

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BIONTECH SE AND PFIZER INC.
Petitioner

v.

MODERNATX, INC.
Patent Owner

IPR2023-01359

Patent No. 10,933,127

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

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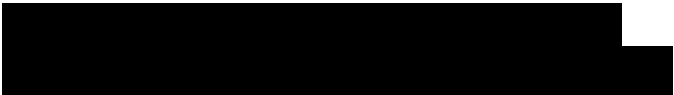
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Ex. 1159	Sealed Reply Declaration of Daniel Griffin
Ex. 1159	Redacted Reply Declaration of Daniel Griffin
Ex. 1160	<i>Reserved</i>
Ex. 1161	Sealed Reply Declaration of James Moon
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Ex. 1264	“Here’s Why COVID-19 Vaccines Like Pfizer’s Need to be Kept So Cold,” Science News, November 20, 2020 (available at https://www.sciencenews.org/article/coronavirus-covid-19-why-vaccines-cold-freeze-pfizer-moderna)
Ex. 1265	“Accelerating Digital Technology for the COVID-19 Vaccine Rollout,” Pfizer website, March 2022 (available at https://www.pfizer.com/news/behind-the-science/accelerating-digital-technology-covid-19-vaccine-rollout)
Ex. 1266	“United Airlines Begins Pfizer COVID-19 Vaccine Charter Flights,” Airline Geeks website, November 28, 2020 (available at https://airlinegeeks.com/2020/11/28/united-airlines-begins-pfizer-charter-flights/)
Ex. 1267	“Update on our COVID-19 vaccine,” BioNTech website, December 22, 2020 (available at https://investors.biontech.de/static-files/3193fc38-2158-45df-a19c-b9e294db3f11)

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Ex. 1268	“Pfizer and BioNTech Conclude Phase 3 Study of COVID-19 Vaccine Candidate, Meeting All Primary Efficacy Endpoints,” Pfizer website, November 18, 2020 (available at https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-conclude-phase-3-study-covid-19-vaccine)
Ex. 1269	“Pfizer Wins 2022 Supply Chain Award,” Gartner (available at https://www.gartner.com/en/supply-chain/trends/supply-chain-award-winner-2022-pfizer)
Ex. 1270	“Pfizer and BioNTech Achieve First Authorization in the World for a Vaccine to Combat COVID-19,” Pfizer website, December 2, 2020 (available at https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-achieve-first-authorization-world)
Ex. 1271	“Moderna struggling to supply promised doses of Covid vaccine,” The Guardian, April 16, 2021 (available at https://www.theguardian.com/world/2021/apr/16/moderna-struggling-to-supply-promised-doses-of-covid-vaccine)
Ex. 1272	Moderna Form 10-K for the fiscal year ended December 31, 2022
Ex. 1273	FDA, Current Good Manufacturing Practices (CGMP) Regulations, May 2023 (available at https://www.fda.gov/drugs/pharmaceutical-quality-resources/current-good-manufacturing-practice-cgmp-regulations)
Ex. 1274	“What Is the Network Effect?” WHARTON UNIVERSITY OF PENNSYLVANIA, January 17, 2023 (available at https://online.wharton.upenn.edu/blog/what-is-the-network-effect/)
Ex. 1275	Pfizer's Form 10-K for the fiscal year ended December 31, 2020

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Ex. 1276	“Number of COVID-19 vaccine doses administered in the United States as of April 26, 2023, by vaccine manufacturer,” Statista, April 2023 (available at https://www.statista.com/statistics/1198516/covid-19-vaccinations-administered-us-by-company/)
Ex. 1277	“Fourth Quarter 2021 Earnings Teleconference,” Pfizer website, February 8, 2022 (available at https://s28.q4cdn.com/781576035/files/doc_financials/2021/q4/Q4-2021-Earnings-Charts-FINAL.pdf)
Ex. 1278	Louise C. Druedahl et al., <i>Collaboration in times of crisis: A study on COVID-19 vaccine R&D partnerships</i> , 39 VACCINE 6291 (2021)
Ex. 1279	“Our Collaborators,” BioNTech website (available at https://www.biontech.com/int/en/home/about/collaborators.html)
Ex. 1280	“Pfizer and BioNTech Announce Collaboration With Brazil's Eurofarma to Manufacture COVID-19 Vaccine Doses for Latin America,” Pfizer website, August 26, 2021 (available at https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-collaboration-brazils)
Ex. 1281	“As COVID vaccine patent dispute drags on, Moderna forks over \$400M to NIH,” ARS Technica, February 24, 2023 (available at https://arstechnica.com/science/2023/02/moderna-forks-over-400m-to-nih-amid-dispute-over-covid-vaccine-ip/)
Ex. 1282	“What happened to the AstraZeneca vaccine? Now rare in rich countries, it's still saving lives around the world,” The Conversation, May 23, 2022 (available at https://theconversation.com/what-happened-to-the-astrazeneca-vaccine-now-rare-in-rich-countries-its-still-saving-lives-around-the-world-181791)

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Ex. 1283	Vaxzevria (previously COVID-19 Vaccine AstraZeneca),” European Medicines Agency (available at https://www.ema.europa.eu/en/medicines/human/EPAR/vaxzevria-previously-covid-19-vaccine-astrazeneca)
Ex. 1284	“VidPrevtyl Beta,” European Medicines Agency (available at https://www.ema.europa.eu/en/medicines/human/EPAR/vidprevtyl-beta)
Ex. 1285	“Coronavirus vaccine trial begun by drug firms GSK and Sanofi,” BBC, September 3, 2020 (available at https://www.bbc.com/news/business-54009633)
Ex. 1286	“Fast-forward: Will the speed of COVID-19 vaccine development reset industry norms?” McKinsey & Company, May 13, 2021 (available at https://www.mckinsey.com/industries/life-sciences/our-insights/fast-forward-will-the-speed-of-covid-19-vaccine-development-reset-industry-norms)
Ex. 1287	“Emergency Use Authorization for Vaccines Explained,” FDA website, November 20, 2020 (available at https://www.fda.gov/vaccines-blood-biologics/vaccines/emergency-use-authorization-vaccines-explained)
Ex. 1288	“FDA Issues Emergency Use Authorization for Third COVID-19 Vaccine,” FDA website, February 27, 2021 (available at https://www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-third-covid-19-vaccine)
Ex. 1289	“Oxford / AstraZeneca vaccine reaches two billion dose milestone,” University of Oxford website, November 16, 2021 (available at https://www.ox.ac.uk/news/2021-11-16-oxford-astrazeneca-vaccine-reaches-two-billion-dose-milestone)

