

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MERCK SHARP & DOHME LLC,  
Petitioner

v.

HALOZYME INC.,  
Patent Owner

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Case PGR2025-00009  
U.S. Patent No. 12,123,035

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**PATENT OWNER'S SUR-REPLY**

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Patent Trial and Appeal Board  
U.S. Patent and Trademark Office  
P.O. Box 1450  
Alexandria, VA 22313-1450

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**PATENT OWNER'S UPDATED EXHIBIT LIST**

| <b>Exhibit No.</b> | <b>Description</b>                                                                                                                                                                                                                          |
|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>2001</b>        | Declaration of Barbara Triggs-Raine, Ph.D. in support of Patent Owner Preliminary Response (WITHDRAWN)                                                                                                                                      |
| <b>2002</b>        | <i>Curriculum Vitae</i> of Barbara Triggs-Raine, Ph.D.                                                                                                                                                                                      |
| <b>2003</b>        | Disclaimer in a Patent under 37 C.F.R. § 1.321(a), filed in U.S. Patent Application No. 18/068,327, April 8, 2025                                                                                                                           |
| <b>2004</b>        | “Halozyme Therapeutics to Present Data on PEGPH20 at the Upcoming 2011 EORTC-NCIASCO Annual Meeting,” Halozyme Therapeutics, Inc. Press Release, October 24, 2011                                                                           |
| <b>2005</b>        | LinkedIn profiles of Michael Shepard, Robert Connor, Ge (Gina) Wei, and Qiping Zhao                                                                                                                                                         |
| <b>2006</b>        | Sequence listing of U.S. Patent Application No. 18/068,327                                                                                                                                                                                  |
| <b>2007</b>        | Gifre, L., et al., “Trends in recombinant protein use in animal production,” <i>Microb Cell Fact</i> 16:40 (2017)                                                                                                                           |
| <b>2008</b>        | “Recombinant Drugs,” Smithsonian Institution, accessible at <a href="https://www.si.edu/spotlight/birth-of-biotech/recombinant-drugs">https://www.si.edu/spotlight/birth-of-biotech/recombinant-drugs</a> (last accessed February 27, 2025) |
| <b>2009</b>        | Naz, R., “Antisperm Contraceptive Vaccines: Where We Are and Where We Are Going?,” <i>American Journal of Reproductive Immunology</i> 66:5-12 (2011)                                                                                        |
| <b>2010</b>        | Primakoff, P., et al., “Fully effective contraception in male and female guinea pigs immunized with the sperm protein PH-20,” <i>Nature</i> 335:543-546 (October 6, 1988)                                                                   |

| Exhibit No. | Description                                                                                                                                                                                                                                                                                                                                                                  |
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| 2011        | Definition of “guinea pig,” Merriam-Webster OnLine, archived by the Internet Archive on February 21, 2010, accessible at <a href="https://web.archive.org/web/20100221175034/http://www.merriam-webster.com/dictionary/guinea%20pig">https://web.archive.org/web/20100221175034/http://www.merriam-webster.com/dictionary/guinea%20pig</a> (last accessed February 27, 2025) |
| 2012        | “A decade in numbers,” <i>Nature Materials</i> 11:743-744 (September 2012)                                                                                                                                                                                                                                                                                                   |
| 2013        | Lin, Y., <i>et al.</i> , “Molecular cloning of the human and monkey sperm surface protein PH-20,” <i>Proc. Natl. Acad. Sci USA</i> 90:10071-10075 (November 1993)                                                                                                                                                                                                            |
| 2014        | <i>Intentionally Left Blank</i>                                                                                                                                                                                                                                                                                                                                              |
| 2015        | File History of U.S. Patent No. 7,872,107                                                                                                                                                                                                                                                                                                                                    |
| 2016        | Pils, B., <i>et al.</i> , “Variation in structural location and amino acid conservation of functional sites in protein domain families,” <i>BMC Bioinformatics</i> 6 (August 25, 2005)                                                                                                                                                                                       |
| 2017        | <i>Intentionally Left Blank</i>                                                                                                                                                                                                                                                                                                                                              |
| 2018        | Duterme, C., <i>et al.</i> , “Two Novel Functions of Hyaluronidase-2 (Hyal2) Are Formation of the Glycocalyx and Control of CD44-ERM Interactions,” <i>The Journal of Biological Chemistry</i> , 284(48):33495-33508 (November 27, 2009)                                                                                                                                     |
| 2019        | Atmuri, V., <i>et al.</i> , “Hyaluronidase 3 (HYAL3) knockout mice do not display evidence of hyaluronan accumulation,” <i>Matrix Biology</i> 27:653-660 (2008)                                                                                                                                                                                                              |
| 2020        | Hemming, R., <i>et al.</i> , “Mouse Hyal3 encodes a 45- to 56-kDa glycoprotein whose overexpression increases hyaluronidase 1 activity in cultured cells,” <i>Glycobiology</i> 18(4):280-289 (2008)                                                                                                                                                                          |

