some embodiments the immunogen elicits an immune response against: pollen allergens (tree-, herb, weed-, and grass pollen allergens); insect or arachnid allergens (inhalant, saliva and venom allergens, *e.g.* mite allergens, cockroach and midges allergens, hymenopthera venom allergens); animal hair and dandruff allergens (from *e.g.* dog, cat, horse, rat, mouse, *etc.*); and food allergens (*e.g.* a gliadin). Important pollen allergens from trees, grasses and herbs are such originating from the

* * *

In some embodiments the immunogen is a tumor antigen

Geall (Ex. 1010), 15:32-22:35

01359 POR, 18-19, 23-24; 01359 Sur-Reply, 8-9; *e.g.*, Fuller '127 Patent Decl. (Ex. 2199), ¶¶286-289, 319-320
01358 POR, 19, 23-25; 01358 Sur-Reply, 7-8; *e.g.*, Fuller '600 Patent Decl. (Ex. 2199), ¶¶271-274, 305-306

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Schrum: Discloses Multiple Delivery Methods



Dr. Warren Chan

Moderna's Expert

106. Schrum discloses a wide range of carriers for delivery of nucleic acids, including mRNA. Right at the outset, Schrum states:

> 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) (PLGA) microspheres**, **lipidoids**, **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**.

Ex. 1009, ¶[0005] (emphasis added).

Chan '127 Patent Decl. (Ex. 2198), ¶106;
see also Chan '600 Patent Decl. (Ex. 2198), ¶106

01359 POR, 10, 21; 01358 POR, 10, 21

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Schrum: Discloses Multiple Delivery Methods



Dr. Deborah H. Fuller

Moderna's Expert

Q. Go to Paragraph 8 [of Schrum].

A. **So it's describing one aspect of formulation that – one formulation of many that are listed in here.**

Q. It's describing many formulations for encapsulating mRNA in lipid nanoparticles. Is that fair?

A. **There are a laundry list, basically a fairly long list here of different types of formulations that could be used.**

Q. One of those includes lipid nanoparticles. Right?

A. **So there are microspheres – there's lipid nanoparticles, there's microspheres, several different types of formulations listed here.**

Fuller Dep. (Ex. 1104), 222:19-223:22 (objection omitted)

01359 Sur-Reply, 8; 01358 Sur-Reply, 7

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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No Anticipation Where No Limited Class with Common Properties

***Mylan Pharmaceuticals Inc. v. Merck Sharp & Dohme Corp.*, 50 F.4th 147 (Fed. Cir. 2022)**

But we agree with Merck and hold that the Board did not err in finding that a **class of 957 predicted salts that may result from the 33 disclosed compounds and eight preferred acids, some of which may not even form under experimental conditions, is insufficient to meet the "at once envisage" standard** set forth in *Petering*.

50 F.4th at 154

01359 POR, 23-24; 01358 POR, 23-24

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Challenged Claims Are Not Obvious

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

No Obviousness

No Motivation to Combine

1. **mRNA was known to have significant challenges**
   - Unstable
   - Low amounts of protein produced

2. **Field was skeptical of mRNA vaccines**
   - 0.3% clinical trials for infectious diseases involved mRNA
   - All ultimately failed

3. **Concerns with using betacoronavirus S protein**
   - Large sized protein
   - Associated with disease enhancement

01359 POR, 28-51, 54-56, 59; 01359 Sur-Reply, 20-25
01358 POR, 28-51, 53-55, 58; 01359 Sur-Reply, 19-25

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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No Obviousness

No Reasonable Expectation of Success

1. mRNA field was highly unpredictable

2. Results from different nucleic acid vaccines, different antigens, and different delivery methods yield different and unpredictable results

3. No teaching of successful delivery of mRNA encoding protein as large as S protein

4. Evidence of failures with mRNA vaccines

01359 POR, 28-51, 54-56, 59; 01359 Sur-Reply, 11-20
01358 POR, 28-51, 53-55, 58; 01358 Sur-Reply, 11-19

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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No Obviousness

Strong Objective Indicia of Non-Obviousness

1. **No dispute Spikevax® and Comirnaty® practice the challenged claims**

2. **Extensive evidence of objective indicia:**
   - Long-Felt Unmet Need
   - Failure of Others
   - Skepticism
   - Unexpected Results
   - Industry Praise
   - Commercial Success

01359 POR, 59-70; 01359 Sur-Reply, 26-28
01338 POR, 58-69; 01358 Sur-Reply, 26-28

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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No Obviousness: Geall

1. Does not disclose mRNA of claimed invention or LNPs encapsulating mRNA

2. Does not disclose claimed full-length S protein

3. Does not disclose neutralizing antibodies to claimed full-length S protein

01359 POR, 10, 17-18, 27-28; 01359 Sur-Reply, 2 n.1, 6-8, 11
01358 POR, 10, 18-19, 27-28; 01358 Sur-Reply, 2 n.1, 6-7, 10

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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No Obviousness: Yang

1. Discloses delivery of DNA, not mRNA

2. Discloses naked (PBS) delivery, not LNPs

3. Discloses data for truncated spike proteins, not for claimed full-length S protein

4. Does not disclose neutralizing antibodies to claimed full-length S protein

01359 POR, 10-11, 53-54; 01359 Sur-Reply, 10-11
01358 POR, 11, 52-53; 01358 Sur-Reply, 9-10

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

moderna

No Obviousness: Altmeyer

1. Does not disclose mRNA vaccines

2. Does not disclose delivery of mRNA, and focuses primarily on protein vaccines

3. Discloses aluminum adjuvant (or naked (PBS) delivery), not LNPs

4. Does not disclose neutralizing antibodies attributed to nucleic acid vaccine, let alone mRNA vaccine

01359 POR, 11, 57-58; 01359 Sur-Reply, 2 n.1, 10-11
01358 POR, 11, 56-58; 01358 Sur-Reply, 2 n.1, 9-10

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

moderna

No Motivation to Combine



DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

mRNA Compositions Encoding Infectious Disease Proteins Failed Before 2015



Dr. Deborah H. Fuller

Moderna's Expert

Q. And as of October 2015, what was your experience with mRNA vaccines?

A. October 2015?

Q. Correct.

A. So I had started nucleic acid vaccine research in 1990 using different technologies, developing technology for delivery.

* * *

So between 1990 and 1998, I did experiments with both DNA and mRNA. mRNA consistently failed in those experiments, but DNA was successful. And for the next two decades after that, my primary focus was on DNA.

* * *

Q. What do you mean when you said mRNA consistently failed in those experiments between 1990 and 1998?

A. When we compared head-to-head a DNA vaccine expressing a given immunogen and an mRNA that we'd make an mRNA transcript off of the DNA expressing the same immunogen, we compared them head-to-head using our different delivery platforms or strategies.

The DNA vaccine would induce an immune response and the mRNA vaccine would fail.

Fuller Dep. (Ex. 1104), 32:3-33:13; *see also id.*, 33:14-20

01359 Sur-Reply, 14-15, 18; 01358 Sur-Reply, 14-15, 18

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Field Was Skeptical of mRNA Compositions Encoding Infectious Disease Proteins

Issues with Expression, Delivery, & Stability



Dr. Deborah H. Fuller

Moderna's Expert

Q. You mentioned skepticism of mRNA vaccines in 2015. Right?

A. **Yes.**

Q. What was the field skeptical of?

A. **So there was a large body of research that had been done on nucleic acid vaccines in general prior to 2015. There were certainly efforts going on with mRNA vaccines, but by far the majority of the field was focused – when we talk about nucleic acid vaccines on DNA and self-amplifying RNA.**

But let me even characterize that further. Even within the whole class of nucleic acid vaccines, there was huge skepticism surrounding the entire body of them.

Among those, if we think of DNA, self-amplifying RNA, mRNA, mRNA was the least promising or I believe the one that was held in greatest skepticism at that time.

Simply, there was just very few studies to demonstrate the mRNA vaccines – issues with both the efficiency of delivery, the expression.

A lot of concerns about mRNA vaccines in terms of their stability existed. There were a lot more publications on DNA vaccines, on self-amplifying RNA vaccines.

Fuller Dep. (Ex. 1104), 194:13-195:16; *see also id.*, 194:13-196:9

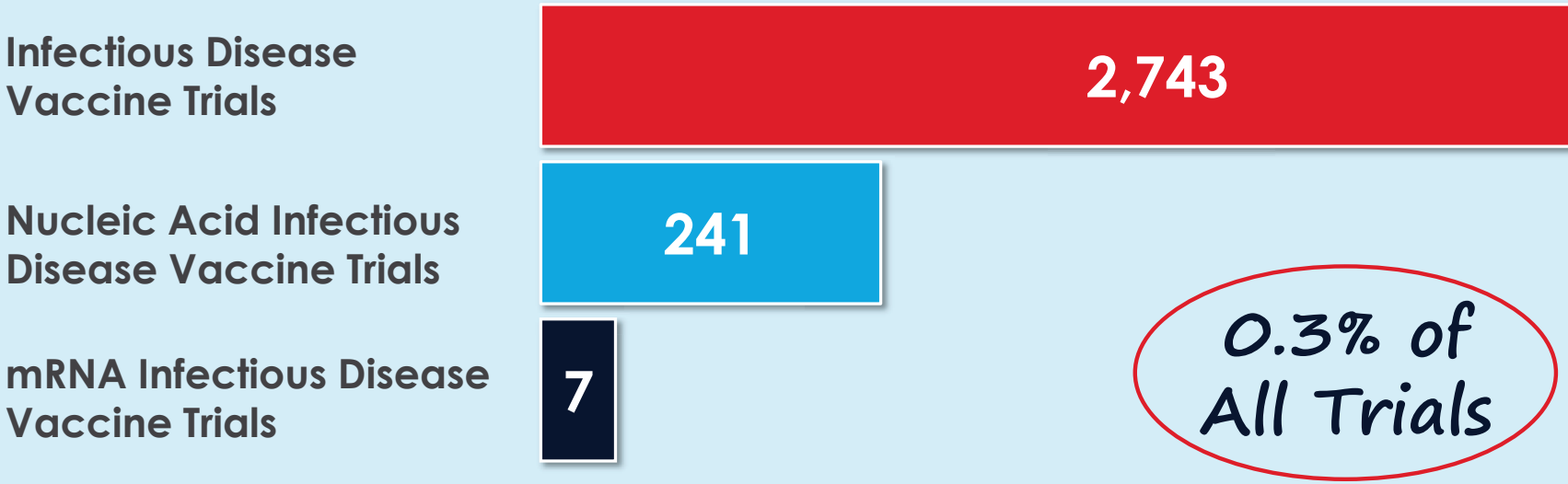
01359 Sur-Reply, 15, 18; 01358 Sur-Reply, 15, 18

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Field Was Skeptical of mRNA Vaccines for Infectious Diseases

Only 7 mRNA Infectious Disease Vaccine Clinical Trials by 2015; All Ultimately Failed



01359 POR, 42, 44, 66; 01359 Sur-Reply, 18-19; *e.g.*, Fuller '127 Patent Decl. (Ex. 2199), ¶¶515, 520-528, 531-532
01358 POR, 42, 44, 65; 01358 Sur-Reply, 18; *e.g.*, Fuller '600 Patent Decl. (Ex. 2199), ¶¶512, 516-525, 528-529

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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DNA Vaccines



Dr. Deborah H. Fuller

Moderna's Expert

834. **Third**, I disagree with Dr. Griffin that in 2015, "mRNA vaccines were known to have significant advantages over DNA vaccines." *See* Ex. 1002, ¶164. To the contrary, in 2015, although the majority of clinical activity was focused on traditional vaccine technology in the context of infectious disease (*see* Section XI.A.3.a), the field was cautiously optimistic about the promise of DNA. *See* my discussion in Section XI.A.3.c. DNA vaccines were considered to have several advantages over mRNA including safety, stability, and immunogenicity. *See* my discussion above in Section XI.A.3.c.

Fuller '127 Patent Decl. (Ex. 2199), ¶834; *see also id.*, ¶¶57-59, 538-543, 834-838;
Fuller '600 Patent Decl. (Ex. 2199), ¶¶58-60, 535-540, 840-844

01359 POR, 10-11, 41, 54-55; 01359 Sur-Reply, 14-15
01358 POR, 11, 40-41, 54; 01358 Sur-Reply, 14-15

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Viral Vector Vaccines



Dr. Deborah H. Fuller

Moderna's Expert

537. Around 2015, viral vector vaccines were the most commonly used non-traditional vaccine technology for infectious diseases. *See* Ex. 2109, 190; *see also* Ex. 2110, 10 (reporting that in 2017: "viral vectors remain by far the most popular approach, having been used in approximately two-thirds of the trials performed to date"). It was thought at the time that one major advantage of viral vector vaccines is that a viral vector is already advantageously packaged in a viral particle (mimicking a real virus), which is an efficient system that allows viral vectors to efficiently transfect cells. Ex. 2021, 14604 ("Viral vector-based technologies **are generally regarded as the most efficient means to deliver nucleic acids into cells** ….").