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Ex. 1290	“A Guide to Global COVID-19 Vaccine Efforts,” Council on Foreign Relations, December 5, 2022 (available at https://www.cfr.org/background/guide-global-covid-19-vaccine-efforts)
Ex. 1291	“Trump signs \$8.3 billion emergency coronavirus spending package,” CNBC News, March 6, 2020 (available at https://www.cnbc.com/2020/03/06/trump-signs-8point3-billion-emergency-coronavirus-spending-package.html)
Ex. 1292	“Pfizer and BioNTech Announce an Agreement with U.S. Government for up to 600 Million Doses of mRNA-based Vaccine Candidate Against SARS-CoV-2,” Pfizer press release, July 22, 2020 (available at https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-agreement-us-government-600)
Ex. 1293	“The Covid Vaccine Is Free, but Not Everyone Believes That,” The New York Times, June 1, 2021 (available at https://www.nytimes.com/2021/06/01/upshot/covid-vaccine-hesitancy-cost.html)
Ex. 1294	“Commercialization of COVID-19 Vaccines, Treatments, and Tests: Implications for Access and Coverage,” KFF, February 6, 2024 (available at https://www.kff.org/coronavirus-covid-19/issue-brief/commercialization-of-covid-19-vaccines-treatments-and-tests-implications-for-access-and-coverage/)
Ex. 1295	“COVID-19 Claims Reimbursement to Health Care Providers and Facilities for Testing, Treatment, and Vaccine Administration for the Uninsured,” HRSA, January 1, 2024 (available at https://www.hrsa.gov/provider-relief/about/covid-uninsured-claim)
Ex. 1296	“Government Warns Doctors and Insurers: Don’t Bill for Covid Vaccines,” The New York Times, June 9, 2021 (available at https://www.nytimes.com/2021/06/09/upshot/covid-vaccines-government-warning-bills.html)

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Ex. 1297	"Incentives for COVID-19 Vaccination: Food, Cash, & Other Perks," GoodRx Health, June 24, 2021 (available at https://www.goodrx.com/health-topic/vaccines/covid-19-vaccination-incentives)
Ex. 1298	"LA Has Imposed One of the US's Strictest Vaccine Mandates. Will It Prevent a Covid Surge?" The Guardian, November 13, 2021 (available at https://www.theguardian.com/us-news/2021/nov/13/los-angeles-vaccine-mandate-covid-surge)
Ex. 1299	"Here Are The U.S. Cities Where You Need A Covid Vaccine To Dine In A Restaurant," Forbes, December 22, 2021 (available at https://www.forbes.com/sites/carlieporterfield/2021/12/22/here-are-the-us-cities-where-you-need-a-covid-vaccine-to-dine-in-a-restaurant/)
Ex. 1300	"'Key to NYC': Indoor vaccine mandate begins on Tuesday," ABC 7 News, August 16, 2021 (available at https://abc7ny.com/nyc-vaccine-pass-proof-of-vaccination-key-to-mandate/10954428/)
Ex. 1301	"NYC Slaps 14 Businesses With \$1,000 Fines for Violating Vaccine Mandate," Eater, October 12, 2021 (available at https://ny.eater.com/2021/10/12/22722297/nyc-business-vaccine-mandate-violations-fines)
Ex. 1302	"Moderna vs Pfizer: Is it OK to mix and match the updated COVID-19 booster shots?" Los Angeles Times, September 23, 2022 (available at https://www.latimes.com/california/story/2022-09-23/moderna-vs-pfizer-is-it-ok-to-mix-and-match-the-updated-covid-19-booster-shots)
Ex. 1303	"Covid-19: Biden tells states to offer \$100 vaccine incentive as cases rise," BBC, July 30, 2021 (available at https://www.bbc.com/news/world-us-canada-58020090)
Ex. 1304	Moderna Form 10-Q for the quarterly period ended June 30, 2024

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Exhibit No.	Document
Ex. 1305	Updated Curriculum Vitae of Daniel O. Griffin, Ph.D.
Ex. 1306	U.S. Patent Number 11,638,693 (Asserted in <i>GlaxoSmithKline Biologicals SA et al v. Pfizer Inc. et al</i> , C.A. No. 24-512 (GBW) (D. Del.))
Ex. 1307	U.S. Patent Number 11,638,694 (Asserted in <i>GlaxoSmithKline Biologicals SA et al v. Pfizer Inc. et al</i> , C.A. No. 24-512 (GBW) (D. Del.))
Ex. 1308	U.S. Patent Number 11,666,534 (Asserted in <i>GlaxoSmithKline Biologicals SA et al v. Pfizer Inc. et al</i> , C.A. No. 24-512 (GBW) (D. Del.))
Ex. 1309	U.S. Patent Number 11,766,401 (Asserted in <i>GlaxoSmithKline Biologicals SA et al v. Pfizer Inc. et al</i> , C.A. No. 24-512 (GBW) (D. Del.))
Ex. 1310	U.S. Patent Number 11,786,467 (Asserted in <i>GlaxoSmithKline Biologicals SA et al v. Pfizer Inc. et al</i> , C.A. No. 24-512 (GBW) (D. Del.))
Ex. 1311	International Publication Number WO 2012/006378 A1 (Asserted in <i>GlaxoSmithKline Biologicals SA et al v. Pfizer Inc. et al</i> , C.A. No. 24-512 (GBW) (D. Del.))
Ex. 1312	Answer, Affirmative Defenses, and Counterclaims in Response to Complaint for Patent Infringement, <i>GlaxoSmithKline Biologicals SA et al v. Pfizer Inc. et al</i> , C.A. No. 24-512 (GBW) (D. Del.)
Ex. 1313	Amended Answer in Response to Complaint for Patent Infringement, <i>GlaxoSmithKline Biologicals SA et al v. Pfizer Inc. et al</i> , C.A. No. 24-512 (GBW) (D. Del.)
Ex. 1314	Petsch, B., et al. <i>Protective efficacy of in vitro synthesized, specific mRNA vaccines against influenza A virus infection</i> , 30 NATURE BIOTECHNOLOGY 121 (2012)