| Exhibit No. | Description                                                                                                                                                                                                                                                         |
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| 2021        | Miller, A., “Hyaluronidase 2 and its intriguing role as a cell-entry receptor for oncogenic sheep retroviruses,” <i>Seminars in Cancer Biology</i> 18:296-301 (2008)                                                                                                |
| 2022        | Kaneiwa, T. <i>et al.</i> , “Identification of human hyaluronidase-4 as a novel chondroitin sulfate hydrolase that preferentially cleaves the galactosaminidic linkage in the trisulfated tetrasaccharide sequence,” <i>Glycobiology</i> 20(3):300-309 (March 2010) |
| 2023        | Petition for Post-Grant Review, <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00004 (P.T.A.B.), November 26, 2024                                                                                                                          |
| 2024        | Petition for Post-Grant Review, <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00006 (P.T.A.B.), December 10, 2024                                                                                                                          |
| 2025        | Petition for Post-Grant Review, <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00003 (P.T.A.B.), November 12, 2024                                                                                                                          |
| 2026        | Petition for Post-Grant Review, <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00017 (P.T.A.B.), January 17, 2025                                                                                                                           |
| 2027        | Petition for Post-Grant Review, <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00030 (P.T.A.B.), February 4, 2025                                                                                                                           |
| 2028        | Petition for Post-Grant Review, <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00024 (P.T.A.B.), February 21, 2025                                                                                                                          |
| 2029        | Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00004 (P.T.A.B.), November 26, 2024                                                                                                      |

| <b>Exhibit No.</b> | <b>Description</b>                                                                                                                                                        |
|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>2030</b>        | Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00006 (P.T.A.B.), December 10, 2024            |
| <b>2031</b>        | Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00003 (P.T.A.B.), November 12, 2024            |
| <b>2032</b>        | Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00017 (P.T.A.B.), January 17, 2025             |
| <b>2033</b>        | Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00030 (P.T.A.B.), February 4, 2025             |
| <b>2034</b>        | Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00024 (P.T.A.B.), February 21, 2025            |
| <b>2035</b>        | Lokeshwar, V., <i>et al.</i> , “Regulation of Hyaluronidase Activity by Alternative mRNA Splicing,” <i>The Journal of Biological Chemistry</i> 277(37):33654-33663 (2002) |
| <b>2036</b>        | Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00033 (P.T.A.B.), March 7, 2025                |
| <b>2037</b>        | Petition for Post-Grant Review, <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00033 (P.T.A.B.), March 7, 2025                                    |
| <b>2038</b>        | Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00039 (P.T.A.B.), March 28, 2025               |
| <b>2039</b>        | Petition for Post-Grant Review, <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00039 (P.T.A.B.), March 28, 2025                                   |

