

Filed: October 16, 2024

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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BIONTECH SE AND PFIZER INC.,  
Petitioner,

v.

MODERNA TX, INC.,  
Patent Owner.

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

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**PATENT OWNER'S SUR-REPLY**

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**PATENT OWNER'S EXHIBIT LIST**

| <b>Exhibit</b> | <b>Description</b>                                                                                                                                                                                                       |
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| 2010           | Package Insert for Spikevax (COVID-19 Vaccine, mRNA) – 2023-2024 Formula                                                                                                                                                 |
| 2011           | Civil Docket Report for <i>ModernaTX, Inc. et al. v. Pfizer Inc. et al.</i> , C.A. No. 22-11378-RGS (D. Mass.)                                                                                                           |
| 2012           | Complaint, <i>ModernaTX, Inc. et al. v. Pfizer Inc et al.</i> , C.A. No. 22-11378, Dkt. No. 1 (D. Mass, Aug. 26, 2022)                                                                                                   |

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| 2013    | United States District Courts – National Judicial Caseload Profile, Federal Court Management Statistics (June 2023), <a href="https://www.uscourts.gov/sites/default/files/data_tables/fcms_na_distprofile0630.2023.pdf">https://www.uscourts.gov/sites/default/files/data_tables/fcms_na_distprofile0630.2023.pdf</a> |
| 2014    | <i>Reserved</i>                                                                                                                                                                                                                                                                                                        |
| 2015    | Excerpts from Defendants’ Supplemental Patent-Related Disclosures, Exhibit D – Invalidity Contentions of U.S. Patent No. 10,933,127 (June 27, 2023)                                                                                                                                                                    |
| 2016    | <i>Reserved</i>                                                                                                                                                                                                                                                                                                        |
| 2017    | Excerpts from U.S. Patent No. 10,702,599 File History                                                                                                                                                                                                                                                                  |
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| 2040    | 'Heroes of Chemistry' recognized for contributions to health, medicine and more, American Chemical Society (2022)                                                                                                                    |
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| 2058    | Redline Stipulated Protective Order                                                                                                                                |
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| 2060    | Petitioner's Chart (PROTECTIVE ORDER MATERIAL)                                                                                                                     |

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| 2061    | Petitioner's Chart – Redacted                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| 2066    | Jeffrey M. Jacobson et al., <i>Dendritic Cell Immunotherapy for HIV-1 Infection Using Autologous HIV-1 RNA: A Randomized, Double- Blind, Placebo- Controlled Clinical Trial</i> , 72 J. Acquired Immune Deficiency Syndromes 31 (2016).                                                                                                                                                                                                                                                                                                                                                  |
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| 2069    | Carolyn Y. Johnson, <i>Moderna's coronavirus vaccine shows encouraging early results</i> , The Washington Post, Lexis+ (2020).                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

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| 2070    | Moderna, Inc., <i>Patents</i> , <a href="https://www.modernatx.com/en-US/patents">https://www.modernatx.com/en-US/patents</a> [ <a href="https://web.archive.org/web/20231116100458/https://www.modernatx.com/en-US/patents">https://web.archive.org/web/20231116100458/https://www.modernatx.com/en-US/patents</a> ].                                                                                                                                                                                           |
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| 2073    | Declaration of Anastasia Greenberg                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 2074    | Declaration of Kevin S. Prussia                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| 2079    | Chemical Structure of DOTMA (1,2-di-O-octadecenyl-3-trimethylammonium propane)                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 2080    | Chemical Structure of DOTAP (Dioleoyl-3-trimethylammonium propane)                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 2081    | Chemical Structure of Cholesterol                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| Exhibit | Description                                                                                                                                                                                                                                                                                              |
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| 2113    | Deposition of James J. Moon, Ph.D. (May 10, 2024) in <i>BioNTech SE and Pfizer Inc. v. Moderna TX, Inc.</i> , No. IPR2023-01359 (P.T.A.B.)                                                                                                                                                               |
| 2114    | Deposition of Daniel O. Griffin, M.D., Ph.D. (May 22, 2024), in <i>BioNTech SE and Pfizer Inc. v. Moderna TX, Inc.</i> , No. IPR2023-01359 (P.T.A.B.)                                                                                                                                                    |

| Exhibit | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| 2115    | FDA, Vaccines and Related Biological Products Advisory Committee Meeting: FDA Briefing Document, Pfizer-BioNTech COVID-19 Vaccine (Dec. 10, 2020), <a href="https://www.fda.gov/media/144245/download">https://www.fda.gov/media/144245/download</a>                                                                                                                                                                                                                                                                                                          |
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| 2120    | BioNTech SE 2021 Form 20-F                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 2121    | BioNTech SE 2023 Form 20-F                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 2122    | Pfizer Inc. 2021 Form 10-K                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 2123    | Pfizer Inc. 2023 Form 10-K                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 2124    | Moderna, Inc. 2020 Form 10-K                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| 2128    | Pfizer, <i>Pfizer and BioNtech Choose Lead mRNA Vaccine Candidate Against COVID-19 and Commence Pivotal Phase 2/3 Global Study</i> (Jul. 27, 2020), <a href="https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-choose-lead-mrna-vaccine-candidate">https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-choose-lead-mrna-vaccine-candidate</a> |
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| 2139    | <i>Reserved</i>                                                                                                                                                                                                               |
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| 2148    | <i>Reserved</i>                                                                                                                                                                                                               |

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| 2149    | Excerpts from Division of Microbiology and Infectious Diseases (DMID) Protocol (Mar. 30, 2020); MOD_000477134- MOD_000477212 at MOD_000477134- MOD_000477139, MOD_000477148- MOD_000477154                                              |
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| 2166    | Pfizer, <i>Pfizer and BioNTech Celebrate Historic First Authorization in the U.S. of Vaccine to Prevent COVID-19</i> (Dec. 11, 2020), <a href="https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-celebrate-historic-first-authorization">https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-celebrate-historic-first-authorization</a>                                                                                                              |
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| Exhibit | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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| 2175    | Berkeley Lovelace Jr. & Noah Higgins-Dunn, <i>Dr. Anthony Fauci Says Chance of Coronavirus Vaccine Being Highly Effective Is 'Not Great'</i> , CNBC.com (last updated Aug. 8, 2020), <a href="https://www.cnbc.com/2020/08/07/coronavirus-vaccine-dr-fauci-says-chances-of-it-being-highly-effective-is-not-great.html">https://www.cnbc.com/2020/08/07/coronavirus-vaccine-dr-fauci-says-chances-of-it-being-highly-effective-is-not-great.html</a>                                                    |
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| 2183    | Thanyawee Puthanakit et al., <i>Phase II Prefusion Non-Stabilised Covid-19 mRNA Vaccine Randomised Study</i> , 14 Sci. Rep. 1 (2024)                                                                                                                                                                                                                                                                                                      |
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| 2192    | Michael D. Buschmann et al., <i>Chitosans for Delivery of Nucleic Acids</i> , 65 Advanced Drug Delivery Reviews 1234 (2013)                                                                                          |
| 2193    | Julia Steitz et al., <i>Effective Induction of Anti-Melanoma Immunity Following Genetic Vaccination with Synthetic mRNA Coding for the Fusion Protein EGFP.TRP2</i> , 55 Cancer Immunology, Immunotherapy 246 (2006) |
| 2194    | 3.2.S.1.2. Structure CX-038839 Excerpt (PROTECTIVE ORDER MATERIAL)                                                                                                                                                   |
| 2195    | 3.2.P.1. BLA Description and Composition of the Drug Product Excerpt (PROTECTIVE ORDER MATERIAL); MOD_001515874                                                                                                      |
| 2196    | 3.2.S.2.2 BLA Structure of LNP Excerpt (PROTECTIVE ORDER MATERIAL); MOD_000104820                                                                                                                                    |
| 2197    | Declaration of James E. Malackowski                                                                                                                                                                                  |
| 2198    | Declaration of Warren C.W. Chan, Ph.D.                                                                                                                                                                               |
| 2199    | Declaration of Deborah H. Fuller, Ph.D. (PROTECTIVE ORDER MATERIAL)                                                                                                                                                  |
| 2200    | Declaration of Philip Krause, M.D. (PROTECTIVE ORDER MATERIAL)                                                                                                                                                       |
| 2201    | PUBLIC Declaration of Deborah H. Fuller, Ph.D. (redacted version of Ex. 2199)                                                                                                                                        |
| 2202    | PUBLIC Declaration of Philp Krause, M.D. (redacted version of Ex. 2200)                                                                                                                                              |
| 2203    | Spyros Chalkias et al., <i>Interim Report of the Reactogenicity and Immunogenicity of Severe Acute Respiratory Syndrome Coronavirus 2 XBB-Containing Vaccines</i> , J. Infectious Diseases (2024)                    |