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Exhibit No.	Document
Ex. 1315	Hattinger, E., et al. <i>Prophylactic mRNA Vaccination against Allergy Confers Long-Term Memory Responses and Persistent Protection in Mice</i> . JOURNAL OF IMMUNOLOGY RESEARCH 2015, 797421 (2015)

Long after its original application was filed—and after COVID-19 emerged—Patent Owner (“PO”) obtained the broad claims challenged in this *inter partes* review.¹ These claims seek to cover the well-known, generic concept of using mRNA encoding for a prior-art antigen (a betacoronavirus spike protein or subunit thereof) formulated in a prior-art mRNA delivery system (lipid nanoparticles) to achieve the prior-art function of a vaccine (inducing an immune response). The claims do not require any specific level of efficacy. They reflect no new invention about the use of mRNA. And they do not describe any “novel” mRNA-LNP “platform” (Response, 25) for a betacoronavirus (or any other) vaccine. Instead, the claims merely ensnare long-established concepts disclosed in PO’s own prior-art application (Schrum) and elsewhere.

Unable to demonstrate any patentable distinctions over Schrum and other prior art (Geall, Yang, and Altmeyer), PO resorts to conflating post-filing research on COVID-19 vaccines with the challenged pre-pandemic specification, misstating the prior art [REDACTED], and applying incorrect legal standards. The prior art, however, continues to compel one clear conclusion: The claims are unpatentable and should be canceled.

¹ Claims 1-3, 6-9, 11-13, 17-18, and 20 (“the challenged claims”) of U.S. Patent No. 10,933,127 (“the ’127 patent”) are at issue in this proceeding.

I. PO'S PROPOSED CONSTRUCTIONS ARE UNNECESSARY

PO proposes construing three terms. While these constructions are unsupported (Ex. 1159, ¶¶19-27), the challenged claims are unpatentable even if applied.²

First, PO argues that “mRNA,” which means “messenger ribonucleic acid,” excludes self-amplifying mRNA. (Response, 7.) Self-amplifying mRNA is a type of mRNA, as PO and its scientists have recognized. (*See* Ex. 2049, 1-2; Ex. 2050, 12-13.) PO's proposed construction is unnecessary to resolve the parties' dispute because the Petition relies upon Schrum's teaching of mRNA vaccines (Petition, 21-25), which PO does not dispute. (Ex. 1159, ¶¶34, 49-59.) *Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1375 (Fed. Cir. 2019).

² Disconnected from merits argument, PO wrongly attacks Dr. Griffin's (and Dr. Moon's) qualifications. (Response, 5-6.) Each possessed the education and experience of a member of the research team that both sides agree embodies the POSA's skillset. (Ex. 1159, ¶¶5-18; Ex. 1161, ¶¶3-17.) PO's experts are the ones who opined beyond their expertise; Dr. Chan, for instance, admitted that his declaration involved “things that are not in my area of purview—or my expertise.” (*Compare* Ex. 2198, ¶68 with Ex. 1152, 160:2-7.)

Second, PO seeks to construe “S protein” as a “full-length spike protein” and “S protein subunit” as an “S1 subunit or S2 subunit.” (Response, 7-9.) “[F]ull-length” appears nowhere in the claim (nor did Moderna propose it in district court, Ex. 1035, 11). Contrary to the interpretation of PO’s expert, Dr. Fuller (Ex. 2199, ¶163), the claims’ recitation of S protein and S1/S2 subunits does not limit “S protein” to “full-length” S protein. As Dr. Fuller recognizes, there are “truncated version[s] of a spike protein,” that are neither full-length S protein nor a S1/S2 subunit thereof. (Ex. 2199, ¶193.) And when the specification refers to a “full-length Spike (s) protein,” it does so expressly (*e.g.*, Ex. 1001, 24:56-25:1; 25:13-22; 217:49-60), suggesting that the claim language lacking that qualifier is not so limited. Moreover, the specification repeatedly equates “S protein” with “S, S1 and/or S2.” (Ex. 1001, 35:19-21; 35:64-36:28.) Thus, PO cannot show lexicography or disclaimer.

Regardless, as explained in Sections II and III below, Geall, Yang, and Altmeyer each disclose a “full-length spike protein” of a betacoronavirus. Therefore, these constructions are unnecessary to resolve the parties’ dispute.³

³ PO touts as undisputed the district court’s “forming a spike” language. (Response, 8.) This language merely clarified which betacoronavirus protein of the

II. THE CHALLENGED CLAIMS ARE ANTICIPATED (GROUND 1)

Schrump anticipates every challenged claim because it expressly discloses the claimed mRNA formulation delivered using lipid nanoparticles used to induce an immune response, and incorporates Geall's identification of the SARS-CoV S protein immunogen.⁴ PO is wrong that Petitioner's analysis requires "forbidden picking and choosing" or recourse to an "envisaging" argument. (Response, 11-12.)⁵

A. Schrump Discloses Each Limitation as Arranged in the Claim

PO charges that "Petitioners must rely on disclosures from different sections of a reference not explicitly connected to each other." (Response, 22.) PO

virus, itself, was at issue to avoid "jury confusion"; it did not impose an additional claim limitation. (Ex. 1035, 12.)