| <b>Exhibit No.</b> | <b>Description</b>                                                                                                                                                                                                                                                                              |
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| <b>2040</b>        | Wilson, C., <i>et al.</i> , “A critical assessment of the secondary structure prediction of $\alpha$ -helices and their termini in proteins,” <i>Protein Engineering</i> , 15(7):545-554 (2002)                                                                                                 |
| <b>2041</b>        | Doig, A., “Stability and Design of $\alpha$ -Helical Peptides,” <i>Progress in Molecular Biology and Translational Science</i> , 83:1-52 (2008)                                                                                                                                                 |
| <b>2042</b>        | Cochran D., <i>et al.</i> , “Effect of the N1 residue on the stability of the $\alpha$ -helix for all 20 amino acids,” <i>Protein Science</i> , 10:463-470 (2001)                                                                                                                               |
| <b>2043</b>        | elMasry, N., <i>et al.</i> , “Mutational analysis of the N-capping box of the $\alpha$ -helix of chymotrypsin inhibitor 2,” <i>Protein Engineering</i> , 7(6):777-782 (1994)                                                                                                                    |
| <b>2044</b>        | <i>Intentionally Left Blank</i>                                                                                                                                                                                                                                                                 |
| <b>2045</b>        | <i>Intentionally Left Blank</i>                                                                                                                                                                                                                                                                 |
| <b>2046</b>        | “2023 Pharma 50: The 50 largest pharma companies in the world,” drugdiscoverytrends.com, accessible at <a href="https://www.drugdiscoverytrends.com/2023-pharma-50-largest-companies/">https://www.drugdiscoverytrends.com/2023-pharma-50-largest-companies/</a> (last accessed April 28, 2025) |
| <b>2047</b>        | “Merck Announces Fourth-Quarter and Full-Year 2024 Financial Results,” Merck Press Release, February 4, 2025                                                                                                                                                                                    |
| <b>2048</b>        | “Products list,” Merck.com, accessible at <a href="https://www.merck.com/products/">https://www.merck.com/products/</a> (last accessed April 22, 2025)                                                                                                                                          |
| <b>2049</b>        | <i>Intentionally Left Blank</i>                                                                                                                                                                                                                                                                 |
| <b>2050</b>        | “Merck & Company, Inc. Common Stock (new) (MRK),” Nasdaq.com, accessible at <a href="https://www.nasdaq.com/market-activity/stocks/mrk">https://www.nasdaq.com/market-activity/stocks/mrk</a> (last accessed April 28, 2025)                                                                    |
| <b>2051</b>        | “Halozyme Therapeutics, Inc. Common Stock (HALO),” Nasdaq.com, accessible at <a href="https://www.nasdaq.com/market-activity/stocks/halo">https://www.nasdaq.com/market-activity/stocks/halo</a> (last accessed April 28, 2025)                                                                 |

| Exhibit No. | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| 2052        | “Halozyme reports full year 2024 record revenue of \$1.015 billion and Exceeds its Financial Guidance for Royalty Revenue, Adjusted EBITDA and Non-GAAP Diluted EPS,” Halozyme.com, accessible at <a href="https://ir.halozyme.com/news/news-details/2025/HALOZYME-REPORTS-FULL-YEAR-2024-RECORD-REVENUE-OF-1.015-BILLION-AND-EXCEEDS-ITS-FINANCIAL-GUIDANCE-FOR-ROYALTY-REVENUE-ADJUSTED-EBITDA-AND-NON-GAAP-DILUTED-EPS/default.aspx">https://ir.halozyme.com/news/news-details/2025/HALOZYME-REPORTS-FULL-YEAR-2024-RECORD-REVENUE-OF-1.015-BILLION-AND-EXCEEDS-ITS-FINANCIAL-GUIDANCE-FOR-ROYALTY-REVENUE-ADJUSTED-EBITDA-AND-NON-GAAP-DILUTED-EPS/default.aspx</a> (last accessed April 28, 2025) |
| 2053        | “Commercial Products,” Halozyme.com, accessible at <a href="https://halozyme.com/commercial-products/">https://halozyme.com/commercial-products/</a> (last accessed April 28, 2025)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 2054        | “About Us,” Halozyme.com, accessible at <a href="https://halozyme.com/about-us/#our-focus">https://halozyme.com/about-us/#our-focus</a> (last accessed April 28, 2025)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 2055        | Declaration of Barbara Triggs-Raine, Ph.D. in support of Patent Owner Discretionary Denial Brief (WITHDRAWN)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 2056        | Petition for Post-Grant Review, <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00042 (P.T.A.B.), April 15, 2025                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 2057        | Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00042 (P.T.A.B.), April 15, 2025                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 2058        | Complaint for Patent Infringement and Declaratory Judgment of Patent Infringement, <i>Halozyme, Inc. v. Merck Sharp &amp; Dohme Corp.</i> , Civil Action No. 2:25-cv-03179-ES (D.N.J.), filed April 24, 2025                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 2059        | “Alteogen announces amendment to license agreement with MSD,” Alteogen Press Release, February 22, 2025, accessible at <a href="https://www.alteogen.com/en/ir_1/?uid=2223&amp;mod=document&amp;pageid=1">https://www.alteogen.com/en/ir_1/?uid=2223&amp;mod=document&amp;pageid=1</a> (last accessed April 28, 2025)                                                                                                                                                                                                                                                                                                                                                                                  |