| Exhibit | Description                                                                                                                                                                                                                                                                                                             |
|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2204    | Moderna, Fact Sheet for Healthcare Providers Administering Vaccine: Emergency Use Authorization of Moderna COVID-19 Vaccine (2023-2024 Formula), for Individuals 6 Months Through 11 Years of Age (Nov. 1, 2023)                                                                                                        |
| 2205    | Package Insert for Spikevax (COVID-19 Vaccine, mRNA) – 2023-2024 Formula (Apr. 2024)                                                                                                                                                                                                                                    |
| 2206    | Moderna Vaccines and Related Biological Products Advisory Committee Presentation: Moderna COVID-19 Variant Vaccines (June 15, 2023); MOD_000767652-MOD_000767686                                                                                                                                                        |
| 2207    | Juleen Gayed et al., <i>Safety and Immunogenicity of the Monovalent Omicron XBB.1.5-Adapted BNT162b2 COVID-19 Vaccine in Individuals <math>\geq 12</math> Years Old: A Phase 2/3 Trial</i> , 12 Vaccines (Basel) 118 (2024)                                                                                             |
| 2208    | European Medicines Agency, Assessment Report for COMIRNATY (Aug. 30, 2023)                                                                                                                                                                                                                                              |
| 2209    | Package Insert for Comirnaty (COVID-19 Vaccine, mRNA) – 2023-2024 Formula                                                                                                                                                                                                                                               |
| 2210    | Pfizer-BioNTech, Fact Sheet for Healthcare Providers Administering Vaccine: Emergency Use Authorization of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula), for 6 Months Through 11 Years of Age (Sept. 11, 2023); MOD_001483910- MOD_001483970                                                                    |
| 2211    | Kayvon Modjarrad et al., <i>Preclinical Characterization of the Omicron XBB.1.5-Adapted BNT162b2 COVID-19 Vaccine</i> , bioRxiv (2023) (preprint),<br><a href="https://www.biorxiv.org/content/10.1101/2023.11.17.567633v1.full.pdf+html">https://www.biorxiv.org/content/10.1101/2023.11.17.567633v1.full.pdf+html</a> |
| 2212    | Annette B. Vogel et al., <i>BNT162b Vaccines Protect Rhesus Macaques from SARS-CoV-2</i> , 592 Nature 283 (2021)                                                                                                                                                                                                        |

| Exhibit | Description                                                                                                                                                                                                                                                                                                                                                                                              |
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| 2213    | European Medicines Agency, Assessment Report for Comirnaty (Dec. 21, 2020)                                                                                                                                                                                                                                                                                                                               |
| 2214    | Avanti Polar Lipids, ALC-0315 Safety Data Sheet Version 8.1 (Nov. 8, 2022)                                                                                                                                                                                                                                                                                                                               |
| 2215    | Avanti Polar Lipids, ALC-0159 Safety Data Sheet Version 8.1 (May 8, 2024)                                                                                                                                                                                                                                                                                                                                |
| 2216    | Avanti Polar Lipids, Cholesterol Safety Data Sheet Version 5.0 (Nov.15, 2018)                                                                                                                                                                                                                                                                                                                            |
| 2217    | Avanti Polar Lipids, 1,2-distearoyl-sn-glycero-3-phosphocholine Safety Data Sheet Version 5.2 (Nov. 15, 2018)                                                                                                                                                                                                                                                                                            |
| 2218    | European Medicines Agency, Assessment Report for Spikevax (Sept. 14, 2023)                                                                                                                                                                                                                                                                                                                               |
| 2219    | BioNTech, <i>BNT162 COVID-19 Vaccine Program Update</i> , BioNTech: Investors (Apr. 23, 2020), <a href="https://investors.biontech.de/static-files/398d9bd8-e2cb-49ca-9d6d-7dfd01c66b8a">https://investors.biontech.de/static-files/398d9bd8-e2cb-49ca-9d6d-7dfd01c66b8a</a>                                                                                                                             |
| 2220    | Angus Liu, <i>AstraZeneca Withdraws US COVID Vaccine Application, Shifts Focus to Antibody Treatments</i> , Fierce Pharma (Nov. 10, 2022), <a href="https://www.fiercepharma.com/pharma/astrazeneca-withdraws-us-covid-vaccine-application-focus-shifts-antibody-treatments">https://www.fiercepharma.com/pharma/astrazeneca-withdraws-us-covid-vaccine-application-focus-shifts-antibody-treatments</a> |
| 2221    | Kenneth Murphy et al., <i>Janeway's Immunobiology</i> (8th ed. 2012)                                                                                                                                                                                                                                                                                                                                     |
| 2222    | International Patent Publication No. WO 2012/068295                                                                                                                                                                                                                                                                                                                                                      |
| 2223    | U.S. Patent Application Publication No. 2012/0213812                                                                                                                                                                                                                                                                                                                                                     |
| 2224    | U.S. Patent No. 9,271,996                                                                                                                                                                                                                                                                                                                                                                                |
| 2225    | U.S. Patent No. 9,295,689                                                                                                                                                                                                                                                                                                                                                                                |
| 2226    | Leaf Huang & Yang Liu, <i>In Vivo Delivery of RNAi with Lipid-Based Nanoparticles</i> , 13 Ann. Rev. Biomed. Eng'g. 507 (2011)                                                                                                                                                                                                                                                                           |

| Exhibit | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
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| 2227    | Jerome Gillerons et al., <i>Image-Based Analysis of Lipid Nanoparticle-Mediated siRNA Delivery, Intracellular Trafficking and Endosomal Escape</i> , 31 Nature Biotech. 638 (2013)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 2228    | Prasath Paramasivam et al., <i>Endosomal Escape of Delivered mRNA from Endosomal Recycling Tubules Visualized at the Nanoscale</i> , 221 J. Cell Biology e202110137 (2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 2229    | <p><i>Coronavirus (COVID-19) Update: FDA Takes Key Action by Approving Second COVID-19 Vaccine</i> (Jan. 31, 2022),<br/> <a href="https://web.archive.org/web/20220201015913/https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-takes-key-action-approving-second-covid-19-vaccine?fbclid=IwAR0EHTmb6-V8H0m5DWXNvWa-q3DAysdYer8jsk41xuAF6zrMD8bdfTQxvSY">https://web.archive.org/web/20220201015913/https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-takes-key-action-approving-second-covid-19-vaccine?fbclid=IwAR0EHTmb6-V8H0m5DWXNvWa-q3DAysdYer8jsk41xuAF6zrMD8bdfTQxvSY</a></p> <p>[SERVICE ONLY]</p>        |
| 2230    | <p>FDA, <i>Vaccines Licensed for Use in the United States</i> (Apr. 26, 2019),<br/> <a href="https://web.archive.org/web/20190427211808/https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states">https://web.archive.org/web/20190427211808/https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states</a></p> <p>[SERVICE ONLY]</p>                                                                                                                                                                                                                                                                                 |
| 2231    | <p>Moderna, <i>Moderna Announces First Participant Dosed in NIH-Led Phase 1 Study of mRNA Vaccine (mRNA-1273) Against Novel Coronavirus</i> (Mar. 16, 2020),<br/> <a href="https://web.archive.org/web/20240305104415/https://investors.modernatx.com/news/news-details/2020/Moderna-Announces-First-Participant-Dosed-in-NIH-led-Phase-1-Study-of-mRNA-Vaccine-mRNA-1273-Against-Novel-Coronavirus/default.aspx">https://web.archive.org/web/20240305104415/https://investors.modernatx.com/news/news-details/2020/Moderna-Announces-First-Participant-Dosed-in-NIH-led-Phase-1-Study-of-mRNA-Vaccine-mRNA-1273-Against-Novel-Coronavirus/default.aspx</a></p> <p>[SERVICE ONLY]</p> |