⁴ PO separately addresses only claim 1 and dependent claim 3. PO has forfeited any independent arguments regarding other claims. 37 C.F.R. § 42.6(a)(3); *Google LLC v. Parus Holdings, Inc.*, IPR2020-00846, Paper 31, 25 (Oct. 19, 2021).

⁵ PO's naked assertion that Petitioners do not "argue Schrump is enabled" (Response, 13), ignores that prior art printed publications are presumptively enabled.

disregards how a POSA would understand Schrum. (Ex. 1159, ¶¶28-127; Ex. 1161, ¶¶22-64.)

The first 300 paragraphs of Schrum's "DETAILED DESCRIPTION" discuss the design and synthesis of mRNA (Ex. 2114, 72:17-73:3), leading the POSA to "wonder[]" what "to do with this technology." (*Id.*, 73:3-20.) Schrum answers that question under the heading "Activation of the Immune Response: Vaccines." (Ex. 1009, ¶340.) There, Schrum explains that its mRNA compositions "may encode an immunogenic peptide or polypeptide," and "may be used to elicit or provoke an immune response in an organism" as a vaccine. (*Id.*)

Schrum then expressly teaches using lipid nanoparticles to deliver mRNA vaccines, stating that "an immune response may be elicited by delivering a lipid nanoparticle which may include . . . an immunogen," which "may be a . . . modified mRNA described herein." (*Id.*, ¶397.) The same paragraph states that "the lipid nanoparticle may be formulated for use in a vaccine such as, but not limited to, against a pathogen." (*Id.*) The "modified mRNA, described herein" used to "elicit[]" an immune response invokes the near-identical language under Schrum's "Vaccine" heading: "mRNA molecules may be used to elicit or provoke an immune response." (*Id.*, ¶340.)

PO argues the last sentence of paragraph 397 is a separate embodiment that "includes a vaccine, but no mRNA." (Response, 22.) But a POSA would have

understood that empty LNPs are not used as vaccines, and must include a payload like mRNA. (Ex. 1161, ¶43.) “*The* lipid nanoparticle” of the last sentence refers to the lipid nanoparticle discussed earlier in the paragraph. (Ex. 1161, ¶¶29-43.) And *the* lipid nanoparticle formulation of Schrum is a four-component lipid nanoparticle formulation, (“LNP”) as recited in the claims. (Ex. 1161, ¶¶22-28, 38-39.) Schrum teaches (and exemplifies) that the disclosed LNP formulations “have a molar ratio [of] 50:10:38.5:1.5-3.0 (cationic lipid: fusogenic lipid: cholesterol: PEG lipid)” (Ex. 1009, ¶6), and specifically “50:10:38.5:1.5 (DLin-KC2-DMA: DSPC: Cholesterol: Peg-c-DOMG” (*id.*, ¶995)—the *very same* formulation used in the '127 patent. (Ex. 1161, ¶¶24-28.)

**B. Schrum Incorporates Geall's
Betacoronavirus S-protein Immunogen**

Schrom discloses, without picking and choosing, the claimed LNP formulation containing an mRNA immunogen. That leaves the selection of *which* immunogen, but here too PO's arguments fail.

First, PO contends that “Schrum does not incorporate Geall's immunogens.” (Response, 15.) PO is wrong. The legal requirements for incorporation are straightforward—the “host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents.” *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000). Schrum does both. Schrum identifies Geall by

publication number *and* specifies that Geall is incorporated “in [its] entirety.” (Ex. 1009, ¶342.) And Schrum explicitly incorporates Geall for its disclosure that modified mRNA “*encoding an immunogen* may be delivered to the vertebrate *in a dose large enough to be immunogenic.*” (*Id.* (emphasis added).)

PO's contrary argument, citing *Cook Biotech Inc. v. Acell, Inc.*, 460 F.3d 1365, 1376 (Fed. Cir. 2006) (Response, 16), is mistaken. The “context” that allegedly “govern[s]” incorporation cites Geall *for mRNA encoding immunogens*, not just for dosage levels. PO's position that Schrum incorporates Geall only for dose amounts is illogical, as the effective dose depends on which immunogen is used, which Dr. Fuller recognized at deposition. (Ex. 1104, 119:15-120:5; Ex. 1159, ¶¶37-39.)

Second, PO claims that “Geall does not . . . specify ‘full-length’ (or subunit)” betacoronavirus S protein. (Response, 17.) Geall, however, expressly discloses the claimed immunogen, teaching that the “coronavirus immunogen may be a spike polypeptide” (Ex. 1010, 19:29-30), *i.e.*, an S protein. (*See* Ex. 1159, ¶¶40-48.) The challenged claims recite nothing more. And even crediting PO's construction of “S protein” *arguendo*, a POSA would have understood that Geall discloses a “full-length” spike protein. (*Id.*, ¶¶45-46.) A “full-length” protein refers to the entirety of a natural protein, not a shortened portion thereof. Geall identifies no truncation or other modification of the S protein, and a POSA would therefore understand its disclosure to refer to a “full-length” spike protein. (*Id.*, ¶¶26, 45-46.) Where the

claims of the '127 patent recite an "S protein," and Geall likewise discloses a "spike polypeptide," (*i.e.*, an S protein) using near-identical language, PO cannot credibly argue that Geall does not teach the claimed immunogen.

PO also is wrong to fault Geall's disclosure of "information or data indicating the 'spike polypeptide' forms a spike." (Response, 18; *see also id.*, 27-28.) It suffices that Geall teaches an S protein, as the claims recite. It was well known by October 2015 that "[t]he *spikes* of SARS-CoV are composed of trimers of S protein." (Ex. 1031, 227.) There is no burden on Petitioner to advance additional "information or data" proving that Geall's eponymous polypeptides actually "form[] a spike"⁶ upon expression—particularly where the '127 patent makes no such showing. Regardless, a POSA would have understood that administering mRNA encoding for a betacoronavirus spike protein would result in expression of a protein that forms "spikes." (*See, e.g.*, Ex. 1001, 3:26-31; Ex. 1159, ¶44.)