| <b>Exhibit No.</b> | <b>Description</b>                                                                                                                                          |
|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>2060</b>        | Declaration of Tyler C. Liu ( <i>served not filed</i> )                                                                                                     |
| <b>2061</b>        | <i>Intentionally Left Blank</i>                                                                                                                             |
| <b>2062</b>        | Petition for Post-Grant Review, <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00046 (P.T.A.B.), April 29, 2025                     |
| <b>2063</b>        | Petition for Post-Grant Review, <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00053 (P.T.A.B.), June 6, 2025                       |
| <b>2064</b>        | Petition for Post-Grant Review, <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00052 (P.T.A.B.), June 27, 2025                      |
| <b>2065</b>        | Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00046 (P.T.A.B.), April 29, 2025 |
| <b>2066</b>        | Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00053 (P.T.A.B.), June 6, 2025   |
| <b>2067</b>        | Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00052 (P.T.A.B.), June 27, 2025  |
| <b>2068</b>        | Declaration of Melanie A. Simpson, Ph.D. in Support of Patent Owner's Response                                                                              |
| <b>2069</b>        | <i>Curriculum Vitae</i> of Melanie A. Simpson, Ph.D.                                                                                                        |
| <b>2070</b>        | Declaration of Gregory A. Petsko, Ph.D. in Support of Patent Owner's Response                                                                               |
| <b>2071</b>        | <i>Curriculum Vitae</i> of Gregory A. Petsko, Ph.D.                                                                                                         |
| <b>2072</b>        | Declaration of Gary N. Cherr, Ph.D. in Support of Patent Owner's Response                                                                                   |
| <b>2073</b>        | <i>Curriculum Vitae</i> of Gary N. Cherr, Ph.D.                                                                                                             |

| <b>Exhibit No.</b> | <b>Description</b>                                                                                                                                                                                                                                            |
|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>2074</b>        | Declaration of James J. Moon, Ph.D. in Support of Patent Owner's Response                                                                                                                                                                                     |
| <b>2075</b>        | <i>Curriculum Vitae</i> of James J. Moon, Ph.D.                                                                                                                                                                                                               |
| <b>2076</b>        | Transcript of the Deposition of Michael Hecht, Ph.D., August 26, 2025                                                                                                                                                                                         |
| <b>2077</b>        | Transcript of the Deposition of Dr. Sheldon Park, August 7, 2025                                                                                                                                                                                              |
| <b>2078</b>        | Transcript of the Deposition of Dr. Sheldon Park, August 21, 2025                                                                                                                                                                                             |
| <b>2079</b>        | Koehl, P. et al., "Structure-based conformational preferences of amino acids," <i>PNAS</i> , 96(22):12524-12529 (October 26, 1999)                                                                                                                            |
| <b>2080</b>        | Pommié, C. et al., "IMGT standardized criteria for statistical analysis of immunoglobulin V-REGION amino acid properties," <i>Journal of Molecular Recognition</i> , 17:17-32 (2004)                                                                          |
| <b>2081</b>        | <i>Intentionally Left Blank</i>                                                                                                                                                                                                                               |
| <b>2082</b>        | Kyte, J. et al., "A Simple Method for Displaying the Hydropathic Character of a Protein," <i>Journal of Molecular Biology</i> , 157:105-132 (1982)                                                                                                            |
| <b>2083</b>        | <i>Assay Guidance Manual</i> , Eli Lilly & Company and the National Center for Advancing Translational Sciences                                                                                                                                               |
| <b>2084</b>        | "The Central Role of Enzymes as Biological Catalysts," NCBI Bookshelf, National Institutes of Health (accessible at <a href="https://www.ncbi.nlm.nih.gov/books/NBK9921/">https://www.ncbi.nlm.nih.gov/books/NBK9921/</a> , last accessed September 22, 2025) |
| <b>2085</b>        | French, S. et al., "What is a Conservative Substitution?", <i>Journal of Molecular Evolution</i> , 19:171-175 (1983)                                                                                                                                          |
| <b>2086</b>        | El-Safory, N. et al., "Hyaluronidases, a group of glycosidases: Current and future perspectives," <i>Carbohydrate Polymers</i> , 81:165-181 (2010)                                                                                                            |