| Exhibit | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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| 2232    | <p>Pfizer, <i>Pfizer and BioNTech Dose First Participants in the U.S. as Part of Global COVID-19 mRNA Vaccine Development Program</i> (May 5, 2020),<br/> <a href="https://web.archive.org/web/20240528163740/https://www.pfizer.com/news/press-release/press-release-detail/pfizer_and_biontech_dose_first_participants_in_the_u_s_as_part_of_global_covid_19_mrna_vaccine_development_program">https://web.archive.org/web/20240528163740/https://www.pfizer.com/news/press-release/press-release-detail/pfizer_and_biontech_dose_first_participants_in_the_u_s_as_part_of_global_covid_19_mrna_vaccine_development_program</a><br/>           [SERVICE ONLY]</p>                                                                                                                                  |
| 2233    | <p>Pfizer, <i>Pfizer and BioNtech Choose Lead mRNA Vaccine Candidate Against COVID-19 and Commence Pivotal Phase 2/3 Global Study</i> (Jul. 27, 2020),<br/> <a href="https://web.archive.org/web/20231001125135/https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-choose-lead-mrna-vaccine-candidate">https://web.archive.org/web/20231001125135/https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-choose-lead-mrna-vaccine-candidate</a><br/>           [SERVICE ONLY]</p>                                                                                                                                                                                                                                                        |
| 2234    | <p>Moderna, <i>Moderna Announces FDA Authorization of Moderna COVID-19 Vaccine in U.S.</i> (Dec. 19, 2020),<br/> <a href="https://web.archive.org/web/20221221101553/https://investors.modernatx.com/news/news-details/2020/Moderna-Announces-FDA-Authorization-of-Moderna-COVID-19-Vaccine-in-U.S/default.aspx">https://web.archive.org/web/20221221101553/https://investors.modernatx.com/news/news-details/2020/Moderna-Announces-FDA-Authorization-of-Moderna-COVID-19-Vaccine-in-U.S/default.aspx</a><br/>           [SERVICE ONLY]</p>                                                                                                                                                                                                                                                         |
| 2235    | <p>BioNTech, <i>BioNTech and Pfizer Announce Regulatory Approval from German Authority Paul-Ehrlich-Institut to Commence First Clinical Trial of COVID-19 Vaccine Candidates</i> (Apr. 22, 2020),<br/> <a href="https://web.archive.org/web/20231001095523/https://www.pfizer.com/news/press-release/press-release-detail/biontech_and_pfizer_announce_regulatory_approval_from_german_authority_paul_ehrlich_institut_to_commence_first_clinical_trial_of_covid_19_vaccine_candidates">https://web.archive.org/web/20231001095523/https://www.pfizer.com/news/press-release/press-release-detail/biontech_and_pfizer_announce_regulatory_approval_from_german_authority_paul_ehrlich_institut_to_commence_first_clinical_trial_of_covid_19_vaccine_candidates</a><br/>           [SERVICE ONLY]</p> |

| Exhibit | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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| 2236    | <p>Moderna, <i>Moderna Announces Positive Interim Phase 1 Data for Its mRNA Vaccine (mRNA-1273) Against Novel Coronavirus</i> (May 18, 2020),<br/> <a href="https://web.archive.org/web/20230927221332/https://investors.modernatx.com/news/news-details/2020/Moderna-Announces-Positive-Interim-Phase-1-Data-for-its-mRNA-Vaccine-mRNA-1273-Against-Novel-Coronavirus/default.aspx">https://web.archive.org/web/20230927221332/https://investors.modernatx.com/news/news-details/2020/Moderna-Announces-Positive-Interim-Phase-1-Data-for-its-mRNA-Vaccine-mRNA-1273-Against-Novel-Coronavirus/default.aspx</a><br/>           [SERVICE ONLY]</p>   |
| 2237    | <p>Pfizer, <i>Pfizer and BioNTech Celebrate Historic First Authorization in the U.S. of Vaccine to Prevent COVID-19</i> (Dec. 11, 2020),<br/> <a href="https://web.archive.org/web/20240221190048/https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-celebrate-historic-first-authorization">https://web.archive.org/web/20240221190048/https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-celebrate-historic-first-authorization</a><br/>           [SERVICE ONLY]</p>                                                                                                              |
| 2238    | <p>Fraiser Kansteiner, <i>It's the End of the Line for J&amp;J's COVID Shot in the US, CDC Says</i>, Fierce Pharma (May 16, 2023),<br/> <a href="https://web.archive.org/web/20240521135506/https://www.fiercepharma.com/pharma/its-end-line-jjs-covid-shot-us-cdc-says">https://web.archive.org/web/20240521135506/https://www.fiercepharma.com/pharma/its-end-line-jjs-covid-shot-us-cdc-says</a><br/>           [SERVICE ONLY]</p>                                                                                                                                                                                                                |
| 2239    | <p>Novavax, <i>U.S. FDA Grants Emergency Use Authorization for Novavax COVID-19 Vaccine, Adjuvanted for Individuals Aged 18 and Over</i> (July 13, 2022),<br/> <a href="https://web.archive.org/web/20240510233937/https://ir.novavax.com/press-releases/2022-07-13-U-S-FDA-Grants-Emergency-Use-Authorization-for-Novavax-COVID-19-Vaccine%2C-Adjuvanted-for-Individuals-Aged-18-and-Over">https://web.archive.org/web/20240510233937/https://ir.novavax.com/press-releases/2022-07-13-U-S-FDA-Grants-Emergency-Use-Authorization-for-Novavax-COVID-19-Vaccine%2C-Adjuvanted-for-Individuals-Aged-18-and-Over</a><br/>           [SERVICE ONLY]</p> |

| Exhibit | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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| 2240    | <p>Morgan Frey, <i>Pharma Peers Cheer Moderna's Unexpectedly Strong COVID-19 Vaccine Results</i>, S&amp;P Global Market Intelligence (Nov. 16, 2020), <a href="https://web.archive.org/web/20201124071818/https://www.spglobal.com/marketintelligence/en/news-insights/latest-news-headlines/pharma-peers-cheer-moderna-s-unexpectedly-strong-covid-19-vaccine-results-61302444">https://web.archive.org/web/20201124071818/https://www.spglobal.com/marketintelligence/en/news-insights/latest-news-headlines/pharma-peers-cheer-moderna-s-unexpectedly-strong-covid-19-vaccine-results-61302444</a></p> <p>[SERVICE ONLY]</p> |
| 2241    | <p>CureVac, <i>CureVac Provides Update on Phase 2b/3 Trial of First-Generation COVID-19 Vaccine Candidate, CVnCoV</i> (June 16, 2021), <a href="https://web.archive.org/web/20240520142553/https://www.curevac.com/en/curevac-provides-update-on-phase-2b-3-trial-of-first-generation-covid-19-vaccine-candidate-cvncov/">https://web.archive.org/web/20240520142553/https://www.curevac.com/en/curevac-provides-update-on-phase-2b-3-trial-of-first-generation-covid-19-vaccine-candidate-cvncov/</a></p> <p>[SERVICE ONLY]</p>                                                                                                |
| 2242    | <p>Angus Liu, <i>AstraZeneca Withdraws US COVID Vaccine Application, Shifts Focus to Antibody Treatments</i>, Fierce Pharma (Nov. 10, 2022), <a href="https://web.archive.org/web/20240516162312/https://www.fiercepharma.com/pharma/astrazeneca-withdraws-us-covid-vaccine-application-focus-shifts-antibody-treatments">https://web.archive.org/web/20240516162312/https://www.fiercepharma.com/pharma/astrazeneca-withdraws-us-covid-vaccine-application-focus-shifts-antibody-treatments</a></p> <p>[SERVICE ONLY]</p>                                                                                                      |
| 2243    | <p>Chemical Structure of DOTMA</p> <p>[SERVICE ONLY]</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 2244    | <p>Chemical Structure of DOTAP</p> <p>[SERVICE ONLY]</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 2245    | <p>Chemical Structure of Cholesterol</p> <p>[SERVICE ONLY]</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

| Exhibit | Description                                                                                                                                                                                                                                                                                                                                                                                         |
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| 2246    | FDA, <i>Vaccines Licensed for Use in the United States</i> (last updated Dec. 1, 2023)<br><a href="https://web.archive.org/web/20240523161036/https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states">https://web.archive.org/web/20240523161036/https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states</a><br>[SERVICE ONLY] |
| 2247    | Declaration of Wenli Gu regarding Exhibits 2079-2081, 2086-2087, 2100, 2104, 2115-2116, 2126-2129, 2144-2145, 2154, 2158-2160, 2163-2164, 2166, 2173-2178, 2184-2185, 2204-2206, 2209-2211, 2214-2217, 2219-2220, 2229-2246<br>[SERVICE ONLY]                                                                                                                                                       |
| 2248    | Declaration of Aaron Fier regarding Exhibits 2194-2196<br>[SERVICE ONLY]                                                                                                                                                                                                                                                                                                                            |
| 2249    | Declaration of Annaleigh E. Curtis                                                                                                                                                                                                                                                                                                                                                                  |
| 2250    | Declaration of Andrew J. Danford                                                                                                                                                                                                                                                                                                                                                                    |
| 2251    | Declaration of Claire M. Specht                                                                                                                                                                                                                                                                                                                                                                     |
| 2252    | <i>Reserved</i>                                                                                                                                                                                                                                                                                                                                                                                     |
| 2253    | Deposition of Daniel O. Griffin, M.D., Ph.D. (September 20, 2024) in <i>BioNTech SE and Pfizer Inc. v. Moderna TX, Inc.</i> , No. IPR2023-01359 (P.T.A.B.)                                                                                                                                                                                                                                          |
| 2254    | Deposition of James J. Moon, Ph.D. (September 13, 2024) in <i>BioNTech SE and Pfizer Inc. v. Moderna TX, Inc.</i> , No. IPR2023-01359 (P.T.A.B.)                                                                                                                                                                                                                                                    |
| 2255    | Deposition of W. Christopher Bakewell (October 3, 2024) in <i>BioNTech SE and Pfizer Inc. v. Moderna TX, Inc.</i> , No. IPR2023-01359 (P.T.A.B.)                                                                                                                                                                                                                                                    |
| 2256    | Deposition of L. Ross Pierce, M.D. (October 4, 2024) in <i>BioNTech SE and Pfizer Inc. v. Moderna TX, Inc.</i> , No. IPR2023-01359 (P.T.A.B.) (PROTECTIVE ORDER MATERIAL)                                                                                                                                                                                                                           |

| Exhibit | Description                                                                                                                                                                         |
|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2257    | PUBLIC Deposition of L. Ross Pierce, M.D. (October 4, 2024) in <i>BioNTech SE and Pfizer Inc. v. Moderna TX, Inc.</i> , No. IPR2023-01359 (P.T.A.B.) (redacted version of Ex. 2256) |