Fuller '127 Patent Decl. (Ex. 2199), ¶537; *see also id.*, ¶¶60-64
Fuller '600 Patent Decl. (Ex. 2199), ¶¶61-65, 534

01359 POR, 11, 41; 01358 POR, 11, 40-41

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

saRNA Vaccines



Dr. Deborah H. Fuller

Moderna's Expert

544. With respect to saRNA, around 2015, saRNA vaccines were considered to have several advantages over other non-traditional vaccines and became increasingly more popular (and eventually became even more popular than DNA, and certainly more popular than mRNA). For example, it was thought that, because saRNA "amplifies" within the cell and leads to the downstream production of many copies of the antigen of interest, it can be highly effective even at low doses. Ex. 1010, 12:15-17 ("The overall results of this sequence of transcriptions is a huge amplification in the number of the introduced replicon RNAs and so the encoded immunogen becomes a major polypeptide product of the cells."); *id.*, 1:20-22 ("[V]ery high doses would be required [with DNA] …."); *id.*, 43:4-7 ("A typical dose for a cow DNA vaccine would be 0.5-1 mg … and so it is very encouraging that immune responses were induced with only 66µg of RNA."); Ex. 2103, 336 ("The RSV SAM vaccine is substantially more potent than a DNA-based vaccine in BALB/c mice.").

547. At the time, saRNA was seen as one of the potential solutions to the known problems with mRNA, including poor stability and issues with delivery that were hypothesized to result in low amounts of protein production in vivo and poor adaptive immune responses. *See, e.g.*, Ex. 1016, 156 ("Messenger RNA is generally considered to be an unstable molecule because of the presence of the hydroxyl group at the 2' position on the ribose sugar."); *id.*, 156 ("The development of RNA vaccines is still in its infancy."); *see also* my discussion in Section XI.A.3.a.

Fuller '127 Patent Decl. (Ex. 2199), ¶¶544, 547; *see also id.*, ¶¶65-70, 544-549
Fuller '600 Patent Decl. (Ex. 2199), ¶¶66-71, 541-546

01359 POR, 10, 41; 01358 POR, 10, 40-41

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Field Was Skeptical of mRNA Vaccines for Infectious Diseases

Only 7 mRNA Infectious Disease Vaccine Clinical Trials by 2015; All Ultimately Failed



Dr. Deborah H. Fuller

Moderna's Expert

523. By October 2015, across the seven total clinical trials, only three unique mRNA vaccines for infectious diseases had entered clinical testing. *See* Ex. 2084, 187. One was against a Rabies virus and the other two were against HIV-1; none was against a betacoronavirus.[26] *See generally* Ex. 2043; Ex. 2046; Ex. 2044; Ex. 2085; *see also* Ex. 2084, 187, Table 6.[27]

[26] None of the mRNA vaccines was formulated in lipid nanoparticles either.

524. As of October 2015, there was **no evidence** that any of the three mRNA vaccines for infectious diseases that entered clinical testing prior to October 2015 would ultimately succeed. Moreover, **all three of these mRNA vaccines** for infectious diseases eventually **failed**.

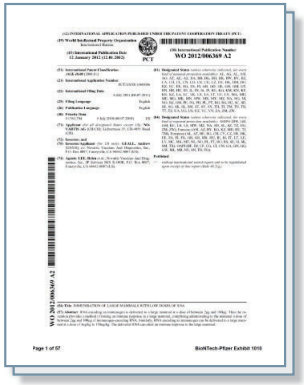
Fuller '127 Patent Decl. (Ex. 2199), ¶¶523-524 & n.26;
see also Fuller '600 Patent Decl. (Ex. 2199), ¶¶520-521 & n.26

01359 POR, 41-44; 01359 Sur-Reply, 20-21
01358 POR, 40-44; 01358 Sur-Reply, 20

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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POSA Would Have Considered Whether Immunogens Failed in mRNA Trials



Rhabdovirus: Viral immunogens include, but are not limited to, those derived from a Rhabdovirus, such as a Lyssavirus (*e.g.* a Rabies virus) and Vesiculovirus (VSV).

* * *

Retrovirus: Viral immunogens include, but are not limited to, those derived from an Oncovirus, a Lentivirus (*e.g.* HIV-1 or HIV-2) or a Spumavirus.

Geall (Ex. 2010), 19:21-22, 20:1-2



Dr. Daniel O. Griffin

Petitioners' Expert

Q. … Would a POSA have taken an interest in whether someone had used one of the immunogens listed in Geall and tested it in connection with an mRNA vaccine?

A. **So a POSA in 2015, who was looking through this list of viral immunogens or other pathogen immunogens, would have found success using mRNA expression of an antigen to be informative.**

Q. You said "success." What about lack of success, would the POSA have found lack of success to have been informative?

A. **So by lack of success, if they tried to use mRNA and failed to express the protein, then I think that also would have been interesting to understand why they were not able to express the antigen.**

Griffin Reply Dep. (Ex. 2253), 24:21-25:15

01359 Sur-Reply, 18-19; 01358 Sur-Reply, 18-19

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Disease Enhancement Concerns with Spike Protein



Dr. Deborah H. Fuller

Moderna's Expert

580. **Second**, a plethora of research by that time had shown that using the spike protein as a vaccine antigen could result in vaccine-mediated enhancement of disease. Vaccine-mediated enhancement of disease "is characterized by a vaccine that results in increased disease severity if the subject is later infected by the natural virus." Ex. 2136, 4784; *see also* my discussion below in Section XI.A.3.i.

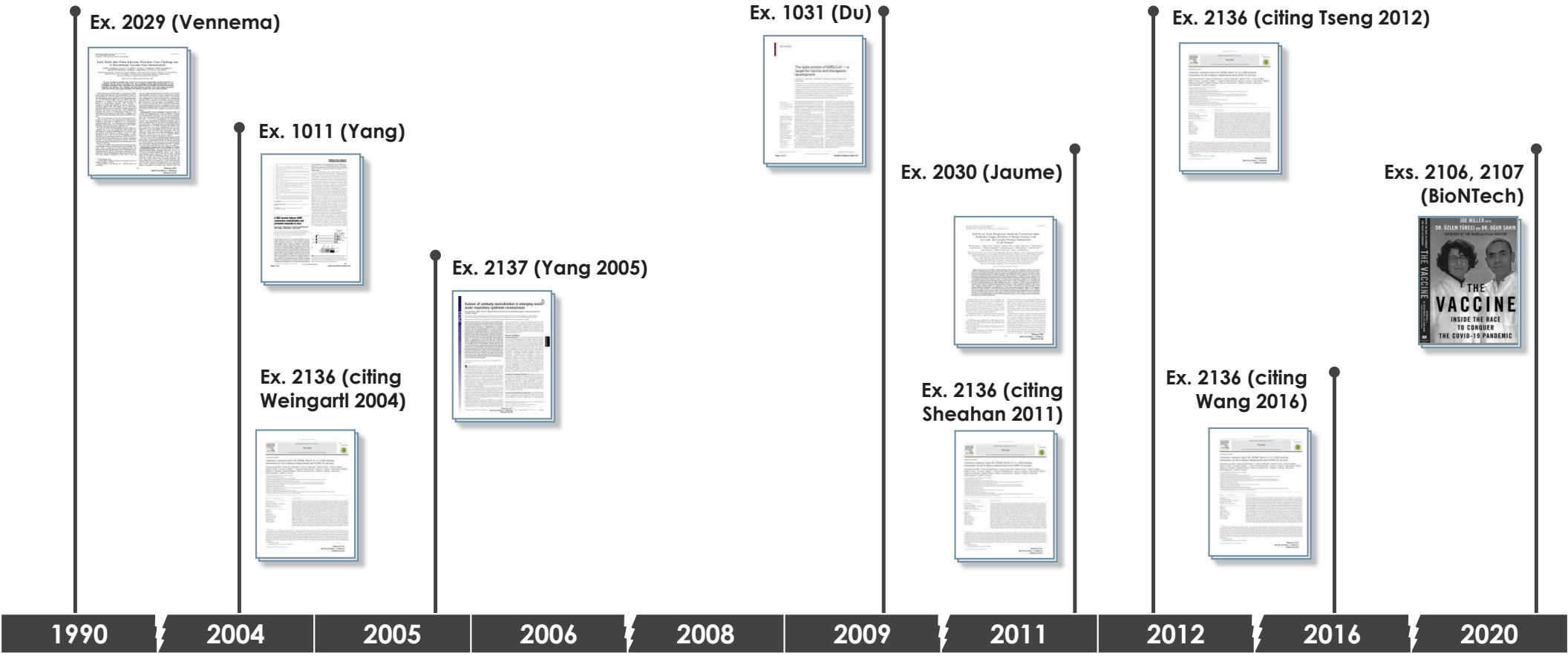
Fuller '127 Patent Decl. (Ex. 2199), ¶580;
see also Fuller '600 Patent Decl. (Ex. 2199), ¶577

01359 POR, 47-48; 01359 Sur-Reply, 21
01358 POR, 47-48; 01358 Sur-Reply, 21

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Disease Enhancement Concerns with Spike Protein



01359 POR, 46-48; 01359 Sur-Reply, 21-23; *e.g.*, Fuller '127 Patent Decl. (Ex. 2199), ¶¶127-130, 580-599. 605-606
01358 POR, 46-48; 01358 Sur-Reply, 21-23; *e.g.*, Fuller '600 Patent Decl. (Ex. 2199), ¶¶128-131, 577-596, 602-603

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Disease Enhancement Concerns with Spike Protein

Petitioners' References Confirm Concern

Du

Although full-length S protein-based SARS vaccines can induce neutralizing antibody responses against SARS-CoV infection, they may also induce harmful immune responses that cause liver damage of the vaccinated animals or enhanced infection after challenge with homologous SARS-CoV[64,65], raising concerns about the safety and ultimate protective efficacy of vaccines that contain the full-length SARS-CoV S protein.

Du (Ex. 1031), 229-230

Yang

protective immunity. The SARS-CoV is a novel coronavirus, but vaccines for other human coronaviruses have not been successfully developed[14]. But considerable experience in developing vaccines against common veterinary coronaviruses has been obtained with animal coronaviruses[11,12]. 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[19]. In the

Yang (Ex. 1011), 563

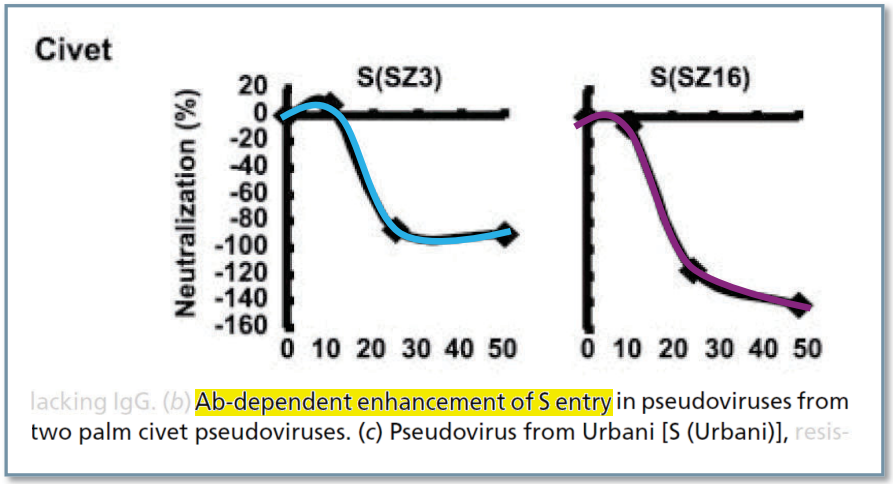
01359 POR, 46-48; 01359 Sur-Reply, 15 n.13, 17 n.14, 21-22 & n.18
01358 POR, 46-48; 01358 Sur-Reply, 15 n.13, 17, 21-22 & n.18

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Disease Enhancement Concerns with Spike Protein