⁶ As the Board noted in the related proceeding, "the claims do not require that the protein the recited composition causes to be expressed have any particular properties, much less that it folds to form a spike." (IPR2023-01358, Paper 19, 59.)

**C. A POSA Would Not Have to Pick and Choose Because
Schrum Expressly Discloses the Claimed Combination**

Finally, PO is mistaken that the presence of other teachings in Schrum weighs against anticipation. (Response, 20-24.)⁷ Schrum expressly discloses combining LNPs with mRNA encoding an immunogen to induce an immune response (Ex. 1009, ¶397), as required by the claim. Schrum's disclosure of additional vaccine technologies is irrelevant. *See Incept LLC v. Palette Life Scis.*, 77 F.4th 1366, 1372 (Fed. Cir. 2023). Unlike PO's cited case law, Schrum "discloses" each limitation of the challenged claims, as arranged. (Response, 20 (citing *Eli Lilly & Co. v. Los Angeles Biomedical Research Inst.*, 849 F.3d 1073 (Fed. Cir. 2017).))

Similarly, PO is wrong to invoke "at once envisage" law that governs combining elements chosen from *multiple* lists. (Response, 23-24.) Schrum discloses, in one embodiment, every element of the challenged claims except the choice of immunogen, (Ex. 1159, ¶¶49-59) requiring selection from a *single* list (incorporated via Geall). Each entry in that list, including the claimed S-protein, is

⁷ PO's expert testimony should be accorded little weight because the experts improperly limited their consideration of the prior art to the documents' subjective "focus," rather than considering the prior art for all its teachings as a POSA would. (Ex. 1152, 55:17-56:18; Ex. 1161, ¶¶60-64; Ex. 1104, 216:4-50, 218:7-219:3; Ex. 1159, ¶¶29-32.)

anticipated. *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1376 (Fed. Cir. 2005); *In re Gleave*, 560 F.3d 1331, 1333 (Fed. Cir. 2009) (prior art list of “more than 1400 sequences” anticipates each disclosed sequence). For a POSA making a betacoronavirus vaccine, the S-protein is the sole betacoronavirus immunogen identified in Geall, further supporting anticipation. (Ex. 1159, ¶58.)

III. THE CHALLENGED CLAIMS WOULD HAVE BEEN OBVIOUS (GROUNDS 2-4)

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, 41-43, 88.) PO disputes that the prior art teaches all claim limitations, and contends that a POSA would lack motivation to combine those teachings with a reasonable expectation of success. PO's counter-arguments lack merit.

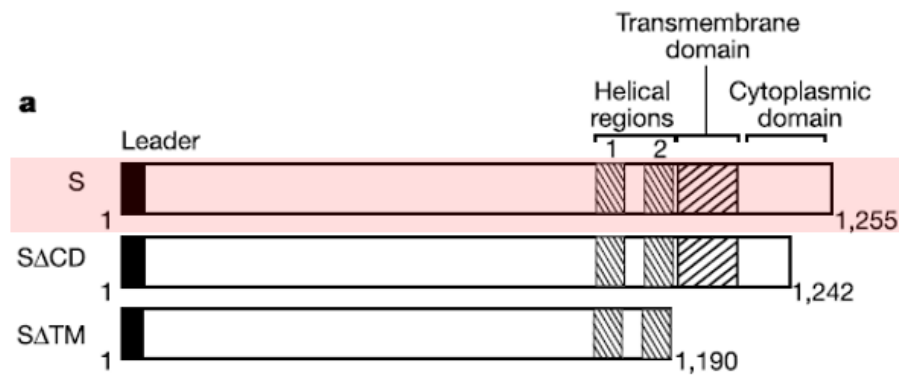
A. The Prior Art Discloses All Claim Limitations

PO first contends, wrongly, that Petitioner's grounds do not teach the recited claim limitations.

Ground 2. As explained in Section II.B above, Geall discloses a betacoronavirus S protein. (Response, 27-28; Ex. 1159, ¶¶128-37, 281-333.)⁸

Ground 3. PO complains that Yang discloses only “data for truncated S protein.” (Response, 52-54 (emphasis in original).) That argument attempts to leverage PO’s unsupported claim construction position to discount relevant data, but regardless, Yang’s teachings are not limited to a truncated S protein. (Ex. 1159, ¶¶335-43, 356-84.) Yang expressly discloses a “DNA vaccine encoding *the spike (S) glycoprotein* of the SARS-CoV [that] induces T cell and neutralizing antibody responses,” and that “[i]njection of *S*, *SΔTM* and *SΔCD* expression vectors induced a substantial immune response.” (Ex. 1011, 561 (emphases added); Petition, 50-51.) As Figure 1a (copied below) illustrates, the “spike (S) glycoprotein” of Yang is a full-length spike protein. (Ex. 1159, ¶¶337-38.) PO’s expert (Dr. Fuller) agrees. (Ex. 2199, ¶¶793-94.)

⁸ PO’s assertion that neither Schrum, Geall, nor Yang disclose the claimed immune response or the neutralizing antibodies (Response, 28, 53-54) altogether ignores the Petition’s analysis of these limitations. (Petition, 39-44, 51-56, 62-66.) Moreover, Schrum expressly teaches the use of an *immunogen* to elicit an immune response. *Supra* II.A.



(Ex. 1011, 561 (annotation added).)

Ground 4. PO does not dispute that Altmeyer discloses an RNA vaccine expressing a SARS-CoV spike protein that induces an immune response. (Response, 57-58; Ex. 1159, ¶¶385-93, 402-31.) Nor could it, as Altmeyer states that “[t]he Spike protein was expressed as a full-length protein.” (Ex. 1012, ¶111.) Instead, PO contends that Altmeyer does not disclose an mRNA vaccine. This is irrelevant; *Schrump* teaches use of an mRNA vaccine encoding an immunogen. Altmeyer is principally relied upon for its immunogen (the S protein). (Decision, 88.)