## I. Introduction

The Petition contains no evidence that, before Moderna's invention, anyone else had tested an mRNA-LNP vaccine, let alone against betacoronavirus. Instead, the field contained a myriad of combinations of different, non-interchangeable vaccine technologies, delivery methods, and immunogens. Petitioners bear the burden of proving that, in an unpredictable field, the claimed combination was disclosed or would have been obvious. They have not carried it.

Moderna has shown—through the testimony of experts, including a preeminent nucleic acid scientist, Dr. Deborah Fuller, and supported by contemporaneous documentary evidence—that the logic of the Grounds is fundamentally flawed.

For anticipation, Petitioners arrive at the claims only by impermissible picking and choosing from a laundry list of potential combinations in two different references and assuming their results.

For obviousness, Petitioners rely on *different*, non-interchangeable technologies and immunogens to augur success with the claimed combination. They rely on conclusory testimony, not from a nucleic acid scientist, but from other POSA “team” members lacking relevant expertise. Faced with the scientific reality that wholesale extrapolation from one type of vaccine technology or immunogen to another is impossible, Petitioners have morphed their Petition theories in ways that

render them untenable.<sup>1</sup> The record confirms a POSA would not have reasonably expected the claimed mRNA-LNP construct would be successful with betacoronavirus S-protein based on results from different nucleic acid vaccines, as each Ground posits.

It was Moderna's pioneering work that led to the claimed inventions Petitioners reach only through hindsight. Paper 42 ("POR"), 2-3, 23-25, 51-52. With no dispute Moderna's and Petitioners' COVID-19 vaccines practice the claims (Ex. 2200, App'x C-F), filled significant unmet need, received widespread praise, and achieved unprecedented commercial success, the claims are patentable and should be upheld.

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<sup>1</sup> Petitioners no longer rely on Geall or Altmeyer for mRNA vaccines or Geall for LNPs. Paper 59 ("Reply"), 10; Ex. 2253, 13:3-11, 29:4-30:11, 32:21-33:3. Petitioners' change is apparently driven by their inconsistent statements. Whereas Petitioners here claimed Geall discloses mRNA and LNPs (Paper 1 ("Petition"), 17 n.8, 39; Paper 14, 2-3; Ex. 1002, ¶¶112 n.186, 196; Ex. 1004, ¶¶93, 96), when sued by GlaxoSmithKline on patents issued to Dr. Geall with overlapping disclosures, Petitioners represented the opposite (Ex. 1312, 80, 85-86, 89-90, 96-98, 100-101; *see* Ex. 1311, 2:15-16, 3:16-17, 4:17-20, 22:17-19, 23:28-41:5; Ex. 1313, 104-148).

## II. The Parties' Declarants

Petitioners' declarant Dr. Griffin is an infectious disease physician (Ex. 1159, ¶16), not an mRNA scientist. Dr. Griffin has no experience extrapolating results between nucleic acid technologies (*e.g.*, from DNA or saRNA to mRNA)—which is the premise of Grounds 2-4. Ex. 2253, 8:20-9:18, 109:13-16, 111:9-20, 125:10-16; Ex. 1305, 1-24. Dr. Fuller is the **only** declarant with such expertise. *E.g.*, Ex. 1104, 266:2-275:17. Dr. Griffin's conclusory declarations should be given little, if any, comparative weight.

## III. Claim Construction

Petitioners wrongly suggest Moderna's constructions are "unnecessary." Reply, 2.<sup>2</sup>

**mRNA.** The patent's statement "mRNA of the invention are **not** self-replicating RNA" (Ex. 1001, 40:22-44<sup>3</sup>) limits the claims. Despite this definition, Petitioners state "self-amplifying mRNA is a type of mRNA" (Reply, 2) and cite saRNA disclosures (*id.*, 4-8). Construction is necessary because Petitioners' arguments contradict this lexicography.

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<sup>2</sup> Petitioners do not dispute Moderna's construction of S-protein subunit or assert prior art disclosure of an S-protein subunit. Reply, 3, 10-12.

<sup>3</sup> Emphasis added unless stated.

**S-protein.** Petitioners present two disputes. First, in a footnote (Reply 3, n.3), Petitioners attempt to avoid *their own proposed construction*—which is *agreed*—that S-protein must “form[] a spike.” Petition, 19 (proposing “structural protein forming a spike”). This language does not “clarif[y]” (Reply, 3 n.3) the claims are directed to S-protein, which the claims already recite. Instead, the district court adopted it following *Petitioners’ request* to add functional claim language. Ex. 1035, 11-12.

Second, Petitioners dispute Moderna’s position that the term “S protein” also requires a full-length spike protein. The claims recite S-protein and/or S-protein subunit. *E.g.*, Ex. 1001, cls. 1-5. Petitioners argue “S protein” includes any spike-related immunogen. Reply, 3. This is illogical, as S-protein subunits are such spike-related immunogens but are separately claimed. *Wasica Finance GmbH v. Continental Automotive Sys., Inc.*, 853 F.3d 1272, 1288, n.10 (Fed. Cir. 2017) (construction rendering term “superfluous” “disfavored”). Instead, because the specification refers to “full-length Spike (S) protein,” includes figures and data for *full-length* spike, and recites only working examples, amino acid sequences, and nucleic acid sequences with *full-length* S-protein (or S2 subunit), S-protein should be construed as “full-length.” Ex. 1001, 7:30-34, 24:56-25:2, 25:14-23, 217:41-218:39, Tables 10-12. Petitioners’ other arguments also fail. The patent discusses “S protein (S, S1 and/or S2),” as opposed to *other* proteins (*e.g.*, N, E).

*See, e.g.*, Ex. 1001, 35:9-12, 35:19-21, 35:64-36:28; Ex. 2199, ¶¶159-170. And though the patent does not recite “full-length” every time, all its substantive disclosure relates to full-length and makes no reference to “truncated” S-protein. This construction distinguishes Geall’s undefined “spike polypeptide” and Yang’s truncated S-proteins. *Infra* §§IV.A, V.A.

#### **IV. Ground 1: Schrum Does Not Anticipate the Challenged Claims**

The Petition’s conclusory analysis did not show Schrum anticipates. Paper 18 (“DI”), 85-86. Petitioners’ new—and, therefore, improper—Reply arguments still fail to show Schrum discloses the claimed betacoronavirus S-protein, the required immune response/neutralizing antibodies, or the elements as arranged in the claims, and the Reply makes no “envisage” argument. Reply, 4<sup>4</sup>; *cf. Microsoft*

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<sup>4</sup> Petitioners’ citations to large expert declaration sections—*e.g.*, Reply, 12-13, 20, 23-24, 28—advancing arguments not in the Reply should be disregarded. 37 C.F.R. §42.6(a)(3); *3M Co. v. Evergreen Adhesives, Inc.*, 860 F. App’x 724, 727-728 (Fed. Cir. 2021).

*Corp. v. Biscotti, Inc.*, 878 F.3d 1052, 1068 (Fed. Cir. 2017). The claims are not anticipated.<sup>5</sup>

**A. Schrum Does Not Disclose the Claimed S-Protein.**

Petitioners do not argue Schrum itself discloses any betacoronavirus immunogen. And even if Schrum incorporated Geall's immunogens (it does not<sup>6</sup>), Geall's statement that "[t]he coronavirus immunogen may be a spike polypeptide" (Ex. 1010, 19:28-29) is insufficiently specific to anticipate.

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<sup>5</sup> Petitioners' suggestion (Reply, 4 n.4) the POR only addresses two claims is incorrect. POR, 12, 25, 52, 57 (each citing Ex. 2199); *id.*, 18, 26, 28, 30, 53, 59 (each addressing claims 1, 3, 17); *id.*, 21, 29 (each addressing claims 11, 12, 13, 20).