Yang's Research Group Confirmed Concern & Used Truncated Protein

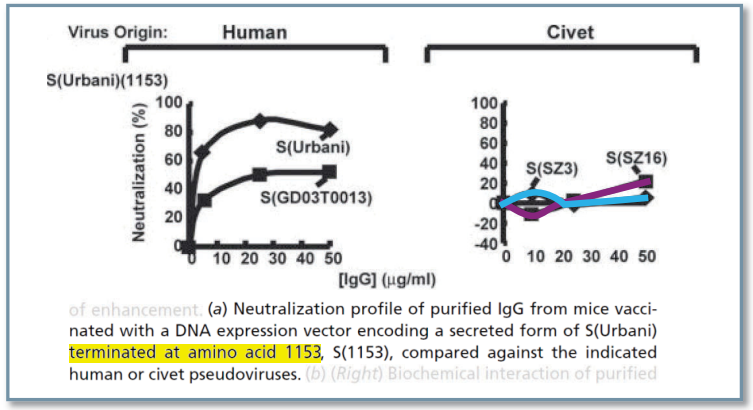


lacking IgG. (*b*) Ab-dependent enhancement of S entry in pseudoviruses from two palm civet pseudoviruses. (*c*) Pseudovirus from Urbani [S (Urbani)], resis-

Yang 2005 (Ex. 2137), Fig. 1b

Development of Alternative Vaccine Candidates That Do Not Enhance Civet S-Dependent Entry. We next sought to determine whether it was possible to modify the S immunogen to avoid Ab-dependent enhancement of entry of the palm civet S pseudoviruses. Because soluble S proteins reacted differentially by immunoprecipitation analysis, a series of transmembrane-deleted immunogens was prepared. One of these mutants, truncated at amino acid 1153, induced neutralizing Abs to human isolates that failed to cause Ab enhancement of entry (Fig. 4*a*). Biochemical

Yang 2005 (Ex. 2137), 800



of enhancement. (*a*) Neutralization profile of purified IgG from mice vaccinated with a DNA expression vector encoding a secreted form of S(Urbani) terminated at amino acid 1153, S(1153), compared against the indicated human or civet pseudoviruses. (*b*) (*Right*) Biochemical interaction of purified

Yang 2005 (Ex. 2137), Fig. 4a

01359 POR, 32-33, 54; 01359 Sur-Reply, 17 n.14, 21, 23-24; *e.g.*, Fuller '127 Patent Decl. (Ex. 2199), ¶¶130, 593-598
01358 POR, 32, 53; 01358 Sur-Reply, 17 n.14, 21, 23-24; *e.g.*, Fuller '600 Patent Decl. (Ex. 2199), ¶¶131, 590-595

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Different Vaccine Technologies Led to Different Disease Enhancement Results

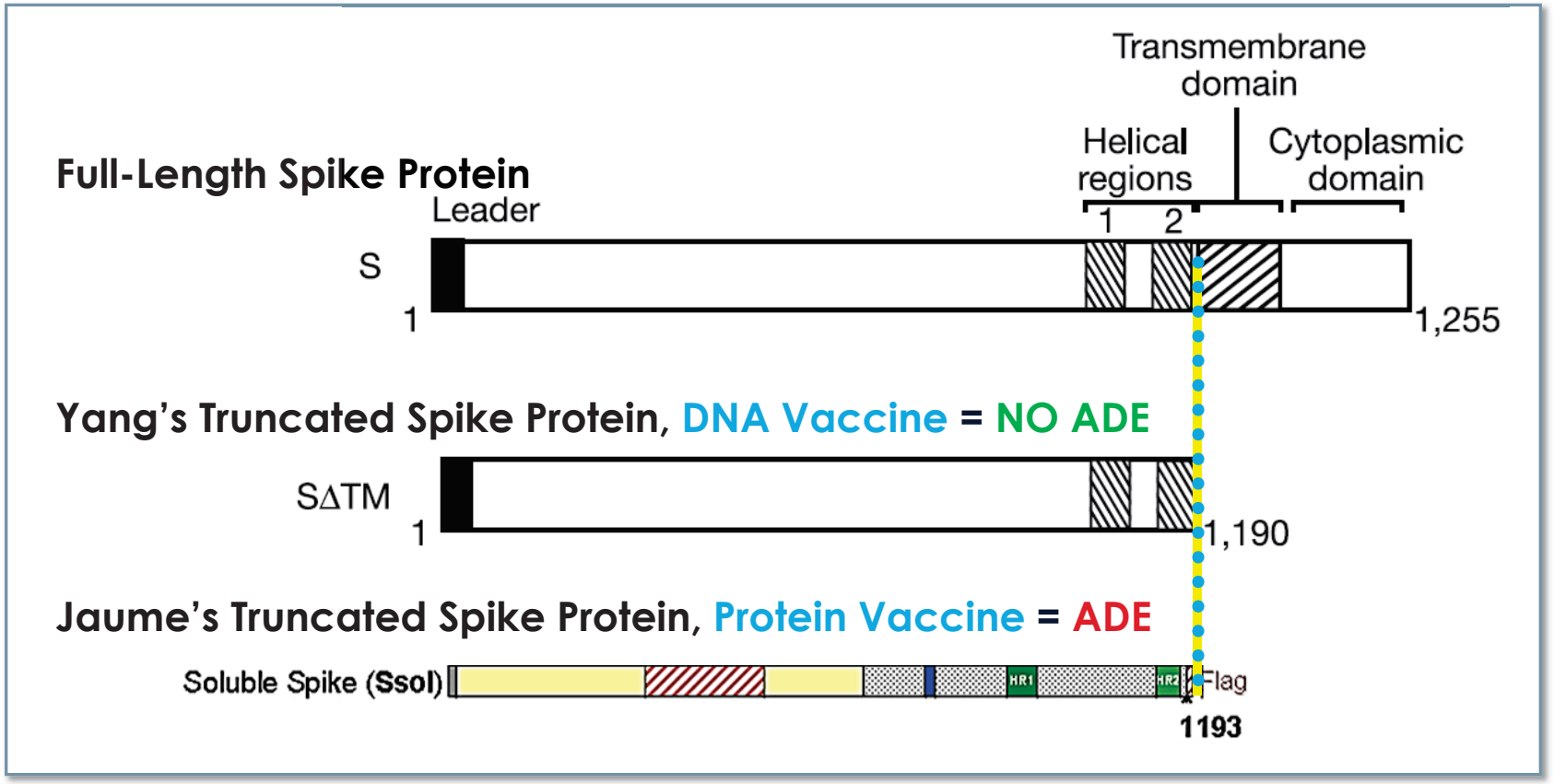
experimental animal models. We previously reported that antibody elicited by a SARS-CoV vaccine candidate based on recombinant full-length Spike-protein trimers potentiated infection of human B cell lines despite eliciting *in vivo* a neutralizing and protective immune response in rodents. These observations prompted us to investigate the mechanisms underlying antibody-dependent enhancement (ADE) of SARS-CoV infection *in vitro*. We demonstrate here that anti-Spike immune serum, while inhibiting viral entry in a permissive cell line, potentiated infection of immune cells by SARS-CoV Spike-pseudotyped lentiviral particles, as well as replication-competent SARS coronavirus. Antibody-mediated infection was dependent on Fcγ receptor II but did not use the endosomal/lysosomal pathway utilized by angiotensin I converting enzyme 2 (ACE2), the accepted receptor for SARS-CoV. This suggests that ADE of SARS-CoV utilizes a novel cell entry mechanism into immune cells. Different SARS vaccine candidates elicit sera that differ in their capacity to induce ADE in immune cells despite their comparable potency to neutralize infection in ACE2-bearing cells. Our results suggest a novel mechanism by which SARS-CoV can enter target cells and illustrate the potential pitfalls associated with immunization against it. These findings should prompt further investigations into SARS pathogenesis.

Jaume (Ex. 2030), Abstract

01359 Sur-Reply, 13, 21-22; e.g., Fuller '127 Patent Decl. (Ex. 2199), ¶¶129, 592
01358 Sur-Reply, 13, 21-22; e.g., Fuller '600 Patent Decl. (Ex. 2199), ¶¶130, 589

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Different Vaccine Technologies Led to Different Disease Enhancement Results



Yang (Ex. 2011), Fig. 1A, 593; Jaume (Ex. 2030), Fig. 8A, 10590

01359 Sur-Reply, 22; 01358 Sur-Reply, 22

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Disease Enhancement Concerns with Spike Protein



Dr. Deborah H. Fuller

Moderna's Expert

Q. Can you explain to me why Vennema's discussion of a viral vector vaccine was relevant to the choice of antigen to be encoded in an mRNA vaccine formulated in a lipid nanoparticle?

A. **So it's one example. It is one vaccine platform that focused on the S protein and observed evidence of enhanced disease when the full-length S protein is used.**

There were other vaccine modalities, such as an inactivated vaccine, that the same sort of thing was observed.

So this – when you have multiple different vaccine modalities exhibiting a similar sort of effect with a single type of immunogen, then it raises the question in an investigator POSA's mind as to whether S protein may be a specific immunogen that could enhance disease when used in the context of a vaccine, any vaccine.

Fuller Dep. (Ex. 1104), 248:5-22; *see also id.*, 249:1-10

01359 Sur-Reply, 21-22; 01358 Sur-Reply, 21-22

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Petitioners' Experts Testified Disease Enhancement Was a Concern



Dr. L. Ross Pierce

Petitioners' Expert

Q. … Prior to your involvement in these proceedings, did you have any personal knowledge of the issue of disease enhancement as it specifically related to SARS-CoV-2?

A. **Prior to my involvement in these proceedings, yes.**

Q. Okay. And what was your understanding of that?

A. **Prior to my understanding of – prior to my involvement in these proceedings, my understanding of disease – possible disease enhancement in the context of vaccines for SARS-CoV-2 was that the possibility of disease enhancement would be something that FDA was interested in having evaluated. …**

Pierce Dep. (Ex. 2256), 55:9-56:3



Dr. Daniel O. Griffin

Petitioners' Expert

Q. And you agree that a POSA would have considered disease enhancement in connection with developing a vaccine for coronavirus as of the priority date, correct?

A. **I would say in considering any prior infection or vaccine development, one would always be aware of the possibility of disease enhancement.**

Griffin Dep. (Ex. 2114), 129:13-20

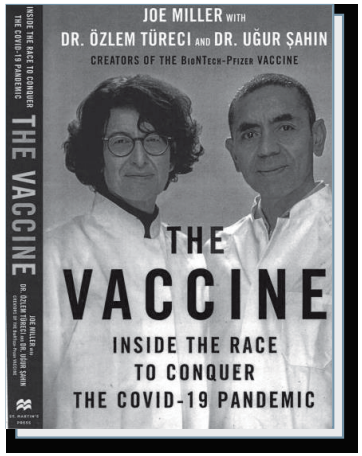
01359 POR, 49; 01359 Sur-Reply, 23
01358 POR, 49; 01358 Sur-Reply, 23

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Disease Enhancement Concerns with Spike Protein

Petitioners' Own Leaders Acknowledged Concern



For Uğur and Özlem, the answer was a resounding *yes*. First, data had been trickling in from BioNTech's studies, and those carried out by other vaccine developers, showing that vaccines encoding for the full spike, like B2.9, were not causing antibody-dependent enhancement—ADE—the potentially dangerous phenomenon that had kept the couple up at night when they first embarked on Project Lightspeed. One of the reasons they had included B.1, which targeted the smaller receptor-binding domain, in the Phase 1 finalists was to mitigate the chances of this dreaded effect, which had plagued early efforts to create vaccines against SARS and MERS, and which, as we learned in chapter 3, had harmed American children injected with an RSV inoculation in the 1960s. Now that it was

Şahin Book (Ex. 2107), 198

01359 POR, 47-48; 01359 Sur-Reply, 21-23; *e.g.*, Fuller '127 Patent Dec. (Ex. 2199), ¶¶605-606
01358 POR, 46-48; 01358 Sur-Reply, 21-23; *e.g.*, Fuller '600 Patent Dec. (Ex. 2199), ¶¶602-603

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Neutralizing Antibodies Alone Do Not Rule Out Disease Enhancement



Dr. Daniel O. Griffin

Petitioners' Expert

Q. … So the presence of neutralizing antibodies in and of itself is not enough to rule out the possibility of enhanced disease?

A. **The concerns about antibody-dependent enhancement are very much tied to levels of neutralizing antibodies, but levels of neutralizing antibodies alone don't fully address vaccine-associated or vaccine-associated disease enhancement.**

Griffin Reply Dep. (Ex. 2253), 77:16-78:4

01359 Sur-Reply, 22; 01358 Sur-Reply, 21-22

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Neutralizing Antibodies Alone Do Not Rule Out Disease Enhancement



Dr. Deborah H. Fuller

Moderna's Expert

"So – and the question is would we want – the purpose here was to induce the highest neutralizing antibody possible.

And so the bigger question is would we want to see higher neutralizing antibody.