B. A POSA Would Have Had Good Reason to Combine the Prior Art's Teachings and Arrive at the Claimed Invention

PO repeats the same motivation arguments that the Board already considered—and rejected—at the institution stage. (See Decision, 44-72.) PO's arguments remain meritless. (Ex. 1159, ¶¶138-280, 344-55, 394-401; Ex. 1161, ¶¶65-99.)

**1. A POSA Would Have Been Motivated to Use the S Protein
as the Encoded Antigen in Schrum's mRNA Vaccine**

PO contends that a POSA would not have been motivated to select the betacoronavirus S protein as the immunogen encoded by Schrum's vaccine. (Response, 44-50.) PO is wrong.

First, the record confirms that “the prior art—as reflected in, for example, Yang and Du—provides good reason to select SARS-CoV from Geall's list of targeted viruses.” (Decision, 55.) As Dr. Griffin testified, SARS-CoV continued to be identified as a top-ten pathogen with pandemic potential by October 2015. (*E.g.*, 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.)

Second, a POSA designing a betacoronavirus vaccine would have been motivated to use the spike protein as its immunogen. (Ex. 1159, ¶¶185-237.) The spike protein is the only betacoronavirus vaccine immunogen pursued by each of Geall, Yang, and Altmeyer. PO's suggestion that a POSA would set aside their teachings (*e.g.*, Response, 36-37) is not credible. Tellingly, Dr. Fuller herself looked at results from other vaccine modalities in selecting the SARS-CoV-2 spike protein as the antigen to be encoded in a self-amplifying mRNA vaccine. (Ex. 1104, 43:15-44:4.)

The identification by Geall, Yang, and Altmeyer of the spike protein as the betacoronavirus immunogen of choice echoed longstanding knowledge. By 2004, NIH scientists determined that, “among the structural proteins” of SARS-CoV, the spike protein was “the *only significant neutralization antigen and protective antigen.*” (Ex. 1132, 9804 (emphasis added).) Dr. Fuller confirmed that the SARS-CoV and MERS-CoV outbreaks (occurring before 2015) demonstrated that the “spike protein would be a target for neutralizing antibody. And if we could raise sufficient neutralizing antibodies against that target, we may have an effective vaccine.” (Ex. 1104, 41:20-42:3.) She further testified that “quite a few [vaccine candidates] focused on the S protein,” (*id.*, 62:11-17), which induced an immune response. (*Id.*, 65:15-66:2). The spike protein was the predominant immunogen of interest for a betacoronavirus vaccine, a conclusion that Yang and Du reinforce. (Ex. 1011, 561-63; Ex. 1031, 229; Decision, 54-56.)

Contrary to PO's assertions (Response, 45), the existence of other SARS-CoV proteins does not teach away from use of the spike protein. Motivation does not require elimination of every alternative—more than one thing can be obvious. *ACCO Brands Corp. v. Fellowes, Inc.*, 813 F.3d 1361, 1367 (Fed. Cir. 2016). Regardless, it was known well before October 2015 that “the N, M, and E proteins [the three other structural proteins of SARS-CoV] did not make a significant

contribution to a neutralizing antibody response or protective immunity” and “were not significant protective antigens.” (Ex. 1132, 9808-09.)

Third, concerns with disease enhancement (Response, 47) do not teach away from the spike protein as a vaccine immunogen. Dr. Griffin made clear that disease enhancement was a known concern for *any* vaccine—a truism that PO tries to twist into an admission. But this “potential or theoretical risk” (per PO’s expert) (Ex. 1105, 23:2-3) would not have dissuaded (and did not dissuade) S-protein-based betacoronavirus vaccine development. (Ex. 1159, ¶¶208-37.)

In fact, concern about disease enhancement would steer a POSA *towards* the spike protein. (Ex. 1159, ¶¶211-12.) As PO’s own declarant testified, enhanced disease is “more likely when the neutralizing antibody response is low.” (Ex. 2200, ¶145.) A POSA would therefore use the vaccine immunogen known to induce neutralizing antibodies—the S protein. (Ex. 1132, 9808.)

None of PO’s other references shows that a POSA would have been dissuaded from selecting the S protein. PO relies on Miller (a book about the development of Comirnaty® that mentions ADE). (Response, 47.) Miller, however, reported “there was little doubt” that the “best way to build a coronavirus vaccine that was both effective and safe . . . [was] to engineer an authentic copy of the spike protein.” (Ex. 2106, 69.)

Fourth, a POSA would have had good reason to use a “full-length” S protein immunogen, contrary to PO’s allegations. (Response, 47.) By 2015, the field was rife with teachings *towards* S protein-based betacoronavirus vaccines, including with “full-length” spike proteins (in PO’s parlance). Each of Geall, Yang, and Altmeyer independently disclose the use of such a vaccine immunogen. Du further reaffirms that vaccines based on the “full-length S protein of SARS-CoV Urbani strain resulted in the production of S protein-specific neutralizing antibodies” (Ex. 1031, 229.)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Finally, PO’s last argument is that the full-length spike protein would be “difficult to translate/express.” (Response, 45-46.) This argument ignores that nucleic acid vaccines encoding betacoronavirus S proteins had already shown successful expression of the S protein. (Ex. 1101; Ex. 1159, ¶¶236-37.) And Dr.

Fuller confirmed, “once we know the genetic sequence or code, we can design an mRNA or DNA molecule that prompts a person’s cells to start making it.” (Ex. 1104, 78:5-10.)

**2. No Alleged “Skepticism” Renders
the Challenged Claims Non-Obvious**

PO spends pages on its contention that a POSA would not have combined Petitioner’s prior art due to purported skepticism of mRNA vaccines. (Response, 40-44.) This is a round-about way of arguing that the prior art taught away from Schrum’s express disclosure of mRNA vaccines, but PO’s choice in not invoking the “teaching away” talisman is telling—teaching away is a high burden that PO cannot satisfy. As the Board found, PO’s cited art—recycled in its Response—debunks any skepticism with mRNA vaccines and instead supports an “expectation that mRNA vaccines can induce” a “long-lasting immune response.” (Decision, 50; Ex. 1159, ¶¶143-84.)