<sup>6</sup> Petitioners' argument that Schrum "incorporates Geall for **[Geall's]** disclosure that modified mRNA 'encoding an immunogen may be delivered...in a dose large enough to be immunogenic'" (Reply 6-7) is wrong. Schrum does not incorporate "mRNA encoding immunogens" in **Geall**, but references mRNA **in Schrum** and **doses** from Geall. Ex. 1009, ¶342; POR, 15-17; Ex. 1104, 236:9-239:3; *cf. Cook Biotech Inc. v. Acell, Inc.*, 460 F.3d 1365, 1376 (Fed. Cir. 2006) (interpreting "expressly incorporated herein by reference" as limited-purpose). Schrum makes similar limited-purpose incorporations throughout. *E.g.*, Ex. 1009, ¶¶57, 342, 346, 458.

**First**, Geall does not specify “full-length” spike polypeptide. As Dr. Griffin concedes, when Geall intends to refer to “full-length” protein, it does so. Ex. 2253, 87:21-89:2, 91:6-21, 99:22-100:4; Ex. 1010, 29:9-13, 32:17-18, 34:11-12, 40:14-16. Geall does not disclose whether its “spike polypeptide” is truncated, a subunit, or something else. Ex. 1010, 19:26-29; Ex. 2199, ¶¶259, 494-495.

**Second**, proteins do not inherently form (Ex. 2253, 48:4-16, 49:2-12, 68:4-69:1; Ex. 1104, 78:17-79:2). Accordingly, without data, Geall does not disclose a “structural protein forming a spike.” Ex. 2199, ¶¶245-252; Ex. 1010, 29:1-43:9. Petitioners’ unsupported conclusion that “administering mRNA encoding for a betacoronavirus spike protein would result in expression of a protein that forms ‘spikes’” (Reply, 8) is contrary to Dr. Griffin’s admissions that proteins can fail to express or misfold and that determining proper formation requires testing. Ex. 2253, 48:4-16, 49:2-12, 68:4-69:1; Ex. 1104, 78:17-79:2.

**B. Schrum Does Not Disclose the Claimed Immune Response or Claim 3’s Neutralizing Antibodies.**

Schrums’ **goal** of a vaccine “immune response” (Reply, 4-6, 9) does not disclose that one was **achieved**. As Dr. Griffin concedes, testing is required to identify the amount of mRNA encoding a given protein needed to induce an immune response. Ex. 2253, 62:12-64:1, 68:4-69:1, 143:20-144:5; Ex. 1104, 119:15-122; Ex. 1010, 29:1-43:9 (RSV-F only). Petitioners cite no example or data in Schrum

(or Geall) of neutralizing antibody generation to a betacoronavirus immunogen as claim 3 requires. Ex. 2114, 211:6-214:1; Ex. 1010, 29:1-43:9; Ex. 2199, ¶¶337-339.

**C. Petitioners Pick and Choose.**

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

Contrary to Petitioners’ argument, Schrum/Geall do not contain only a “single list.” Reply, 9-10. Schrum/Geall disclose broad genera from which one would have to pick and choose, at least (1) nucleic acid technology; (2) delivery method; and (3) immunogen. POR, 23-25; Ex. 1104, 222:19-223:22, 225:15-226:7. Nothing in Schrum connects an mRNA-LNP vaccine specifically,<sup>7</sup> and Petitioners must rely on

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<sup>7</sup> Petitioners newly suggest Schrum’s paragraph 397 connects separate embodiments to form an mRNA-LNP infectious disease vaccine because the second embodiment refers to “the” LNP. Reply, 5-6. But paragraph 397 refers to **modified** RNA (of which there are many types, see Ex. 2198, ¶¶100-101 (saRNA, RNAi, siRNA, etc.)), not **messenger** RNA; the second embodiment does not specify a payload; and paragraph 397 does not identify any infectious disease. POR, 21-23.

picking one of over 500 disparate immunogens from Geall. Contrary to Petitioners' argument otherwise (Reply, 10), Geall identifies other coronavirus genera and other coronavirus immunogens, *e.g.*, envelope protein. Ex. 1010, 16:6-7, 19:26-29; Ex. 1002, ¶72; Ex. 2114, 104:12-106:8; Ex. 2199, ¶¶294-295. Regardless, even if Petitioners were right that "S-protein is the sole betacoronavirus immunogen" Geall identifies (Reply, 10), that does not mean Schrum **directs** a POSA to betacoronavirus immunogens. It does not. Geall identifies **hundreds** of other immunogens spanning a wide taxonomy. Ex. 1010, 15:3-22:35; Ex. 2199, ¶¶287-289.

The many options in Schrum/Geall are not in a "recognizable class with common properties." *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1084 (Fed. Cir. 2008). Unlike *Incept LLC v. Palette Life Sciences*, 77 F.4th 1366 (Fed. Cir. 2023), where the art provided options **with claimed characteristics**, here, the options span unclaimed immunogens, nucleic acid technology, and delivery methods.

#### **V. Grounds 2-4 Do Not Establish Obviousness.**

In October 2015, the field was unpredictable. It was understood that vaccine platforms and proteins were not interchangeable, there was no data showing delivery of mRNA encoding a protein as large as the S-protein, and there were extensive failures. There was no "efficacy data or any other reliable indicator of success" for an mRNA vaccine encoding a betacoronavirus S-protein in an LNP, let alone one generating an immune response/neutralizing antibodies. *OSI Pharms. LLC v. Apotex*

*Corp.*, 939 F.3d 1375, 1385 (Fed. Cir. 2019). Compounding the lack of data or indicator of success, a POSA would have faced significant skepticism, disease enhancement risk with S-protein-based vaccines, and reasons not to use LNPs. Petitioners cannot show obviousness in this context.<sup>8</sup>

**A. The Grounds Have Insurmountable Gaps.**

Petitioners now rely only on Schrum for mRNA-LNP vaccines, and Geall, Yang, or Altmeyer for S-protein. Reply, 10. However, the latter three references relate to *different* technologies:

| Reference | Vaccine Technology              | Delivery Method                                                                       |
|-----------|---------------------------------|---------------------------------------------------------------------------------------|
| Geall     | saRNA                           | Liposomes, CNE, Polymeric Nanoparticles, Virion-Packaged Replicon, Naked <sup>9</sup> |
| Yang      | DNA                             | Naked <sup>9</sup>                                                                    |
| Altmeyer  | Protein & Non-mRNA Nucleic Acid | Naked, <sup>9</sup> Alum                                                              |

Ex. 1010, 12:6-27, 29:29-38:6, 40:14-16; Ex. 1011, 561-562, Ex. 1012, ¶¶9-36, 114-131; Ex. 2198, ¶¶146-153; 208; 211; Ex. 2199, ¶¶197-223; POR, §V.

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<sup>8</sup> Moderna addressed all claims. *See supra* n.5.

<sup>9</sup> Using buffer only.

None contains relevant S-protein data. **Geall's** data concerns RSV-F or reporter proteins. POR, 10; Ex. 1010, 29:1-43:9; Ex. 2199, ¶¶200-202, 247-251, 494-495; Ex. 1104, 239:14-20. Geall does not disclose immune response/neutralizing antibodies of claims 1, 3, and 17. *Supra* §IV.B. **Yang** does not (as Petitioners suggest, Reply, 11) report full-length S-protein data. Ex. 2114, 228:15-22, 229:11-18, 230:19-231:7. Yang references a full-length S-protein *schematic*, but discloses data only for naked DNA encoding *truncated* S-proteins. Ex. 1011, 561, Figs. 1-4; Ex. 2199, ¶¶788-810. **Altmeyer** does not teach mRNA vaccines or LNPs or contain data attributed to nucleic acid vaccine(s) using spike protein. Ex. 1012, ¶¶114-131; Ex. 2199, ¶¶215-223, 956-986.

Petitioners have not shown a POSA would have expected the claimed combination to have its desirable properties, such as inducing an immune response/neutralizing antibodies. *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1362 (Fed. Cir. 2007); *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000).

**B. A POSA Would Not Have Been Motivated to Combine with Reasonable Expectation of Success.**

**1. The Grounds Contain No Data or Reliable Indicator of Success.**

Petitioners concede no asserted reference contains data attributed to (1) any mRNA-LNP vaccine or (2) any nucleic acid vaccine encoding full-length

betacoronavirus spike. Instead, Petitioners and their declarants summarily conclude a POSA would have had a reasonable expectation of success with an mRNA-LNP betacoronavirus vaccine based on *different* nucleic acid technologies, delivery methods, and proteins. The prior art, however, provided no data or reliable indicator the claimed combination would have its desirable properties. *OSI*, 939 F.3d at 1385; *Takeda*, 492 F.3d at 1362; *Yamanouchi*, 231 F.3d at 1345.