And my answer to that is that maybe not necessarily. And one of the reasons is because in 2015 there was already evidence that the full-length S protein could be associated with enhancement of infection.

I'm familiar with a paper that explored the development of the delta transmembrane spike protein as a strategy to avoid enhancement of infection.

So getting more antibody is not necessarily always better. You had to take into context whether the higher antibody response now increases the risk for that vaccine to enhance disease."

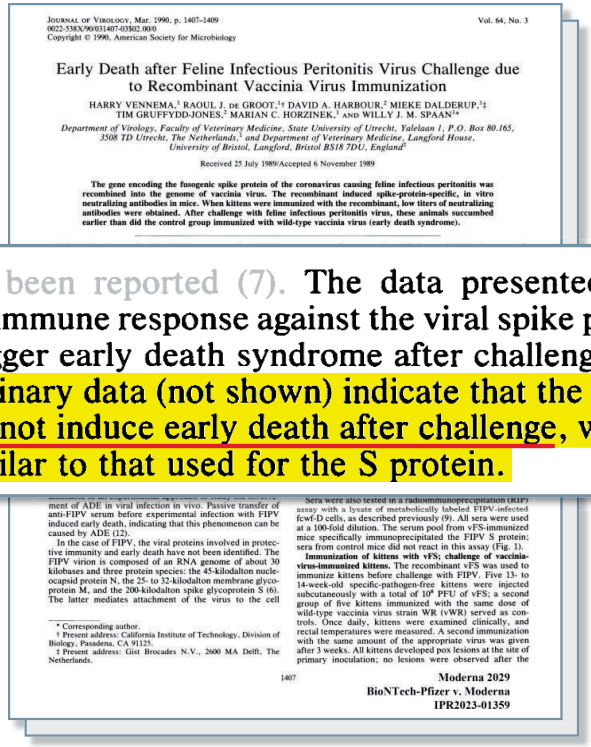
Fuller Dep. (Ex. 1104), 151:20-152:22; *see also id.*, 258:1-262:8

01359 Sur-Reply, 22; 01358 Sur-Reply, 22

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POSAs in 2015 Were Considering Other Betacoronavirus Immunogens



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0022-538X/90/031407-03$02.00/0
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Early Death after Feline Infectious Peritonitis Virus Challenge due to Recombinant Vaccinia Virus Immunization

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Received 25 July 1989/Accepted 6 November 1989

The gene encoding the fusogenic spike protein of the coronavirus causing feline infectious peritonitis was recombined into the genome of vaccinia virus. The recombinant induced spike-protein-specific, in vitro neutralizing antibodies in mice. When kittens were immunized with the recombinant, low titers of neutralizing antibodies were obtained. After challenge with feline infectious peritonitis virus, these animals succumbed earlier than did the control group immunized with wild-type vaccinia virus (early death syndrome).

has recently been reported (7). **The data presented here show that an immune response against the viral spike protein alone can trigger early death syndrome after challenge with FIPV. Preliminary data (not shown) indicate that the M and N protein do not induce early death after challenge, with an approach similar to that used for the S protein.**

ment of ADE in viral infection in vivo. Passive transfer of anti-FIPV serum before experimental infection with FIPV induced early death, indicating that this phenomenon can be caused by ADE (12).

In the case of FIPV, the viral proteins involved in protective immunity and early death have not been identified. The FIPV virion is composed of an RNA genome of about 30 kilobases and three protein species: the 45-kilodalton nucleocapsid protein N, the 25- to 32-kilodalton membrane glycoprotein M, and the 200-kilodalton spike glycoprotein S (6). The latter mediates attachment of the virus to the cell

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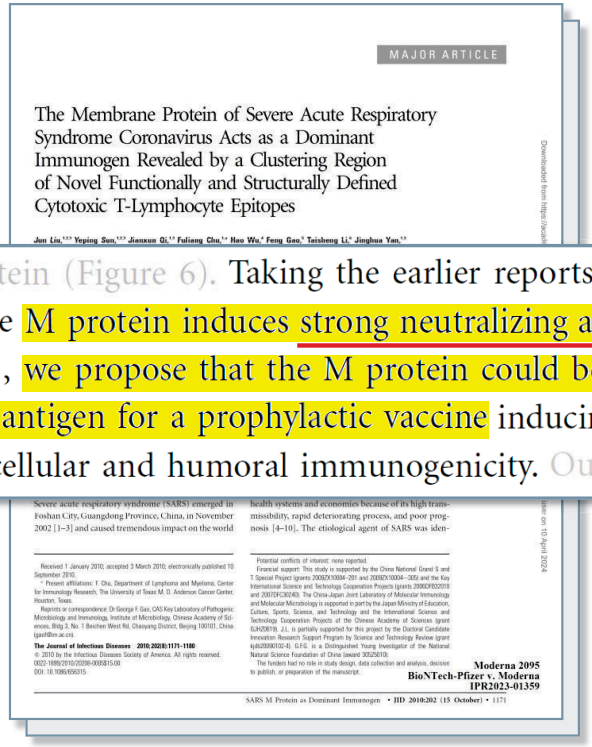
Sera were also tested in a radioimmunoprecipitation (RIP) assay with a lysate of metabolically labeled FIPV-infected fcwf-D cells, as described previously (9). All sera were used at a 100-fold dilution. The serum pool from vFS-immunized mice specifically immunoprecipitated the FIPV S protein; sera from control mice did not react in this assay (Fig. 1).

Immunization of kittens with vFS; challenge of vaccinia-virus-immunized kittens. The recombinant vFS was used to immunize kittens before challenge with FIPV. Five 13- to 14-week-old specific-pathogen-free kittens were injected subcutaneously with a total of 10^8 PFU of vFS; a second group of five kittens immunized with the same dose of wild-type vaccinia virus strain WR (vWR) served as controls. Once daily, kittens were examined clinically, and rectal temperatures were measured. A second immunization with the same amount of the appropriate virus was given after 3 weeks. All kittens developed pox lesions at the site of primary inoculation; no lesions were observed after the

1407

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BioNTech-Pfizer v. Moderna
IPR2023-01359

Vennema (Ex. 2029),1409



MAJOR ARTICLE

The Membrane Protein of Severe Acute Respiratory Syndrome Coronavirus Acts as a Dominant Immunogen Revealed by a Clustering Region of Novel Functionally and Structurally Defined Cytotoxic T-Lymphocyte Epitopes

Jun Liu,[1,2,3] Yeping Sun,[1,2,3] Jianxun Qi,[1,2] Fuliang Chu,[1,2] Hao Wu,[4] Feng Gao,[5] Taisheng Li,[4] Jinghua Yan,[1,2]

M protein (Figure 6). Taking the earlier reports into account that the M protein induces strong neutralizing antibodies [18, 30, 48], we propose that the M protein could be a good candidate antigen for a prophylactic vaccine inducing both dominant cellular and humoral immunogenicity. Our current and

Severe acute respiratory syndrome (SARS) emerged in Foshan City, Guangdong Province, China, in November 2002 [1–3] and caused tremendous impact on the world health systems and economies because of its high transmissibility, rapid deteriorating process, and poor prognosis [4–10]. The etiological agent of SARS was iden-

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Potential conflicts of interest: none reported.

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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DOI: 10.1086/656315

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Liu (Ex. 2095),1179

01359 POR, 45-46; 01359 Sur-Reply, 23; *e.g.*, Fuller '127 Patent Decl. (Ex. 2199), ¶¶610-623
01358 POR, 45-46; 01358 Sur-Reply, 23; *e.g.*, Fuller '600 Patent Decl. (Ex. 2199), ¶¶607-620

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Goals of Therapeutics and Vaccines Are Different

Minimize Immunogenicity for Therapeutics; Promote Immunogenicity for Vaccines



Dr. Deborah H. Fuller

Moderna's Expert

Q. So if there was such data with an mRNA LNP system involving expression of a reporter protein, with that data, the data that counsel did not show you, would that data be relevant to draw conclusions about the applicability of that mRNA LNP system to a betacoronavirus vaccine?

A. In my opinion, it would not be because the objective of a reporter such as SEAP and the like is really along the lines of a therapeutic.

And again, as I had mentioned in my discussion earlier is that systems that are designed to optimize for a therapeutic — in other words, a replacement of a protein or a production of max amount of protein — are designed to primarily maximize the amount of protein while minimizing immunogenicity.

And so the combination of different things you would put together to try to optimize a therapeutic is going to involve dampening immunogenicity.

* * *

So if you're a POSA looking to develop a vaccine, you're going to look for platforms that are going to be driving immuno — not just increased protein expression but protein expression of the antigen and immunogenicity. …

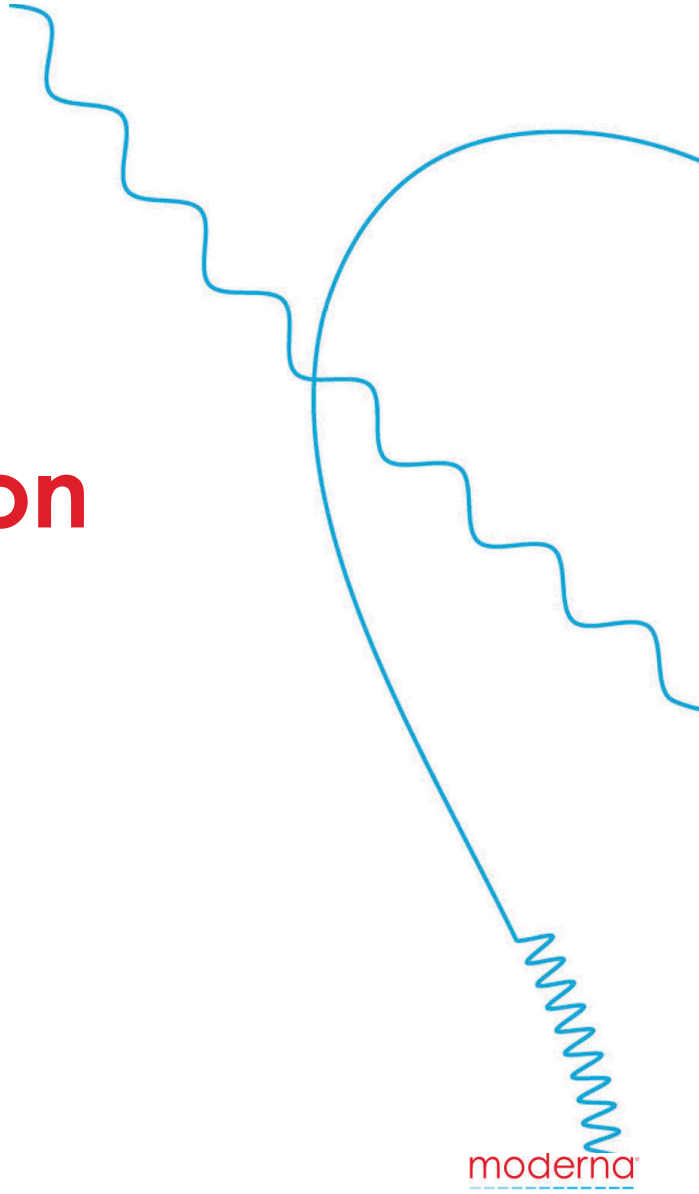
Fuller Dep. (Ex. 1104), 264:13-266:1 (objection omitted)

01359 Sur-Reply, 25; 01358 Sur-Reply, 25

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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No Reasonable Expectation of Success



DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Combinations Depend on Prior Art with Different Vaccine Technologies and/or Delivery Methods

Reference	Vaccine Technology	Delivery Method
Geall	saRNA	Liposomes, CNE, Polymeric Nanoparticles, Virions, Naked
Yang	DNA	Naked
Altmeyer	Protein & Non-mRNA Nucleic Acid	Naked, Alum

Geall (Ex. 1010), 12:6-27, 29:29-38:6, 40:14-16; Yang (Ex. 1011), 561-562, 564; Altmeyer (Ex. 1012), ¶¶9-36, 114-131; Chan '127 Patent Decl. (Ex. 2198), ¶¶146-153, 208, 211; Fuller '127 Patent Decl. (Ex. 2199), ¶¶197-223; *see also* Chan '600 Patent Decl. (Ex. 2198), ¶¶146-153, 208, 211; Fuller '600 Patent Decl. (Ex. 2199), ¶¶198-223

01359 POR, 9-11, 30-33, 54-55, 59; 01359 Sur-Reply, 10
01358 POR, 9-11, 29-33, 53-54, 58; 01358 Sur-Reply, 10

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Vaccine Technology Is Not Interchangeable



Dr. Deborah H. Fuller

Moderna's Expert

552. In 2015, the nucleic acid vaccine field was highly unpredictable. Research showed that there is a relationship between the chosen vaccine technology and chosen protein choice. In other words, vaccine technology (e.g., DNA, viral vectors, saRNA, mRNA) or the protein choice (e.g., full-length spike protein, full-length influenza HA protein, truncated spike protein, etc.) were not interchangeable. It was not possible to assume that a POSA would obtain the same (or similar) results with different vaccine technologies (e.g., saRNA versus mRNA) and/or with different protein choices (e.g., full-length spike protein versus truncated spike protein). Instead, at that time, there was evidence of lack of interchangeability: (1) choosing the same protein (e.g., full-length RSV F) but different vaccine technology (e.g., mRNA, DNA, saRNA) resulted in different outcomes; and (2) using the same vaccine technology (e.g., DNA) but a different protein choice (e.g., HIV gp160, HIV gp120) also resulted in different outcomes.