| Exhibit No. | Description                                                                                                                                                                                              |
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| 2087        | Lu, J. et al., “Hyaluronidase: structure, mechanism of action, diseases and therapeutic targets,” <i>Molecular Biomedicine</i> , 6:50-77 (2025)                                                          |
| 2088        | Stern, R. et al., “Mammalian Hyaluronidases,” Hyaluronan Index (2000)                                                                                                                                    |
| 2089        | Gmachl, M. et al., “The human sperm protein PH-20 has hyaluronidase activity,” <i>FEBS Letters</i> , 336(3):545-548 (December 1993)                                                                      |
| 2090        | Gmachl, M. et al., “Bee venom hyaluronidase is homologous to a membrane protein of mammalian sperm,” <i>PNAS USA</i> , 90:3569-3573 (April 1993)                                                         |
| 2091        | Davies, G. et al., “Structures and mechanisms of glycosyl hydrolases,” <i>Current Biology</i> , 3:853-859 (1995)                                                                                         |
| 2092        | Marković-Housley, Z. et al., “Crystal Structure of Hyaluronidase, a Major Allergen of Bee Venom,” <i>Structure</i> , 8:1025-1035 (October 2000)                                                          |
| 2093        | U.S. Patent No. 8,343,487 B2 to Baker et al., issued January 1, 2013                                                                                                                                     |
| 2094        | MULTIDROP 384 Liquid Handling Device Manual 2008                                                                                                                                                         |
| 2095        | <i>Intentionally Left Blank</i>                                                                                                                                                                          |
| 2096        | Frost, G. et al., “A Microtiter-Based Assay for Hyaluronidase Activity Not Requiring Specialized Reagents,” <i>Analytical Biochemistry</i> , 251:263-269 (1997)                                          |
| 2097        | U.S. Patent Application Publication No. 2005/0260186 A1 to Bookbinder et al., published November 24, 2005                                                                                                |
| 2098        | Delpech, B. et al., “Enzyme-Linked Hyaluronectin: A Unique Reagent for Hyaluronan Assay and Tissue Location and for Hyaluronidase Activity Detection,” <i>Analytical Biochemistry</i> , 229:35-41 (1995) |

| <b>Exhibit<br/>No.</b> | <b>Description</b>                                                                                                                                                                                                                |
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| <b>2099</b>            | Takahashi, T. et al., “A fluorimetric Morgan-Elson assay method for hyaluronidase activity,” <i>Analytical Biochemistry</i> , 322:257-263 (2003)                                                                                  |
| <b>2100</b>            | Vines, C.V. et al., “Identification of a Hyaluronic Acid (HA) Binding Domain in the PH-20 Protein That May Function in Cell Signaling,” <i>Molecular Reproduction and Development</i> , 60:542-552 (2001)                         |
| <b>2101</b>            | Wassarman, P. et al., “Structure and Function of the Mammalian Egg Zona Pellucida,” <i>Journal of Experimental Zoology (Mol Dev Evol)</i> , 285:251-258 (1999)                                                                    |
| <b>2102</b>            | Yudin, A. et al., “Structure of the cumulus matrix and zona pellucida in the golden hamster: A new view of sperm interaction with oocyte-associated extracellular matrices,” <i>Cell Tissue Res</i> 251:555-564 (1988)            |
| <b>2103</b>            | Tollner, T. et al., “Multifunctional glycoprotein DEFB126 – a curious story of defensin-clad spermatozoa,” <i>Nature Reviews   Urology</i> , Vol. 9, pp. 365-375 (July 2012)                                                      |
| <b>2104</b>            | Visconti, P. et al., “The Molecular Basis of Sperm Capacitation,” <i>Journal of Andrology</i> , 19(2):242-248 (March/April 1998)                                                                                                  |
| <b>2105</b>            | Wassarman, P. et al., “A profile of fertilization in mammals,” <i>Nature Cell Biology</i> , Vol. 3, pp. E59-E64 (February 2001)                                                                                                   |
| <b>2106</b>            | Bailey, J., “Factors Regulating Sperm Capacitation,” <i>Systems Biology in Reproductive Medicine</i> , 56:334-348 (2010)                                                                                                          |
| <b>2107</b>            | Sabeur, K. et al., “The PH-20 Protein in Human Spermatozoa,” <i>Journal of Andrology</i> , 18(2):151-158 (March/April 1997)                                                                                                       |
| <b>2108</b>            | Hunnicut, G. et al., “Sperm Surface Protein PH-20 Is Bifunctional: One Activity Is a Hyaluronidase and a Second, Distinct Activity is Required in Secondary Sperm-Zona Binding,” <i>Biology of Reproduction</i> , 55:80-86 (1996) |