**a. It Was Known Vaccine Technologies and Delivery Methods Were Not Interchangeable.**

Petitioners' obviousness arguments rest on extrapolating results from non-mRNA vaccine technologies—like saRNA (Geall),<sup>10</sup> DNA (Yang), or protein and non-mRNA nucleic acid (Altmeyer)<sup>11</sup>—to make predictions about mRNA-LNP. But Petitioners, bearing the burden, adduce no evidence anyone did or would successfully make such extrapolation. The evidence establishes that jumping successfully from other platforms to mRNA had never been done and was unpredictable. POR, 31-37, 54-56, 59. Indeed, Dr. Geall's group showed in

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<sup>10</sup> Dr. Griffin confirmed Geall does not disclose the claimed mRNA. Ex. 2253, 12:1-9, 29:4-15; POR, 16-17.

<sup>11</sup> Altmeyer does not report results attributed to the non-mRNA nucleic acid vaccine. POR, 57-59.

December 2014 (Exhibit 2005) that saRNA, mRNA, and DNA vaccines targeting the **same** RSV-F protein or HIV protein yielded **different** immune responses, and mRNA **failed**. Ex. 2005, 2119-2122, Figs. 2-3; Ex. 2199, ¶¶552-565.<sup>12</sup> Moreover, varying delivery method also led to different results. Ex. 1010, 40:14-42:15; Ex. 2198, ¶153 (different results in Geall for RSV-F saRNA vaccine formulated in CNE compared to liposomes); Ex. 1104, 48:17-49:7. And, as discussed further below, a POSA would have known disease enhancement results vary across vaccine technologies. Ex. 2030; Ex. 1011; *infra* §V.B.2.b. Dr. Fuller has performed head-to-head comparisons that confirm saRNA, DNA, and mRNA are not interchangeable and lead to different, unpredictable results. Ex. 1104, 266:2-275:17, 24:19-25:15, 26:2-16, 27:2-22. Dr. Griffin has never performed such work and could not respond to Dr. Fuller on this critical point. Ex. 2253, 109:13-16, 111:16-20, 125:10-16.

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<sup>12</sup> Brito's reference to dosing as a cause (Ex. 2005, 2124; DI, 65) was, as Dr. Griffin admitted, just "speculation." Ex. 2253, 53:10-19. Dr. Fuller explained dosing "does not resolve the lack of interchangeability" because: (1) Brito administered 1000x the amount of mRNA (that failed to elicit a response) versus the saRNA amount that elicited a response; and (2) the 15µg mRNA dose is above the upper limit for which one would expect a response in mice. Ex. 2199, ¶557.

The Federal Circuit has consistently rejected arguments, like Petitioners', that premise reasonable expectation of success on extrapolating results from one technology to another. *See Eli Lilly & Co. v. Teva Pharms. Int'l, GmbH*, 8 F.4th 1331, 1346-1347 (Fed. Cir. 2021); *Novartis Pharms. Corp. v. West-Ward Pharms. Int'l Ltd.*, 923 F.3d 1051, 1060-1062 (Fed. Cir. 2019); *see also Eli Lilly & Co. v. Teva Pharms. Int'l, GmbH*, IPR2018-01710, Paper 69, 139-143 (P.T.A.B. Mar. 31, 2020) (“[A] jump from one molecule to another may result in a lack of a reasonable expectation of success in an area with uncertainty[.]”). Petitioners' arguments fail for similar reasons.

**First**, Petitioners simply assume results with DNA vaccines will “necessarily” apply to mRNA vaccines because mRNA is transcribed from DNA and mRNA may have a “more efficient cellular pathway.” Reply, 22-23. But unlike mRNA transcribed from DNA vaccines **after** the DNA vaccine has been successfully delivered to cells, mRNA of an mRNA vaccine must, itself, be delivered to cells. Successfully delivering exogenous mRNA to cells to achieve protein expression and adaptive immune responses presented unique challenges. DNA was known to be **more stable** and **less innately immunogenic** than mRNA, with higher likelihood of successful delivery, expression, and immune response generation. *See* Ex. 1016, 156; Ex. 2027, 261; Ex. 2132, 776, 780-781; Ex. 1104, 33:3-20, 91:11-18; Ex. 2199, §XI.A.3.c. These differences were not just hypothesized, but demonstrated in

pre-priority studies where mRNA vaccines yielded different (worse) results than DNA, even with the same immunogen. *Supra* pp.13-14 (citing Ex. 2005, 2119); Ex. 2005, Fig. 2a; Ex. 2199, ¶837 (Dr. Fuller explaining pre-2015 “focus[] on DNA vaccines where the immunogenicity results were stronger” versus mRNA); Ex. 1104, 32:3-33:20.

**Second**, Petitioners wrongly suggest expressing protein and provoking an immune response via a nucleic acid vaccine is inherent. Reply, 20-23. Just because mRNA is potentially **capable** of expressing a protein, does not mean it necessarily **will** express it. Reply, 20. As Dr. Griffin testified, proteins do not always express and may misfold (*supra* §IV.A), and mRNA vaccines were known to suffer from “limited potency.” Ex. 1016, 154; Ex. 2199, ¶¶576-579, 837; Ex. 1104, 32:3-33:20, 78:17-79:2, 194:13-196:9.<sup>13</sup>

Petitioners also seriously misrepresent Dr. Fuller’s testimony. Reply, 20-23. Dr. Fuller did **not** testify that any attempted S-protein vaccine will necessarily induce an immune response, as Petitioners’ selective quotation suggests. Dr. Fuller testified

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<sup>13</sup> That some vaccines **sometimes** generate immune responses (Reply 21) is not enough for inherency, or reasonable expectation of success, with different claimed technology, particularly given known risks. See Ex. 1031, 229-230 (disease enhancement risk); *infra* §V.B.2.b.

that once it has been “**validate[d]** that [a DNA or RNA vaccine] expresses a protein in vitro,” it leads to a **hypothesis** it will express in vivo. Ex. 1104, 51:17-52:9; see also *id.*, 45:16-46:11, 49:17-50:19. Here, the asserted prior art contains **no data** for any mRNA-LNP vaccine expressing any immunogen, let alone a protein as large as betacoronavirus S-protein. Ex. 2199, ¶¶576-579; Ex. 2253, 73:4-76:16.

**Third**, Petitioners misleadingly suggest Dr. Fuller looked at results from other vaccine technologies in developing a SARS-CoV-2 vaccine. Reply, 13. Petitioners omit that, in this post-priority experience developing an saRNA vaccine, Dr. Fuller simply did a literature review on coronaviruses. Ex. 1104, 44:11-45:4. Dr. Fuller did **not** testify that different vaccine technologies were predictive of each other, but the opposite. Ex. 1104, 269:17-271:9 (discussing differences that “would result in a potentially entirely different immune response”); Ex. 2199, ¶¶551-565.

**Last**, Petitioners wrongly argue Moderna represented to the FDA that results in DNA/saRNA were predictive of results in mRNA. This ignores Dr. Krause’s testimony that the cited post-priority statements were made (1) to educate potential investigators primarily about safety—not predicted success—of a potential mRNA vaccine; and (2) primarily using Moderna’s own, non-public mRNA-LNP vaccine platform data. POR, 37-39, 55-56; Ex. 1105, 37:13-38:14; Ex. 2256, 16:17-17:15, 20:16-21:10, 24:1-5, 47:5-49:4, 66:11-19. Indeed, the documents explicitly state

“

██████████” Ex. 2146, 13, 18-19, 28-29; Ex. 2147, 16-18; *cf.* Ex. 2151, 17-18, 20-22, Fig. 1; Ex. 1105, 42:7-44:15, 49:5-12. Petitioners misrepresent Dr. Krause’s declaration as saying “the words in [Moderna’s] FDA submissions may be ignored.” Reply, 23-24. He said the ***opposite***—Moderna’s words must be read in context. Ex. 2200 ¶¶41, 66-89, 100-115, 121-137.

**b. It Was Known Protein Choice Was Not Interchangeable.**

Geall (Ground 2) only includes data with RSV-F protein, and Yang (Ground 3) only includes data with truncated S-protein. Petitioners’ Reply does not respond to evidence that varying the vaccine’s protein choice (holding other elements constant)—as would have been required to get to the claims’ betacoronavirus S-protein—yielded ***different results***. POR, 32-33; Ex. 2199, ¶¶552, 566-573. This had been demonstrated across nucleic acid vaccines. Ex. 2025, 1213, Fig. 4a-b; Ex. 2088, 151, 153-154; Ex. 2089, 4949-4950, 4953, 4957.<sup>14</sup>

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<sup>14</sup> Dr. Yang’s group found DNA vaccines encoding full-length S-protein—but not truncated S-protein—caused enhanced disease. Ex. 2137, 797-800, Fig. 1b, Fig 4a; Ex. 2138; Ex. 2199, ¶¶593-598; Ex. 2114, 245:8-18; Ex. 1011, 563.