Fuller '127 Patent Decl. (Ex. 2199), ¶552;
see also Fuller '600 Patent Decl. (Ex. 2199), ¶549

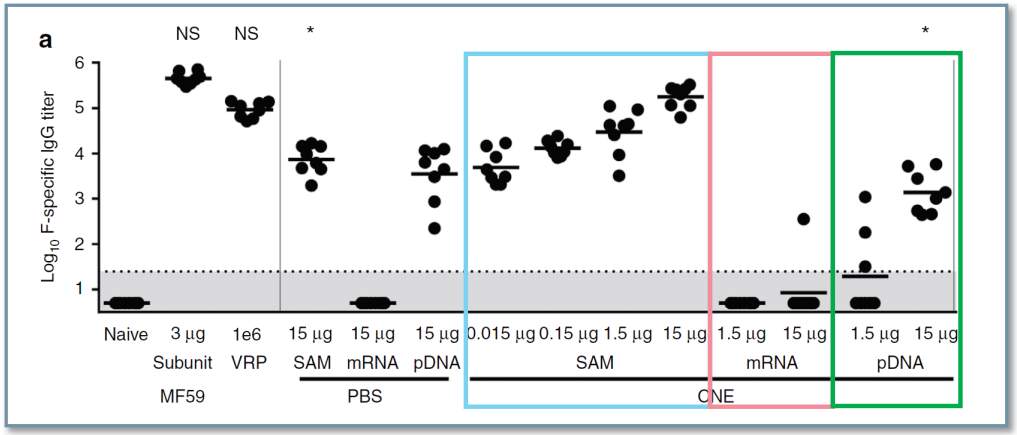
01359 POR, 30-33; 01359 Sur-Reply, 12-13
01358 POR, 30-33; 01358 Sur-Reply, 12-13

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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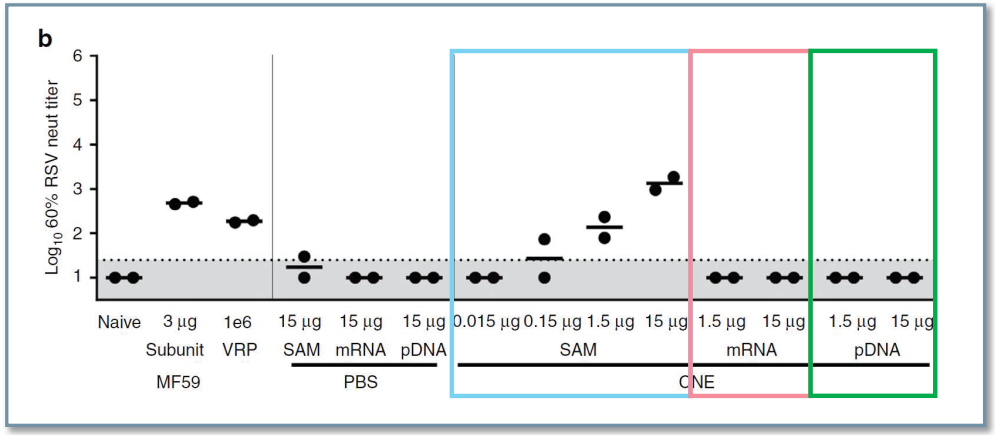
Vaccine Technology Is Not Interchangeable: Brito's 2005 Study

Antibody Titers



Brito (Ex. 2005), Fig. 2a

Neutralizing Antibody Titers



Brito (Ex. 2005), Fig. 2b

01359 POR, 31; 01359 Sur-Reply, 12-15; *e.g.*, Fuller '127 Patent Decl. (Ex. 2199), ¶¶553-561
01358 POR, 30-31; 01358 Sur-Reply, 12-15; *e.g.*, Fuller '600 Patent Decl. (Ex. 2199), ¶¶550-558

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Vaccine Technology Is Not Interchangeable: Brito's 2005 Study



Dr. Deborah H. Fuller

Moderna's Expert

557. I understand that the Board in its Institution Decision stated with respect to Exhibit 2005: "Although it supports that saRNA can be used at much lower doses than mRNA, on the present record, we do not understand it to teach that immunogens targeted by saRNA are inapplicable to mRNA …." Paper No. 20 (Institution Decision), 61 (citing to Ex. 2026 which references Ex. 2005). I disagree. As can be seen in Figure 21 and Figure 22 of my Declaration, mRNA administered at a **1000-fold higher** dose compared to saRNA (15 µg vs 0.015 µg, respectively), still failed to produce any detectable F-specific or neutralizing antibodies. Although, as noted by the Board, Brito speculates that "'mRNA was unable to induce responses … perhaps due to the low dose being tested here,'" there is no evidence in Brito that mRNA and saRNA (or DNA) are interchangeable. *See* Paper No. 20 (Institution Decision), 66 (citing to Ex. 2005 at 2124.)

Brito's pure speculation, without any data, is insufficient to provide a reasonable expectation of success with a higher dose of mRNA. 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. Therefore, the difference in dose does not resolve the lack of interchangeability between mRNA and saRNA.

Fuller '127 Patent Decl. (Ex. 2199), ¶557;
see also Fuller '600 Patent Decl. (Ex. 2199), ¶554

01359 POR, 31, 35-36; 01359 Sur-Reply, 12-15 & n.12
01358 POR, 30-31, 35-36; 01358 Sur-Reply, 12-15 & n.12

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Vaccine Technology Is Not Interchangeable



Dr. Deborah H. Fuller

Moderna's Expert

837. The state of the field described above is consistent with my own experience. I first experimented with mRNA vaccines in the late 1990s, but when using mRNA vaccine technology, I did not obtain sufficient immunogenicity. Therefore, as of approximately 2000, I shelved working with mRNA vaccines and instead focused on DNA vaccines where the immunogenicity results were stronger.

Fuller '127 Patent Decl. (Ex. 2199), ¶837;
see also Fuller '600 Patent Decl. (Ex. 2199), ¶843

01359 POR, 54; 01359 Sur-Reply, 15
01358 POR, 53; 01358 Sur-Reply, 14-15

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Yang Used Naked (PBS) Delivery

Combinations Rely on Different Delivery Systems

Vaccination

Female BALB/c mice (6–8 weeks old; Charles River Labs) were immunized with 25 μg of plasmid DNA in 200 μl of PBS (pH 7.4) at weeks 0, 3 and 6.

Yang (Ex. 1011), 564

01359 POR, 10-11; 01359 Sur-Reply, 10; Fuller '127 Patent Decl. (Ex. 2199), ¶211; Chan '127 Patent Decl. (Ex. 2198), ¶208
01358 POR, 11; 01358 Sur-Reply, 9-10; Fuller '600 Patent Decl. (Ex. 2199), ¶212; Chan '600 Patent Decl. (Ex. 2198), ¶208

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Altmeyer Used Aluminum Adjuvant and Naked (PBS) Delivery

Combinations Rely on Different Delivery Systems

EXAMPLE 8

[0128] An enhanced serum IgG response was obtained in animals immunized with TriSpike in Alum adjuvant. Previous studies on the mucosal and systemic response to recombinant HagB from *Porphyromonas gingivalis* indicated that a higher serum IgG and mucosal IgA response from HagB + alum was induced compared to HagB without adjuvant immunization in Balb/c mice (Vaccine, 2003, 21, 4459-4471). TriSpike candidate vaccine was analyzed to determine whether it could induce not only serum IgG, but also mucosal IgA with neutralizing ability for SARS CoV. TriSpike preparation in PBS was compared with TriSpike preparation in Alum adjuvant for their capacity to induce SARS CoV specific serum IgG. Two groups of mice were immunized by the intraperitoneal route: group A represents mice which received 3 doses of 20 μg of TriSpike protein alone and group B represents mice which received 3 doses of 20 μg of TriSpike pre-mixed with 1mg of Alum adjuvant. Western blot analysis indicated a stronger antibody response from mice immunized with TriSpike + alum as compared with mice immunized with TriSpike alone (Figure 17). The TriSpike + Alum group also showed a higher neutralization titer (Figure 17). TriSpike + Alum adjuvant induced a strong neutralizing and long lasting serum IgG response.

Altmeyer (Ex. 1012), ¶128; *see also, id.*, ¶¶56-58, 114-116, 129, 131

01359 POR, 11; 01359 Sur-Reply, 10; Fuller '127 Patent Decl. (Ex. 2199), ¶222; Chan '127 Patent Decl. (Ex. 2198), ¶211
01358 POR, 11; 01358 Sur-Reply 9-10; Fuller '600 Patent Decl. (Ex. 2199), ¶222; Chan '600 Patent Decl. (Ex. 2198), ¶211

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Delivery Systems Are Not Interchangeable



Dr. Warren Chan

Moderna's Expert

C. The Carrier for One Nucleic Vaccine Does Not Necessarily Work for Another

* * *

191. Geall PNAS 2012 shows that the same carrier, stable nucleic acid lipid particles (SNALPs), enhanced the immunogenicity of an saRNA vaccine but not a pDNA vaccine, which achieved higher immunogenicity when it was administered via electroporation.

Chan '127 Patent Decl. (Ex. 2198), ¶191;
see also Chan '600 Patent Decl. (Ex. 2198), ¶191

01359 POR, 36-37; 01358 POR, 36

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Delivery Systems Are Not Interchangeable



Dr. Deborah H. Fuller

Moderna's Expert

Q. … That same delivery system research that you mentioned as being reliable in informing your decision to move forward with such a carrier for a different immunogen, that would apply equally whether it was an mRNA that was being delivered or some other type of nucleic acid. Is that fair?

A. **No, I don't think that's fair.**

We would have to test that delivery formulation with that particular nucleic acid platform.

Fuller Dep. (Ex. 1104), 48:17-49:7

01359 Sur-Reply, 13; 01358 Sur-Reply, 13

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Dr. Griffin Cited No Document to Support Extrapolating Results from One Vaccine Technology to Another



Dr. Daniel O. Griffin

Petitioners' Expert

Cited Documents:



Q. So what is your best evidence in terms of documentation, paper, publication, fill in the blank that a person of … skill in the art as of the priority date could extrapolate results from an saRNA vaccine to make predictions or have a reasonable expectation as to the function of an mRNA vaccine? What's your best evidence?

A. **So my response is that this is a basic science concept for vaccine technology to provoke an immune response to educate the adaptive immune system in an effort to establish memory. ...**

Griffin Dep. (Ex. 2114), 225:14-226:12 (objection omitted)

01359 POR, 36; 01358 POR, 36

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Dr. Fuller: Only Expert with Experience with Head-to-Head Modality Experiments



Dr. Deborah H. Fuller

Moderna's Expert

Q. So you have direct firsthand experience testing whether one nucleic acid system is interchangeable or predictive of another. Right?

A. **That's right.**

* * *

Q. [I]f you took an saRNA vaccine with a particular protein choice and took that same protein choice and made an mRNA vaccine, would you expect the same results?

A. **No.**

* * *

Q. Is the same true between DNA and mRNA? Are those two nucleic acid modalities interchangeable?

A. **They are not. They are not interchangeable.**

Fuller Dep. (Ex. 1104), 266:16-19, 272:11-275:17, 273:16-22 (objections omitted); *see also id.*, 266:2-275:17

01359 Sur-Reply, 3, 13, 16; 01358 Sur-Reply, 3, 13, 16

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

No Expectation of Success Based on Non-mRNA-LNP Platforms

***Eli Lilly & Co. v. Teva Pharmaceuticals Int'l, GmbH*, IPR2018-01710, Paper 69 (P.T.A.B. Mar. 31, 2020)**

> Petitioner is arguing that a person of ordinary skill would have taken the leap from a small molecule antagonist such as BIBN to a large molecule anti-CGRP antagonist antibody.