By 2015, mRNA vaccines were known to have significant advantages over both “traditional” and other nucleic acid vaccines. (Petition, 7, 10-11.) There was confidence that mRNA vaccines could induce an immune response against an encoded immunogen, encompassing neutralizing antibodies, which is all that the challenged claims require. (Ex. 1159, ¶¶146-59.) [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Even PO's cited references (Response, 41-42, citing Geall (Ex. 1016) and Pardi (Ex. 2027)) describe mRNA 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 unpredictability needed to dissuade a POSA from mRNA vaccines existed in the prior art.

3. A POSA Would Have Been Motivated to Utilize a Lipid Nanoparticle Delivery System

In an attempt at undermining the motivation to use LNPs, PO proffers that "non-LNP options" were known in the art. (Response, 39-40.) But PO cannot dispute that Schrum discloses (and exemplifies) the *exact same* lipid nanoparticle formulations in the '127 patent's working examples (and covered by its claims). (See Petition, 26-27; Ex. 1161, ¶¶24-28.) Nor does PO dispute that Schrum teaches that a "lipid nanoparticle may be formulated for use in a vaccine, such as, but not limited to, against a pathogen." (Ex. 1009, ¶397.) And by 2015, a POSA would have known that formulating an RNA vaccine using lipid nanoparticles

“substantially” improved vaccine performance (Ex. 2021, 14604), providing good reason to apply lipid nanoparticle systems to deliver betacoronavirus S protein-encoding mRNA vaccines. (Ex. 1161, ¶¶65-99; Ex. 1159, ¶¶238-56.)

Schrum's vaccine-specific teachings are further supported by its working examples, which demonstrate that “administration of mRNA [formulated in a lipid nanoparticle system] causes cells to produce a desired protein.” (Decision, 47.) PO's IPR-inspired contention that a POSA would disregard these teachings because “Schrum exemplified LNPs for *therapeutics*” (Response, 39-40) ignores that both mRNA vaccines and mRNA therapeutics require the protein-encoding mRNA to be taken up by the cells and expressed by the body. (Ex. 1159, ¶¶239-43; Ex. 1161, ¶71.)

Based on these disclosures, PO's charge of hindsight (Response, 51) rings hollow. Schrum instructs a POSA to use LNPs to deliver an mRNA vaccine to elicit an immune response, and the prior art (including Geall, Yang, and Altmeyer) had long disclosed a betacoronavirus spike protein vaccine immunogen. That Geall also discloses alternative immunogens (or delivery approaches) does not make the claimed method any less obvious. *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009); *ACCO Brands*, 813 F.3d at 1367.

C. A POSA Would Have Reasonably Expected to Induce an Immune Response Using a Lipid Nanoparticle-Encapsulated mRNA Vaccine Encoding a Betacoronavirus Spike Protein

Schrum, as discussed in Section II.A, discloses an LNP encapsulating a modified mRNA molecule encoding an immunogen administered to induce an immune response, which is combined with Geall, Yang, and Altmeyer's teachings of a betacoronavirus spike protein vaccine immunogen. Petitioner has demonstrated that a POSA would expect that (a) Schrum's mRNA vaccine could encode—and upon administration, express—the spike protein, and (b) the resulting spike protein could induce an immune response, as required by *the claims*. (Petition, 42-43, Ex. 1159, ¶¶138-256, 344-55, 394-401; Ex. 1161, ¶¶68-99.) No more is required to demonstrate a “reasonable expectation of success of developing the claimed invention.” *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013).

As to (a), PO *does not dispute* that a POSA would reasonably expect that Schrum's mRNA vaccine could encode and express a betacoronavirus S protein. It was known that “any protein can be expressed from mRNA without the need to adjust the production process” (Ex. 1019, 1; Ex. 1159, ¶44)—a fact confirmed by the '127 patent. (Ex. 1001, 3:26-31.)

As to (b), Petitioner has adduced extensive evidence (multiple prior art studies) demonstrating that S protein-based vaccines induce an immune response, and PO cites *no* studies showing a contrary result. (Ex. 1159, ¶¶185-207.) This is

fatal to PO's argument against a reasonable expectation of success.⁹ PO's failure to adduce evidence supporting its argument is unsurprising because its own declarant, Dr. Fuller, testified that "[i]t's just *basic fundamental nucleic acid vaccine biology*" that a DNA or RNA vaccine that expresses a protein immunogen will elicit an immune response. (Ex. 1104, 51:8-52:9 (emphasis added).)

Dr. Fuller's admission is confirmed by the prior art, which discloses that S protein-based vaccines induce an immune response—in multiple vaccine modalities and against at least two betacoronaviruses. Du, for instance, summarizes that four separate "[v]accines based on the full-length S protein" were protective, and concludes that such "reports suggest that the full-length S protein is highly immunogenic and induces protection against SARS-CoV challenge." (Ex. 1031, 229.)

⁹ PO's suggestion that Dr. Griffin agreed that reasonable expectation of success requires clinical data (Response, 28) is wrong. Dr. Griffin's opinion that a POSA would have needed data to determine that M or N protein-based vaccines would conclusively lead to enhanced disease or early death (Ex. 2114, 124:21-125:12) is irrelevant because reasonable expectation of success does not require conclusively eliminating the risk of enhanced disease—an unclaimed aspect and a concern for every vaccine.