**c. No Teaching of Successful Delivery of mRNA  
Encoding Protein as Large as S-Protein.**

Because S-protein is large (over two times larger than RSV-F and influenza hemagglutinin), POSAs understood it was difficult to translate using mRNA. Ex. 2199, ¶¶252, 576-579, 680-682. There is no prior-art teaching of delivering any mRNA encoding a protein as large as S-protein. Ex. 2253, 73:4-76:16.<sup>15</sup> Instead, known stability/immunogenicity issues with mRNA would have made expressing and forming the large S-protein unpredictable. Ex. 2199, ¶¶513-514, 576-579; Ex. 2253, 47:1-49:12; Ex. 1104, 32:3-33:20, 194:13-196:9; Ex. 1105, 97:9-105:17, 111:8-113:15.

**d. Evidence of Failure Defeats Reasonable Expectation  
of Success.**

By 2015, no mRNA vaccine was approved for infectious disease. Ex. 2027, 268. Of thousands of infectious disease vaccine clinical trials, only seven were testing mRNA vaccines. Ex. 2084, Table 6; Ex. 2027, 268, Table 2. None tested betacoronavirus, none was formulated in LNP, and all ultimately *failed*, even those encoding for immunogens (rabies, HIV) on Geall's laundry list. Ex. 2084, 187; Ex. 2027, 267-268; Ex. 2043, 2; Ex. 2046, 7-8; Ex. 2044, 7; Ex. 2085, 250-252; Ex.

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<sup>15</sup> Dr. Griffin stated *saRNA* encoding RSV-F is larger (Ex. 1159, ¶44), but admitted he conflated nucleic acid size with encoded protein size. Ex. 2253, 73:4-76:16.

2199, ¶¶513-528; Ex. 1010, 19:21-22, 20:1-2; Ex. 2253, 24:21-25:20 (Dr. Griffin: POSA would consider that particular immunogens were unsuccessful with mRNA). “[T]he only reasonable expectation at the time of the invention was failure, not success.” *OSI*, 939 F.3d at 1385.

Petitioners’ argument that clinical efficacy is not required for reasonable expectation of success (Reply, 23) is a red-herring. The skepticism in the art (with corresponding failures) and absence of *any* indicator of success defeat reasonable expectation of success.<sup>16</sup> *See Eli Lilly*, 8 F.4th at 1356 (unpredictability “‘equates...with nonobviousness’”).

**e. No Reasonable Expectation of Success for Claim 3.**

Claim 3 requires administering an effective amount that generates neutralizing antibodies. Ex. 1001, cl.3; *see* Ex. 1104, 154:6-17, 254:16-257:10. Dr. Griffin conceded identifying an effective amount to induce an immune response: (1) varies based on nucleic acid technology, protein choice, and delivery method; and (2) requires testing. Ex. 2253, 62:14-64:1, 143:20-144:5; *see also* Ex. 1104, 45:16-46:11. The Grounds contain no data with an mRNA-LNP vaccine at all, let

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<sup>16</sup> *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013) is inapposite—Moderna does not argue lack of reasonable expectation due to difficulty in developing Spikevax®.

alone data supporting expectation of neutralizing antibodies to S-protein. *Supra* §V.A.

## **2. A POSA Would Have Had Reasons Not to Combine.**

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

### **a. Skepticism of mRNA Vaccines for Infectious Diseases**

The POR provides evidence of lack of success and skepticism with mRNA vaccines. POR, 41-44; Ex. 2199, ¶¶513-528; Ex. 1104, 128:22-129:20.<sup>17</sup> Petitioners' two responses fail. First, Petitioners' citation to a small number of potentially "promising" studies (Reply, 17-18) ignores they taught protamine or other adjuvants were necessary and used impractically large doses. Ex. 2025, 1210-1211, 1215; Ex. 2024, 2265-2266. Second, Petitioners again mischaracterize

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<sup>17</sup> The Reply does not respond to Moderna's thorough discussion of Petitioners' arguments regarding Petsch and Kallen. Reply, 17-18; POR, 37-39, 42-44.

Dr. Fuller's testimony. Reply, 18. She testified POSAs would need "specific examples or data" to know whether a particular protein that **could** (potentially) work in a nucleic acid vaccine **would** (in fact) express, not that any nucleic acid vaccine would express protein and provoke an immune response. Ex. 1104, 212:18-213:14; *id.*, 78:17-79:2. "Could" is insufficient for obviousness. *E.g.*, *OSI*, 939 F.3d at 1385 ("hope" insufficient).

**b. Reasons to Avoid Betacoronavirus S-Protein**

There were multiple reasons a POSA would not have chosen betacoronavirus S-protein. POR, 45-51. Petitioners' arguments to the contrary fail.

**First**, a POSA would have been dissuaded from S-protein by "unequivocal" risks of disease enhancement associated with full-length S-protein. Ex. 2253, 82:10-84:17; POR, 47-51; Ex. 2029 (1990); Ex. 1011 (2004); Ex. 2137 (2005); Ex. 1031 (2009); Ex. 2030 (2011); Ex. 2136 (discussing studies, 2004-2016); Ex. 2057 (discussing studies, 2005-2017). Petitioners say vaccines always risk disease enhancement (Reply, 15), but ignore that there were **specific** concerns of a "novel...mechanism" for betacoronavirus disease enhancement; antibodies elicited by **full-length spike** were thought to enhance spike protein's natural function mediating viral entry. Ex. 2030, Abstract, 10589-10591; POR, 47-48; Ex. 2199, ¶¶580-609; Ex. 2200, ¶¶187-192; Ex. 1104, 62:18-63:13, 246:7-18, 248:5-249:10, 250:10-251:15, 251:16-254:3; Ex. 2137, 800.

Petitioners' conclusory suggestion that a POSA would assume (without data) that neutralizing antibodies (in other technologies) alone would make enhanced disease less likely (Reply, 15) is contradicted by Dr. Griffin's admission that "levels of neutralizing antibodies alone **don't** fully address...vaccine associated disease enhancement [ADE]." Ex. 2253, 76:19-78:4, 82:10-83:15; POR, 50.<sup>18</sup> As Dr. Fuller confirmed, those elicited antibodies may be "bad antibodies"—*i.e.*, antibodies that **contribute** to enhanced disease, rather than solving it. Ex. 1104, 258:1-262:8, 151:21-152:22. Petitioners also fail to acknowledge disease enhancement results **vary** across vaccine technologies, irrespective of neutralizing antibody generation. Ex. 2030, Abstract, 10583-10584, 10589-10590, 10594-10595, Fig. 8A-C<sup>19</sup>; Ex. 2199, ¶¶126, 592; *compare* Ex. 2030, 10590, Fig. 8A, Fig. 8C, *with* Ex. 1011, 561, 563, Fig. 1a (showing disease enhancement in protein vaccine despite nearly identical truncation as Yang's DNA vaccine); *cf.* Ex. 1104, 248:5-249:10.

This skepticism was confirmed by BioNTech's CEO who explained his team remained concerned about avoiding "an ADE disaster" and expressed concerns that

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<sup>18</sup> Petitioners make the same inapposite arguments about Exhibits 1031, 1101, and 1132.

<sup>19</sup> That less than 50% (2/5) of candidates tested in Jaume did not "trigger[] ADE" (DI, 68) confirms nonobviousness. *See Eli Lilly*, 8 F.4th at 1349.

using full-length spike protein in an mRNA-LNP vaccine could be catastrophic. Ex. 2106, 68-70, 72-73. Petitioners suggest they “‘had little doubt’” full-length S-protein was “the ‘best way to build a coronavirus vaccine.’” Reply, 15. But BioNTech considered full-length “more attractive” only *after* receiving data from “other vaccine developers [*i.e.*, Moderna], showing that vaccines encoding for the full spike...were not causing [disease enhancement]....” Ex. 2107, 198; *see also* Ex. 2256, 55:2-56:3 (FDA interested in disease enhancement); *id.*, 54:5-13.

**Second**, Petitioners’ argument that S-protein was “the predominant immunogen of interest” is unsupported. Reply, 14. As Section V.A. discusses, none of Geall, Yang, or Altmeyer shows data attributed to any nucleic acid vaccine encoding full-length S-protein. Petitioners cite a 2004 article discussing S-protein (Ex. 1132) (Reply, 14-15), but ignore the fact that many other proteins were under consideration as of 2015 (POR, 45-47; Ex. 2199, ¶¶610-623). For example, published studies showed that M protein induced strong neutralizing antibodies and was unlikely to cause enhanced disease (Ex. 2095, 1172, 1178-1179 (citing 2003-2005 studies); Ex. 2029, 1409), and Geall identifies other potential targets, including “envelope glycoprotein” (Ex. 1010, 16:6-7, 19:26-29; *supra* p.9). The sole pre-priority clinical trial involving a betacoronavirus (DNA) vaccine utilized truncated, not full-length, spike out of disease enhancement concerns. Ex. 2199,

¶¶593-598, 842-845; Ex. 2138, 6338-6341; Ex. 2137, 797-800, Figs. 1b, 4a; *see also supra* p.22.<sup>20</sup>

**Third**, Petitioners' suggestion (Reply, 13) that long-felt unmet need for pandemic preparedness vaccines would have pointed to betacoronavirus in Geall ignores Dr. Fuller's testimony that "by 2015 a lot of the enthusiasm [for coronavirus vaccine development] had declined" because the field shifted focus from SARS/MERS to Zika. Ex. 1104, 126:5-127:10.