Paper 69 at 140

> Similar to *West-Ward* where clinical results had been obtained with temsirolimus but not with everolimus, **clinical results had been obtained with BIBN (e.g., Olesen, Ex. 1025) but not with anti-CGRP antagonist antibodies**.
>
> * * *
>
> In any event, we agree with Patent Owner that West-Ward illustrates how **a jump from one molecule to another may result in a lack of a reasonable expectation of success in an area with uncertainty**, and agree with Patent Owner that this case bears similarities to *West-Ward*.

Paper 69 at 143

01359 Sur-Reply, 14; 01358 Sur-Reply, 14

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Uncertainty Equates with Non-Obviousness

***Eli Lilly & Co. v. Teva Pharmaceuticals Int'l, GmbH*, 8 F.4th 1331 (Fed. Cir. 2021)**

But, in considering what constitutes a reasonable expectation of success, we must also consider that **the law places the burden of proof on the petitioner** to prove a proposition of unpatentability by a preponderance of the evidence. 35 U.S.C. § 316(e).

8 F.4th at 1348

"**[U]npredictability of results equates more with nonobviousness** rather than obviousness."

8 F.4th at 1349 (quoting Honeywell Int'l Inc. v. Mexichem Amanco Holding S.A. DE C.V., 865 F.3d 1348, 1356 (Fed. Cir. 2017))

01359 Sur-Reply, 14, 19, 22 n.19; 01358 Sur-Reply, 14, 19, 22 n.19

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Protein Choice Can Result in Different Outcomes



Dr. Deborah H. Fuller

Moderna's Expert

566. Research as of October 2015 showed that using the same vaccine technology (e.g., DNA) but different protein choice also resulted in different outcomes. Scientists developing a nucleic acid vaccine can choose a target antigen from among different proteins of a virus or even different pieces of a given protein. For example, for a given protein, a scientist could design a vaccine using the full-length protein, a truncated version of that protein, a subunit of that protein, or other options. A scientist can also choose different proteins to target, for example, a spike protein (S protein), a nucleocapsid protein (N protein), or other proteins of a betacoronavirus, or other proteins from other viruses. Making the same protein choice within a virus genus would have been expected to yield similar results. For example, choosing the full-length S protein of MERS-CoV or choosing the full-length S protein of SARS-CoV would have been expected to yield similar results. Amino acid substitutions that do not affect the protein choice would also have been expected to yield similar results. For example, a stabilized full-length spike protein that has two proline substitutions would have been expected to yield similar results to a wild-type full-length spike protein. On the other hand, those of ordinary skill in the art would not have expected different protein choices, even of the same virus, to yield similar) results. For example, a full-length spike protein and a truncated spike protein would not have been expected to yield similar results.

Fuller '127 Patent Decl. (Ex. 2199), ¶566;
see also Fuller '600 Patent Decl. (Ex. 2199), ¶563

01359 POR, 32-33; 01359 Sur-Reply, 17
01358 POR, 32; 01358 Sur-Reply, 17

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Protein Choice Can Result in Different Outcomes

Different Immune Responses & Different Disease Enhancement Results



Dr. Deborah H. Fuller

Moderna's Expert

> 570. These studies demonstrate that vaccines using the identical technology, e.g., DNA, but using different protein choices—even different pieces of the same protein (e.g., different pieces of the same HIV protein)—result in different immune responses.

Fuller '127 Patent Decl. (Ex. 2199), ¶570; *see also* Fuller '600 Patent Decl. (Ex. 2199), ¶567

> 573. Likewise, in the specific context of betacoronaviruses, protein choice was not trivial. In an article published in 2005, Yang and colleagues (from the same group of researchers as Yang (Ex. 1011) on which Dr. Griffin and the Petition rely) found that a DNA vaccine encoding a full-length S protein enhanced disease, whereas a DNA vaccine encoding a truncated S protein (truncated at amino acid 1,153) was successful at avoiding disease enhancement. *See* Ex. 2137, 797-800; *id.* at 800 ("**One of these mutants, truncated at amino acid 1153**, induced neutralizing Abs to human isolates that **failed to cause Ab enhancement of entry** (Fig. 4*a*).)").

Fuller '127 Patent Decl. (Ex. 2199), ¶573; *see also* Fuller '600 Patent Decl. (Ex. 2199), ¶570

01359 POR, 32-33; 01359 Sur-Reply, 17
01358 POR, 32; 01358 Sur-Reply, 17

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Betacoronavirus Spike Protein Is Large and Difficult to Express



Dr. Deborah H. Fuller

Moderna's Expert

> 252. Even if mRNA was synthesized to include the sequence for a betacoronavirus full-length spike protein (which neither Schrum nor Geall shows), that does not mean that a full-length spike protein would "form." For example, it was known that large proteins are difficult to express due to protein synthesis errors and that mRNA encoding other proteins (e.g., RSV F) failed to elicit immune responses. *See* Ex. 2111, 716-717; Ex. 2005, 2119-2121; *see also* my discussion in Section XI.A.2.d.i and Section XI.A.2.e.

Fuller '127 Patent Decl. (Ex. 2199), ¶252; *see also* Fuller '600 Patent Decl. (Ex. 2199), ¶252

> 680. Moreover, the RSV F protein antigen tested in Geall is significantly smaller than a full-length betacoronavirus S protein—it is about half the size of a full-length betacoronavirus S protein. A betacoronavirus S protein is a large trimeric

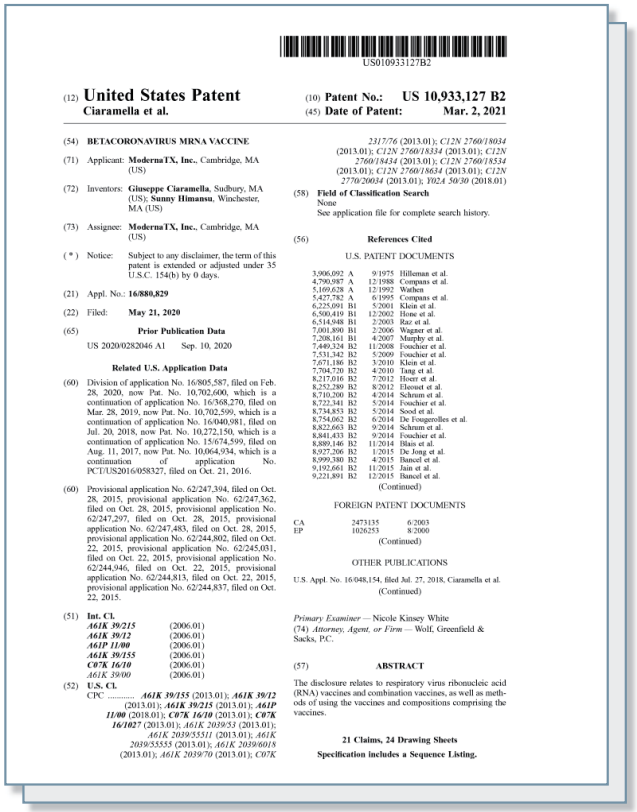
Fuller '127 Patent Decl. (Ex. 2199), ¶680; *see also* Fuller '600 Patent Decl. (Ex. 2199), ¶677

01359 POR, 46; 01359 Sur-Reply, 18
01358 POR, 45-46; 01358 Sur-Reply, 18

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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'127 Patent Claims



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. 62/245,051, 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 2039/5531* (2013.01); *A61K 2039/5555* (2013.01); *A61K 2039/6018* (2013.01); *A61K 2039/70* (2013.01); *C07K 231/76* (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.

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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.

'127 Patent (Ex. 1001), Cl. 1

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

'127 Patent (Ex. 1001), Cl. 3

01359 POR, 15, 18, 26-28, 53-54, 57-58;
01359 Sur-Reply, 6-8, 11, 19-20

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Effective Amount Requires Testing and Depends on Delivery Method, Immunogen



Dr. Daniel O. Griffin

Petitioners' Expert

Q. … Is it your opinion that for any antigen for which an mRNA vaccine is encoded for, that the same dose would be required, or are different doses found to be effective for different antigens?

A. **So the amount of mRNA required for an mRNA vaccine to produce a specific level of protein would depend upon the formulation, the encapsulation of the mRNA, as well as the specific protein being produced.**

Q. How does a person of skill in the art determine the amount of mRNA that would be required to generate a protective immune response if that specific protein had never before been tested in that mRNA construct?

A. **So there would be several steps to answering the exact dose question. The first would start with in vitro assays where the mRNA was put in cells, and then ultimately one would have to administer different doses in the target organism to get the exact dose that correlates with an exact level of protein production.**

Griffin Reply Dep. (Ex. 2253), 62:14-63:13

Q. And so the effective amount of mRNA that would be required to generate a protective immune response to a betacoronavirus, that was not something that had been tested and determined as of 2015; right?

A. **So in 2015 a POSA would not have known the exact mRNA content required to produce a specific SARS coronavirus immune response.**

Griffin Reply Dep. (Ex. 2253), 143:20-144:5

01359 Sur-Reply, 19-20

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Effective Amount Requires Testing



Dr. Deborah H. Fuller

Moderna's Expert

Q. While we're on the topic of self-amplifying RNA or self-replicating RNA, saRNA would be administered at a different dose than nonself-replicating RNA. Is that fair?

A. It depends.

Q. Is it fair to say that it's typically administered at a different dose?

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. That can be the platform that you use. Some work in lower doses. Some work in higher doses. So multiple variables can influence the dose that you use.

So when you have a given vaccine, you have to do the dose escalation curve to actually determine what dosing range or what dose is going to give you sufficient immune response to provide protection.

You've got that additional variable. What do you actually need in terms of immune response to get to a level of protection?

So when we want to know whether if it's DNA or RNA, self-amplifying RNA or mRNA, what dose is going to be optimal, it has to be tested, and we can't just conclusively say that the dose of one modality is going to automatically always be higher or lower than the other.

Fuller Dep. (Ex. 1104), 119:15-120:22; *see also id.*, 121:1-7

01359 Sur-Reply, 7-8

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Uncertainty in Field and Known Failures Insufficient for Reasonable Expectation of Success

***OSI Pharmaceuticals, LLC v. Apotex Inc.*, 939 F.3d 1375 (Fed. Cir. 2019)**

These references provide no more than hope—and **hope** that a potentially promising drug will treat a particular cancer **is not enough to create a reasonable expectation of success in a highly unpredictable art** such as this. Indeed, **given a 99.5% failure rate and no efficacy data or any other reliable indicator of success, the only reasonable expectation at the time of the invention was failure, not success**. It is only with the benefit of hindsight that a person of skill in the art would have had a reasonable expectation of success in view of the asserted references.

939 F.3d at 1385

01359 POR, 26, 29, 33, 44, 55; 01359 Sur-Reply, 9-10, 12, 18-19, 21
01358 POR, 26, 29, 32, 44, 54; 01358 Sur-Reply, 9, 11, 18-20

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Known Failures Undermine Reasonable Expectation of Success

***University of Strathclyde v. Clear-Vu Lighting LLC*, 17 F.4th 155 (Fed. Cir. 2021)**

Thus, not only is there a complete lack of evidence in the record that any bacteria were inactivated after exposure to 407–420 nm blue light without using a photosensitizer, **there is also evidence showing that others had failed to inactivate MRSA**—one of the claimed Gram-positive bacteria—without using a photosensitizer, despite experimenting with different light doses and different wavelength ranges of blue light. **We have found that such failures undermine a finding of a reasonable expectation of success.**

* * *

Such is the case here. In view of Dr. Nitzan's reported failures for MRSA and lack of any "reliable indicator of success," we fail to see how Ashkenazi's prophetic statement about what "may" happen when "other bacterial cells" are exposed to blue light would lead a skilled artisan to reasonably expect that MRSA could be inactivated when exposed to 407–420 nm blue light without using a photosensitizer.

17 F.4th at 164-165

01359 POR, 40; 01359 Sur-Reply, 20
01358 POR, 40; 01358 Sur-Reply, 20
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

moderna

Yamanouchi: Expectation of Desirable Properties

Yamanouchi Pharmaceutical Co., Ltd. v. Danbury Pharmacal, Inc.,
231 F.3d 1339 (Fed. Cir. 2000)

This level of motivation **does not show a "reasonable expectation of success."** *In re Longi*, 759 F.2d at 897. The success of discovering famotidine was not discovering one of the tens of thousands of compounds that exhibit baseline H_2 antagonist activity. Rather, the success was **finding a compound that had high activity, few side effects, and lacked toxicity**. As Danbury's expert testified, the ordinary medicinal chemist would **not have expected famotidine to have the "most desirable combination of pharmacological properties" that it possesses**. J.A. at 1052.