Unable to counter these express prior art disclosures, PO suggests that the immune response achieved by an S protein-based vaccine in a non-mRNA platform (like Yang) could not inform a POSA's expectation in the mRNA context. (Response, 31-32, 36.) PO, however, ignores Dr. Fuller's explanation of "basic fundamental nucleic acid vaccine biology," and her testimony that DNA vaccines (as in Yang or Wang) encoding a betacoronavirus spike protein are necessarily transcribed into mRNA before leading to expression of the betacoronavirus spike protein per the "central dogma of biology." (Ex. 2199, ¶54.) That is, the S protein-based DNA vaccines achieved a significant, protective immune response (including neutralizing antibodies) by causing the body's cells to express the encoded immunogen using a *less efficient* cellular pathway than the claimed mRNA vaccines. Based on those results, a POSA would reasonably expect to induce an immune response via the *more efficient* cellular pathway of mRNA for *the same antigen* (S protein). (Ex. 1159, ¶¶202-07, 230-37, 344-55.) [REDACTED]

[REDACTED]

¹⁰ Despite not reviewing Schrum, Geall, or Altmeyer in forming his opinions (Ex. 1105, 11:3-14:13), Dr. Krause offered opinions as to whether a POSA would reasonably expect to successfully combine the Petition's prior art (*e.g.*, Ex. 2200, ¶47.) These opinions are entitled to no weight.

[REDACTED]

[REDACTED]

PO notes the lack of “approved mRNA vaccines for infectious disease” by 2015 and boldly claims that “[i]t was only when Moderna did substantial work—including as reflected in the patent—that there was *success*.” (Response, 44.) An “approved” vaccine is not the barometer for a reasonable expectation of success—particularly here, where the claims do not require any level of efficacy. *Allergan*, 726 F.3d at 1292.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

¹² Days ago, PO accused Petitioners by e-mail of taking inconsistent positions in litigation against GlaxoSmithKline (“GSK”). GSK alleges that Comirnaty[®] infringes several patents issued in 2023 (claiming priority to 2010) to Andrew Geall, which are not family members to Ex. 1010. The pleadings address, *inter alia*, whether there is written description support under 35 U.S.C. § 112 for GSK’s broad claims. In its Answer & Counterclaims, BioNTech/Pfizer stated that the GSK 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.” (Ex. 1312, 80, *see also id.* at 80-102.) Petitioner’s positions here are, in fact, **consistent** with the GSK pleadings. Comirnaty[®] does not use the lipid formulation or mRNA described in Geall (although, the Geall lipid formulation is **identical** to one identified by the ’127 patent, Ex. 1004, ¶¶ 56-57). And the

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

incongruence of the species described in the 2023 Geall patents versus the breadth of **GSK's** claims has no bearing on the question here of whether Geall teaches elements of **Moderna's** claims. The GSK pleadings do not support Moderna's positions that self-amplifying mRNA is categorically different from mRNA claimed here, or that what GSK and Geall call "liposomes" are somehow different from the LNPs claimed here. Petitioner also notes that an amended Complaint and Answer were filed, further clarifying BioNTech/Pfizer's positions in the GSK litigation. (Ex. 1313.) Regardless, the issue is immaterial, as Petitioners point to **Schrump** for the LNP and mRNA limitations and meet them without Geall.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**E. No Secondary Considerations Rebut
the Clear *Prima Facie* Obviousness Case**

Secondary considerations are probative of nonobviousness only where “there is a nexus between the claimed invention and the [alleged secondary consideration].” *In re Affinity Labs of Tex., LLC*, 856 F.3d 883, 901 (Fed. Cir. 2017) (internal quotation omitted). PO has not met *its* burden of establishing nexus. PO is not entitled to a presumption of nexus based on alleged coextensiveness between the claims and Comirnaty[®] or Spikevax[®] (Response, 60-63) because it has failed to prove that either product is the claimed invention. *Fox Factory, Inc. v. Sram, LLC*, 944 F.3d 1366, 1377 (Fed. Cir. 2019). The “claims purport to encompass immunogenic vaccines encoding a spike protein (or subunit) for *any* betacoronavirus.” (Decision, 77 (emphasis added).) Comirnaty[®] and Spikevax[®]

encode antigens not in existence as of the priority date. (Ex. 1159, ¶¶435-42.)¹³ In addition to different LNP formulations, these vaccines have “different [mRNA] sequences, 5’ caps, 5’ and 3’ untranslated regions, [and] codon optimizations”—each of which impact vaccine performance. (Response, 63.) None of these specific features are claimed. (*Id.*, ¶¶443-54.)¹⁴

PO’s claim of coextensiveness is further undermined by its claim that eleven distinct issued patents cover Spikevax[®]. (Ex. 1223.) PO cannot show that each of those eleven patents “covers essentially the same invention.” *Fox Factory, Inc.*, 944 F.3d at 1377.

Even if PO could establish nexus, the cited secondary considerations do not demonstrate nonobviousness. The applications were filed in 2015. PO cannot point to any evidence of secondary considerations until five years later, when a novel

¹³ The claims lack the necessary detail that a POSA would need to make Comirnaty[®] or Spikevax[®]. (Ex. 1159, ¶¶435-54.)

¹⁴ PO contends that the 1-methylpseudouridine modification (recited **only** in dependent claims 12 and 20) was critical to vaccine performance. (Response, 63.) Schrum discloses the limitation rendering it “not pertinent” to any alleged objective indicia. (Petition, 34.) *Ormco Corp. v. Align Technology, Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006).

virus—previously unknown to PO and the world—started a pandemic. PO cannot show a long-felt-but-unmet need satisfied by the challenged claims. *See Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 989, 997 (Fed. Cir. 2009). Further, the generic concept of an mRNA-LNP formulation encoding a betacoronavirus S protein to induce an immune response was squarely in the prior art. PO can show no failure of others, skepticism, or unexpected results.

Any industry praise or commercial success is not due to the claimed features. (Ex. 1163, ¶¶1-154; Ex. 1159, ¶¶455-67.) It is instead attributable to unclaimed aspects of the BioNTech/Pfizer and Moderna vaccines, the independent work of companies (and governments) unrelated to the '127 patent, and Petitioners' success in addressing a global emergency. (*Id.*)

The challenged claims are unpatentable and should be canceled.

* * *

Respectfully submitted,

Dated: August 30, 2024

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing Petitioner's Reply to Patent Owner's Response contains, as measured by the word-processing system used to prepare this paper, 5,578 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

Respectfully submitted,

Dated: August 30, 2024

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