**Fourth**, it was unknown whether full-length S-protein would express from mRNA vaccines. As of 2015, there was no known mRNA vaccine that had been successfully delivered, expressed, and induced an immune response or neutralizing antibodies to a protein as large as S protein. Ex. 2253, 75:19-76:16, 142:19-143:19; *supra* §V.B.1.c. Petitioners' suggestion that expression/subsequent immune response is a foregone conclusion (Reply, 16-17) is wrong given unpredictability, variability, and lack of data. *Supra* §V.B. Proteins may not express, may insufficiently express or improperly fold, and may not produce any immune response. *Supra* §§IV.A, V.B.1.a. Petitioners again take Dr. Fuller's testimony out

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<sup>20</sup> Wang (Ex. 1101, Reply 16) is inapposite: Wang did not involve a clinical trial, involved DNA and protein (not mRNA) vaccines, and its report of antibody responses does not rule out disease enhancement. *Supra* p.22.

of context to suggest any attempted mRNA or DNA vaccine will express a protein (Reply, 17), when she testified that is only so after “validating that the sequence encoded by the RNA or DNA is expressing properly folded protein and the like.” Ex. 1104, 78:5-79:2.

**c. A POSA Would Have Had Reason Not to Use LNPs.**

The Reply does not address Moderna’s evidence that different delivery methods were known to have different benefits, such as adjuvant effects, sustained release, and manufacturing benefits (POR, 39-40; Ex. 2198, ¶¶37-66, 164-179, 208-212), or that protamine was thought necessary for mRNA vaccine immune response (Ex. 2024, 2264; Ex. 2025, 1210-1216; Ex. 2198, ¶¶46-50). *Virtek Vision Int’l ULC v. Assembly Guidance Sys., Inc.*, 97 F.4th 882, 886-887 (Fed. Cir. 2024). Both defeat motivation to use LNPs as claimed.

Petitioners’ claim that Schrum discusses the same LNP formulation as the patent (Reply, 18-19) is beside the point, as Schrum discloses data only on LNPs for use with therapeutics. POR, 39-40. As Dr. Moon admitted, the goals of therapy and vaccination are different: to **reduce** immune response versus **trigger** an immune response, respectively. Ex. 2254, 63:8-64:3; Ex. 1104, 95:22-98:3, 234:5-235:9, 264:13-266:1. A POSA would not have had reasonable expectation of success combining Schrum with Geall, Yang, or Altmeyer to achieve the claimed invention.

**VI. Objective Indicia Confirm Non-Obviousness.**

Objective indicia “play a critical role,” and here strongly confirm non-obviousness. *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013). Petitioners do not dispute their Comirnaty® and Moderna’s Spikevax® vaccines practice the challenged claims. Ex. 2200, App’x C-F; *see* Ex. 2253, 103:18-106:6. Nor do they rebut key evidence. POR, 64-70.

**Industry Praise/Commercial Success.** Moderna’s clinical trials and development speed for Spikevax® were praised as “remarkable,” “unbelievable,” and “the light at the end of this tunnel” (Exs. 2176-2178); Moderna’s results were published in top journals (Exs. 2035-2036, 2179, 2181; Ex. 2200, ¶¶212-213); Moderna received industry awards (Exs. 2040-2042; Ex. 2200, ¶214); and Spikevax® and Comirnaty® achieved tremendous market success (Ex. 2197, ¶¶8-10, 13-29, App’x B; Ex. 2255, 72:5-17).

**Long-Felt Unmet Need.** Petitioners argue, citing *Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 989 (Fed. Cir. 2009), that Moderna must show the claimed invention *satisfied* a long-felt need **at the time of filing**. Reply, 27-28. Not so. *P&G* says an unmet need must *exist* at the time of filing (566 F.3d at 998)—which Petitioners endorse, calling coronavirus a “top-ten pathogen with pandemic potential by October 2015.” Reply, 13. It need not be *met* as of filing. *P&G*, 566 F.3d at 998.

**Failure of Others/Skepticism/Unexpected Results.** Significant industry skepticism of both mRNA infectious disease vaccines and S-protein existed. *Supra* §§V.B.1.d, V.B.2.a-V.B.2.b. Nonetheless, the patent showed mRNA-LNP-betacoronavirus S-protein vaccines could generate a protective immune response, and tested MERS-CoV vaccines resulted in reduced viral load, neutralizing antibodies, and complete protection in animals. POR, 67-68.

Even *after* the patent, hundreds of companies attempted to create COVID-19 vaccines, yet most failed or were abandoned. Ex. 2200, ¶¶198-199; Exs. 2169, 2171-2174, 2220; Ex. 2197, ¶¶13-17. Petitioners' expert Mr. Bakewell suggests "[m]acroeconomic and [r]egulatory [c]onsiderations" aided commercialization (Ex. 1163, §4.3), but this reinforces the need for vaccines and the patent's value: the earliest and most successful COVID-19 vaccines use Moderna's claimed platform. Ex. 2200, ¶¶198-199; Ex. 2197, ¶¶13-17, 22-29; Ex. 2255, 83:14-86:9; Ex. 1105, 115:21-118:1.

**Nexus.** Petitioners argue the claims are not "coextensive" with the embodying vaccines. Reply, 26-27. Coextensiveness is relevant only to *presumption* of nexus. *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1374 (Fed. Cir. 2019). Nexus also exists where objective indicia are *reasonably commensurate* with the claims and/or where evidence of objective indicia results from unique features of the claimed combination (even if individual elements were known).

*Rambus Inc. v. Rea*, 731 F.3d 1248, 1257 (Fed. Cir. 2013); *Chemours Co. FC, LLC v. Daikin Indus., Ltd.*, 4 F.4th 1370, 1378 (Fed. Cir. 2021). Spikevax® and Comirnaty® are reasonably commensurate with the claims—Petitioners have not asserted otherwise. POR, 61-64; Ex. 2200, ¶¶224-244.

Petitioners identify features (different codon optimizations, LNP composition, or mRNA structural components) to which they attribute success. Reply, 27. But Spikevax® and Comirnaty® have ***nearly identical*** efficacy ***despite*** differences in these features. Ex. 2169, Table 2; Ex. 2168, Fig. 2; Ex. 2200, ¶¶230-231, 239. And research demonstrates the 2P mutation has minimal effect on immune response and protective effect. Ex. 2200, ¶¶232-238; Ex. 2142, Extended Data Fig. 1; Ex. 2182, 1987, 1991; Ex. 2183, 8. Thus, there is nexus between Comirnaty® and Spikevax® and the claims. *Fox Factory*, 994 F.3d at 1373-1374.

Finally, Petitioners are wrong that “the generic concept” of the patent was known. Reply, 28. Dr. Griffin confirmed he cited ***no reference*** before October 2015 testing an mRNA vaccine for a betacoronavirus, much less in LNPs. Ex. 2253, 142:19-143:19. In any event, objective indicia can apply to a unique combination of known elements. *Chemours*, 4 F.4th at 1378.

## VII. Conclusion

Patentability must be confirmed.

Respectfully submitted,

Date: October 16, 2024

By: /Emily R. Whelan/  
Emily R. Whelan (Reg. No. 50,391)

**CERTIFICATE OF WORD COUNT UNDER 37 C.F.R. § 42.24(d)**

I hereby certify that the foregoing Patent Owner's Sur-Reply contains 5,581 words as measured by the word processing software used to prepare the document, in compliance with 37 C.F.R. § 42.24(d), excluding the parts exempted from the word count by 37 C.F.R. § 42.24(a)(1).

By: Emily R. Whelan/

Emily R. Whelan (Reg. No. 50,391)

Wilmer Cutler Pickering Hale and Dorr LLP

60 State Street

Boston, MA 02109

Tel: (617) 526-6567

Email: Emily.Whelelan@wilmerhale.com

**CERTIFICATE OF SERVICE**

I hereby certify that on October 16, 2024, I caused a true and correct copy of the following documents:

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COVIDPatentPfizer@wc.com  
BioNTech-Moderna-IPR@paulhastings.com

By: /Wenli Gu/  
Wenli Gu (Reg. No. 72,124)  
Wilmer Cutler Pickering Hale and Dorr LLP  
60 State Street  
Boston, MA 02109  
Tel: (617) 526-6093  
Email: Wenli.Gu@wilmerhale.com