231 F.3d at 1345

01359 POR, 26, 30, 33; 01359 Sur-Reply, 11-12
01358 POR, 26, 29-30, 32-33; 01358 Sur-Reply, 11
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Petitioners' Reliance on Post-Priority Documents Reflecting Moderna's Own Work Is Misplaced



DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Petitioners' Reliance on Post-Priority Documents Reflecting Moderna's Own Work Is Misplaced

ModernaTX, Inc. has developed a rapid response, proprietary messenger RNA (mRNA)-based vaccine platform. This is based on the principle and observations that antigens can be produced

* * *

the genome, is nonreplicating, and expression is transient. mRNA vaccines thereby offer a mechanism to stimulate endogenous production of structurally intact protein antigens in a way that mimics wild-type viral infection and are able to induce good immune responses against infectious pathogens such as cytomegalovirus (CMV) (NCT03382405), human metapneumovirus (hMPV) and parainfluenza virus type 3 (PIV3) (NCT03392389) and influenza virus (NCT03076385 and NCT03345043). ModernaTX, Inc. is using its mRNA-based technology to develop a novel LNP-encapsulated messenger RNA (mRNA)-based vaccine against SARS-CoV-2. mRNA-1273 is a novel LNP mRNA-based vaccine that encodes for the full-length spike (S) protein of SARS-CoV-2, modified to introduce two proline residues to stabilize the S protein into a pre-fusogenic form.

Moderna's May 2020 DMID Protocol for mRNA-1273 (Ex. 2055), 17
Moderna's May 2020 DMID Protocol for mRNA-1273 (Ex. 2151), 17

The expression of functional prefusion stabilized S-protein delivered by mRNA was evaluated in HEK293 cells (Figure 1).

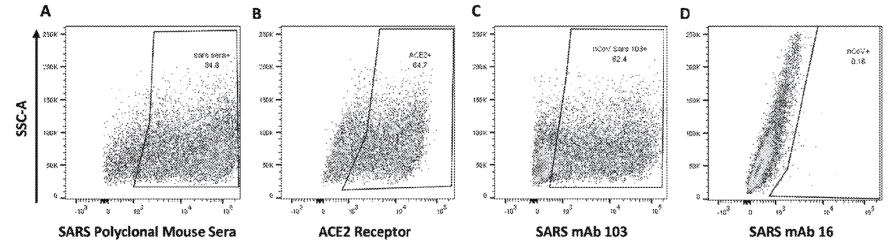


Figure 1. The SARS-CoV-2 full-length stabilized spike protein (S-2P) delivered by mRNA is expressed on the cell surface. HEK293T cells were transfected with mRNA encoding for the SARS-CoV-2 S-2P protein. After 24hrs, cell flow cytometry was used to measure surface expression by staining with (A) mouse polyclonal antibody raised against SARS S-2P protein; (B) a flag-tagged ace2 receptor and anti-flag antibody; (C) a SARS S-protein monoclonal antibody (mAb-103) that cross-reacts with SARS-CoV-2 S-2P; (D) a SARS S protein-specific monoclonal antibody (mAb 16) that does not bind SARS-CoV-2 was used as a negative control.

Moderna's May 2020 DMID Protocol for mRNA-1273 (Ex. 2055), 18
Moderna's May 2020 DMID Protocol for mRNA-1273 (Ex. 2151), 18

01359 POR, 48-50, 56; *e.g.*, Fuller '127 Patent Decl. (Ex. 2199), ¶¶637-656; Krause Decl. (Ex. 2200), ¶¶121-137
01358 POR, 48-49, 55; *e.g.*, Fuller '600 Patent Decl. (Ex. 2199), ¶¶634-653; Krause Decl. (Ex. 2200), ¶¶121-137

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Petitioners' Reliance on Post-Priority Documents Is Misplaced



Dr. Philip Krause

Moderna's Expert

106. In this context, Moderna's statements regarding the results shown by Petsch's protamine-complexed vaccine and Geall's and Hekele's replicon-based vaccine do not indicate or suggest that those results would indicate to a POSA in 2015 that they could reasonably expect an mRNA-LNP vaccine like Moderna's proposed Zika vaccine candidates to produce a protective immune response. Instead, these statements are one part of a broader submission focused on providing a rationale from which an investigator can understand that Moderna's proposed Zika vaccine candidates were worth at least testing, in phase 1, in humans. They provide background information to an investigator who may have no background in mRNA vaccines to illustrate the concept that exogenously delivered nucleic acids of different kinds—including mRNA complexed with protamine, RNA with self-replicating capabilities, or Moderna's own mRNA-LNP vaccines—can be administered and may lead to endogenous production of an antigen that may in turn stimulate antigen specific immunity, and that certain such vaccines had been administered and not found unsafe.

Krause Decl. (Ex. 2200), ¶106

01359 POR, 37-39, 44; 01359 Sur-Reply, 16-17
01358 POR, 36-38, 43; 01358 Sur-Reply, 16-17

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Petitioners Mischaracterize Dr. Fuller's Testimony



Dr. Deborah H. Fuller

Moderna's Expert

Q. I don't think so. I think you said that you had hypotheses that it was able to induce an immune response. I think that was your testimony.

I just want to understand what you meant when you said "hypotheses."

A. **Right. So it's just basic fundamental nucleic acid vaccine biology…**

Fuller Dep. (Ex. 1104), 51:7-52:9

01359 Sur-Reply, 15-16; 01358 Sur-Reply, 15-16

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

moderna

Petitioners Mischaracterize Dr. Fuller's Testimony



Dr. Deborah H. Fuller

Moderna's Expert

Q. I don't think so. I think you said that you had hypotheses that it was able to induce an immune response. I think that was your testimony.

I just want to understand what you meant when you said "hypotheses."

A. **Right. So it's just basic fundamental nucleic acid vaccine biology…that when you have a DNA or an RNA vaccine and you can validate that it expresses a protein in vitro, then the hypothesis is that if you inject that DNA or RNA vaccine into an animal, the muscle cell, or in the case of gene gun delivery, the skin cell will express that antigen. You can give that antigen to express in animal, and the hypothesis is that it will elicit an immune response.**

Fuller Dep. (Ex. 1104), 51:7-52:9

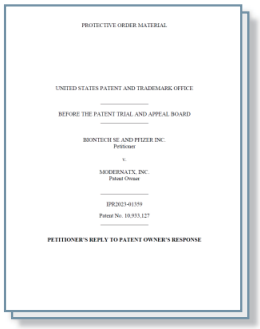
01359 Sur-Reply, 15-16; 01358 Sur-Reply, 15-16

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Petitioners Mischaracterize Dr. Fuller's Testimony

Dr. Fuller Testified That POSA Would Need Examples or Data to Know Whether Protein Would Express


PROTECTIVE ORDER MATERIAL

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BIONTECH SE AND PFIZER INC.
Petitioner
v.
MODERNATX, INC.
Patent Owner

IPR2021-01359
Patent No. 10,933,127

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE



Dr. Deborah H. Fuller

Moderna's Expert

vaccines as "effective" and "promising." In fact, Dr. Fuller testified that "[b]y 2013, it was pretty well known that you could do different nucleic acids [vaccines] and inject those into cells and those nucleic acids could express an immune response." (Ex. 1104, 212:18-213:4.) This confirms that nothing close to the skepticism or

01359 Petitioners' Reply, 18; *see also* 01358 Petitioners' Reply, 17

Q. You don't dispute that Schrum discloses an mRNA vaccine to elicit or provoke an immune response. Right?

A. By 2013, it was pretty well known that you could do different nucleic acids and inject those into cells and those nucleic acids could express something and maybe provoke an immune response.

So in generic language, I think to include if you're going to work on any sort of mRNA, to mention that, even though there's no specific examples or data to support that.

I see that as – as a POSA, I see that as a generic statement, not something that is actually being – that I would take actually seriously.

Q. **And why would you not take it seriously?**

A. **Because there's no data to back that up.**

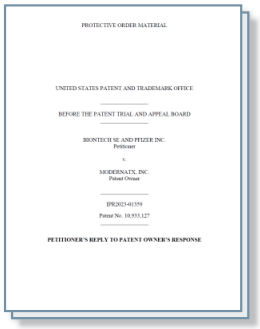
Fuller Dep. (Ex. 1104), 212:18-213:14 (objection omitted)

01359 Sur-Reply, 20-21; 01358 Sur-Reply, 20

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Petitioners Take Dr. Fuller's Testimony Out of Context


PROTECTIVE ORDER MATERIAL

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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v.
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IPR2021-01359
Patent No. 10,933,127

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE



Dr. Deborah H. Fuller

Moderna's Expert

Ex. 2114, 68:14-69:11.) Dr. Fuller agreed that, in October 2015, there was a "recognized need for a betacoronavirus vaccine." (Ex. 1104, 126:5-11; Ex. 2200, ¶170.)

01359 Petitioners' Reply, 13; *see also* 01358 Petitioners' Reply, 12

Q. Do you agree that as of 2015 there remained a latent need for a betacoronavirus vaccine to be ready in the event of a future pandemic, even though the SARS and MERS outbreaks had been controlled?

A. **There was still a recognized need for a coronavirus vaccine, although by 2015 a lot of that enthusiasm had declined simply because once – this is kind of the way the field is. You get sort of an outbreak and everybody beehives towards it and tries to solve the problem.**

And then it goes away, and people's attention turns to the next thing, such as a MERS outbreak, such as a Zika outbreak. …

Fuller Dep. (Ex. 1104), 126:5-127:10

01359 Sur-Reply, 24; 01358 Sur-Reply, 24

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Petitioners' Dropped Positions: Geall Teaches mRNA & LNPs

Petitioners' District Court Statements About Geall Patents

7. The Asserted Patents only describe liposomes and self-replicating RNA. They do not describe the lipid nanoparticles ("LNPs") or mRNA of Pfizer and BioNTech's COVID-19 vaccine.

Petitioners' District Court Answer (Ex. 1312), 80 (¶7)

(Emphasis added). The specification states "[t]he RNA is +-stranded" and "[p]referred +-stranded RNAs are **self-replicating**." (Emphasis added). Encapsulation of mRNA is not reported.

Petitioners' District Court Answer (Ex. 1312), 86 (¶46)

122. All embodiments encapsulating an RNA in the '693 Patent disclose only self-replicating RNA molecules as the RNA, unlike the mRNA used in Comirnaty®.

123. All embodiments encapsulating an RNA in the '693 Patent disclose only liposomes encapsulating the RNA, unlike the LNPs used in Comirnaty®.

Petitioners' District Court Answer (Ex. 1312), 96 (¶¶122-123)

01359 Sur-Reply, 2 n.1; 01358 Sur-Reply, 2 n.1

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Petitioners' Dropped Positions: Geall Teaches mRNA



Dr. Daniel O. Griffin

Petitioners' Expert

Dr. Griffin's Opening Declaration

> [186] Geall instructs that the immunogen-encoding RNA "is +-stranded, and thus it can be translated without needing any intervening replication steps such as reverse transcription," which a POSA would understand as encompassing mRNA. Ex. 1010 at 12:4-5.

Griffin '127 Patent Opening Decl. (Ex. 1002), ¶112 n.186;
see also Griffin '600 Patent Opening Decl. (Ex. 1002), ¶109 n.165

Dr. Griffin's Reply Deposition

Q. … [Y]ou are not offering the opinion that Geall teaches non-amplifying mRNA; right?

A. **… So as I explained, I get the mRNA from Schrum, the LNPs from Schrum. I go to Geall for the antigen, and I acknowledge that all of the working examples in Geall use self-amplifying mRNA, and I am not able to point to a working example in Geall where non-amplifying mRNA vaccines are used to produce a protein.**

Griffin Reply Dep. (Ex. 2253), 29:4-15; *see also id.*, 13:3-11

01359 Sur-Reply, 2 n.1; 01358 Sur-Reply, 2 n.1

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Petitioners' Dropped Positions: Geall Teaches LNPs



Dr. James Moon

Petitioners' Expert

Dr. Moon's Opening Declaration

> a diameter in the range of 50-220nm (*id.* at 5:8-9). A POSA would have therefore understood Geall as teaching the use of lipid nanoparticles (*i.e.*, particles made of lipids that are nanosized, in the form of liposomes) for delivery of RNA.

Moon '127 Patent Opening Decl. (Ex. 1004), ¶93;
see also Moon '600 Patent Opening Decl. (Ex. 1004), ¶1000

Petitioners' Reply

> Petitioner's obviousness grounds combine Schrum's teachings of an LNP-formulated mRNA vaccine with Geall, Yang, or Altmeyer's disclosure of the claimed immunogen (betacoronavirus S protein). (*See* Decision, 56, 89-90.) PO

01359 Petitioners' Reply, 10; *see also* 01358 Petitioners' Reply, 10

01359 Sur-Reply, 2 n.1; 01358 Sur-Reply, 2 n.1

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Petitioners' Dropped Positions: Altmeyer Teaches mRNA



Dr. Daniel O. Griffin

Petitioners' Expert

Dr. Griffin's Opening Declaration

196. Altmeyer also reports on data demonstrating that mRNA administered in an effective amount induces an immune response to the BetaCoV S protein or S protein subunit. Namely, Altmeyer explains that "[m]ice were immunized intramuscularly with SFV Spike RNA, followed by intraperitoneal (IP) injection of Spike protein at day 14 and at day 35."[274] Altmeyer provides that "[s]erum taken at

Griffin '127 Patent Opening Decl. (Ex. 1002), ¶196;
see also Griffin '600 Patent Opening Decl. (Ex. 1002), ¶180

Dr. Griffin's Reply Deposition

Q. … And you are not relying on Altmeyer for vaccine technology?

A. **In preparing this declaration, I was going to Altmeyer and relying on Altmeyer for the antigen.**

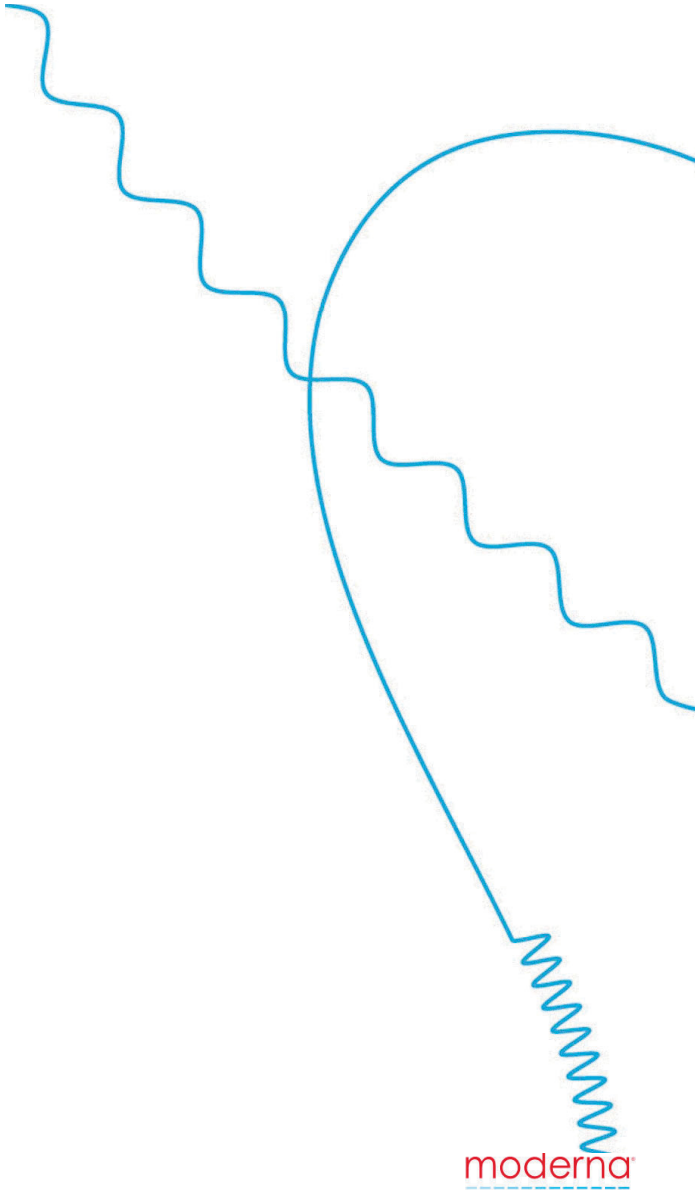
Griffin Reply Dep. (Ex. 2253), 32:21-33:3

01359 Sur-Reply, 2 n.1; 01358 Sur-Reply, 2 n.1

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Objective Indicia of Non-Obviousness



DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Objective Indicia of Non-Obviousness

Long-Felt Unmet Need	✓
Failure of Others	✓
Skepticism	✓
Unexpected Results	✓
Industry Praise	✓
Commercial Success	✓

01359 POR, 64-70; 01359 Sur-Reply, 26-28; Krause Decl. (Ex. 2200), ¶¶162-223; Malackowski Decl. (Ex. 2197), ¶¶13-29; Fuller '127 Decl. (Ex. 2199), ¶¶1139-1143
01358 POR, 63-69; 01358 Sur-Reply, 26-28; Krause Decl. (Ex. 2200), ¶¶162-223; Malackowski Decl. (Ex. 2197), ¶¶13-29; Fuller '600 Decl. (Ex. 2199), ¶¶1146-1150

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Coextensiveness Is Not Required for Nexus

***Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366 (Fed. Cir. 2019)**

A finding that a presumption of nexus is inappropriate does not end the inquiry into secondary considerations. *See In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996). To the contrary, **the patent owner is still afforded an opportunity to prove nexus by showing that the evidence of secondary considerations is the "direct result of the unique characteristics of the claimed invention."**

994 F.3d at 1373-1374

01359 POR, 62-63; 01359 Sur-Reply, 27-28
01358 POR, 61-62; 01358 Sur-Reply, 27-28
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Coextensiveness Is Not Required for Nexus

***Rambus Inc. v. Rea*, 731 F.3d 1248, 1257 (Fed. Cir. 2013)**

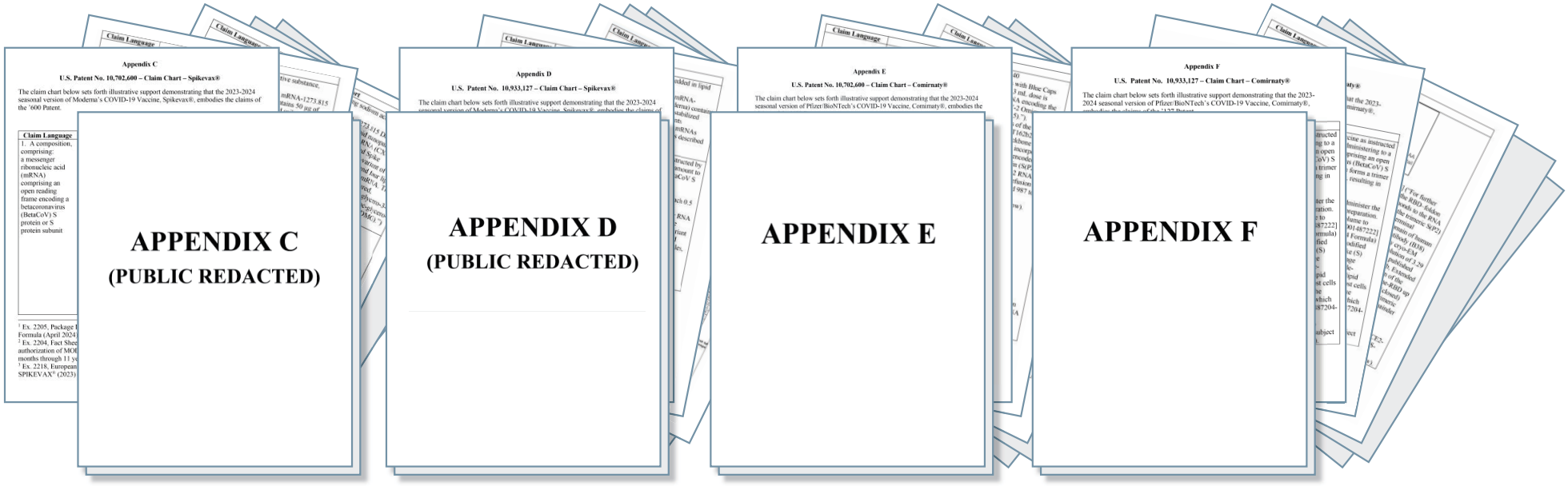
Objective evidence of nonobviousness need only be **'reasonably commensurate with the scope of the claims,'** and we do not require a patentee to produce objective evidence of nonobviousness for every potential embodiment of the claim.

731 F.3d at 1257

01359 POR, 60-61; 01359 Sur-Reply, 27-28
01358 POR, 59-60; 01358 Sur-Reply, 27-28
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Dr. Krause Provided Claim Charts Showing Spikevax® and Comirnaty® Practice the Challenged Claims



01359 POR, 62-64; 01359 Sur-Reply, 26; Krause Decl. (Ex. 2200), ¶¶225-226, App'x D, F
01358 POR, 61-62; 01358 Sur-Reply, 26; Krause Decl. (Ex. 2200), ¶¶225-226, App'x C, E

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

moderna

Petitioners Do Not Dispute Spikevax® and Comirnaty® Practice the Challenged Claims

Dr. Griffin Did Not Prepare Claim Charts or Identify Missing Claim Limitations



Dr. Daniel O. Griffin

Petitioners' Expert

Q. … You didn't prepare any claim charts of your own in response to Dr. Krause; right?

A. **I did not prepare any claim charts.**

Griffin Reply Dep. (Ex. 2253), 103:18-21

Q. … With respect to the claimed aspects of the challenged claims, you don't identify any limitation that's not present in Spikevax and Comirnaty; right?

A. **So I don't know if this – if this makes my response a little more clear, but I go on to talk about other elements of the vaccine's mRNA technology that affect protein translation and immunogenicity not claimed in the '127 patent. I also talk about codon optimization.**

Griffin Reply Dep. (Ex. 2253), 105:17-106:5

01359 Sur-Reply, 26; 01358 Sur-Reply, 26

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Purported "Unclaimed Features" Have Minimal Impact on Efficacy

Comirnaty® and Spikevax® Have Nearly Identical Efficacy

Table 2. Randomized, placebo-controlled efficacy trial outcomes

Sponsor	Vaccine	Trial name	Dose/regimen	Trial launch	Number of volunteers	Case accrual	Distribution of cases (vaccine/ placebo)	Overall VE
Pfizer/ BioNTech	BNT162b2	C4591001	2 doses of 30 μg/21 days apart	July 27, 2020	43,548	170	8/162	95.0% (95% CI 90.3; 97.6)
Moderna	mRNA-1273	COVE Study	2 doses of 100 μg/28 days apart	July 27, 2020	30,420	196	11/185	94.1% (95% CI 89.3; 96.8)

Bok 2021(Ex. 2169), 1642 (Table 2)

01359 POR, 62-63; 01359 Sur-Reply, 28; Krause Decl. (Ex. 2200), ¶¶230-232, 239
01358 POR, 61-62; 01358 Sur-Reply, 28; Krause Decl. (Ex. 2200), ¶¶230-232, 239

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Unclaimed Features Do Not Defeat Nexus

***Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366 (Fed. Cir. 2019)**

To be sure, we have never held that the existence of one or more unclaimed features, standing alone, means nexus may not be presumed. Indeed, there is rarely a perfect correspondence between the claimed invention and the product. As we explained, the purpose of the coextensiveness requirement is to ensure that nexus is only presumed when the product tied to the evidence of secondary considerations "is the invention disclosed and claimed." *Demaco*, 851 F.2d at 1392 (emphasis added). **Thus, if the unclaimed features amount to nothing more than additional insignificant features, presuming nexus may nevertheless be appropriate**.

944 F.3d at 1374

01359 Sur-Reply, 27-28; 01358 Sur-Reply, 27-28

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Objective Indicia Apply to Novel Combination of Elements

Chemours Co. FC, LLC v. Daikin Industries Ltd., 4 F.4th 1370 (Fed. Cir. 2021)

Evidence of commercial success, therefore, **can be linked to an "inventive combination of known elements" to show a sufficient nexus**. *Id.*; *see also Rambus Inc. v. Rea*, 731 F.3d 1248, 1256–58 (Fed. Cir. 2013) (holding that the Board erred when it found objective evidence lacked a nexus where at least some of the evidence related to the "patented design as a whole").

The Board found no nexus between the claimed invention and the alleged commercial success because Kaulbach disclosed all features except for the claimed melt flow rate. J.A. 56. The Board then found that other prior art of record disclosed melt flow rates of 50 g/10 min. *Id*.

Contrary to the Board's decision, the separate disclosure of individual limitations, where the invention is a unique combination of three interdependent properties, does not negate a nexus. Concluding otherwise would mean that nexus could never exist where the claimed invention is a unique combination of known elements from the prior art. *See WBIP*, 829 F.3d at 1332.

4 F.4th at 1378

01359 POR, 60-61; 01359 Sur-Reply, 28
01358 POR, 59-60; 01358 Sur-Reply, 28
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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