| <b>Exhibit<br/>No.</b> | <b>Description</b>                                                                                                                                                                                                                    |
|------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>2109</b>            | Tollner, T. et al., “Beta-Defensin 126 on the Surface of Macaque Sperm Mediates Attachment of Sperm to Oviductal Epithelia,” <i>Biology of Reproduction</i> , 78:400-412 (2008)                                                       |
| <b>2110</b>            | Tollner, T. et al., “Release of DEFB126 From Macaque Sperm and Completion of Capacitation Are Triggered by Conditions That Simulate Periovarial Oviductal Fluid,” <i>Molecular Reproduction &amp; Development</i> , 76:431-443 (2009) |
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| <b>2112</b>            | Yudin, A. et al., “The Carbohydrate Structure of DEFB126, the Major Component of the Cynomolgus Macaque Sperm Plasma Membrane Glycocalyx,” <i>Journal of Membrane Biology</i> , 207:119-129 (2005)                                    |
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| <b>2114</b>            | Frayne, J. et al., “The potential use of sperm antigens as targets for immunocontraception; past, present and future,” <i>Journal of Reproductive Immunology</i> , 43:1-33 (1999)                                                     |
| <b>2115</b>            | Yanagimachi, R., “Acceleration of the Acrosome Reaction and Activation of Guinea Pig Spermatozoa by Detergents and Other Reagents,” <i>Biology of Reproduction</i> , 13:519-526 (1975)                                                |
| <b>2116</b>            | Chamley, L. et al., “Antisperm antibodies and conception,” <i>Seminars in Immunopathology</i> , 29:169-184 (2007)                                                                                                                     |
| <b>2117</b>            | Kremer, J. et al., “The significance of antisperm antibodies for sperm-cervical mucus interaction,” <i>Human Reproduction</i> , 7(6):781-784 (1992)                                                                                   |

| <b>Exhibit No.</b> | <b>Description</b>                                                                                                                                                               |
|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>2118</b>        | Primakoff, P. et al., “A Map of the Guinea Pig Sperm Surface Constructed with Monoclonal Antibodies,” <i>Developmental Biology</i> , 98:417-428 (1983)                           |
| <b>2119</b>        | Myles, D. et al., “Localized Surface Antigens of Guinea Pig Sperm Migrate to New Regions Prior to Fertilization,” <i>The Journal of Cell Biology</i> , 99:1634-1641 (1984)       |
| <b>2120</b>        | Chan, C. et al., “Identification of Linear Surface Epitopes on the Guinea Pig Sperm Membrane Protein PH-20,” <i>Life Sciences</i> , 64(22):1989-2000 (1999)                      |
| <b>2121</b>        | Ganesan, R. et al., “Structural and mechanistic insight into how antibodies inhibit serine proteases,” <i>Biochemistry Journal</i> , 430:179-189 (2010)                          |
| <b>2122</b>        | Mestecky, J. et al., “Mucosal Immune System of the Human Genital Tract,” <i>The Journal of Infectious Diseases</i> , 179(Suppl 3):S470-S474 (1999)                               |
| <b>2123</b>        | <i>Intentionally Left Blank</i>                                                                                                                                                  |
| <b>2124</b>        | <i>Intentionally Left Blank</i>                                                                                                                                                  |
| <b>2125</b>        | <i>Intentionally Left Blank</i>                                                                                                                                                  |
| <b>2126</b>        | Suri, A., “Contraceptive vaccines targeting sperm,” <i>Expert Opinion on Biological Therapy</i> , 5(3):381-392 (2005)                                                            |
| <b>2127</b>        | Morrow, R. et al., “Sustained release of proteins from a modified vaginal ring device,” <i>European Journal of Pharmaceutics and Biopharmaceutics</i> , 77:3-10 (2011)           |
| <b>2128</b>        | Hussain, A. et al., “The vagina as a route for systemic drug delivery,” <i>Journal of Controlled Release</i> , 103:301-313 (2005)                                                |
| <b>2129</b>        | Veazey, R. et al., “Prevention of virus transmission to macaque monkeys by a vaginally applied monoclonal antibody to HIV-1 gp120,” <i>Nature Medicine</i> , 9(3):343-346 (2003) |

| Exhibit No. | Description                                                                                                                                                                                                                   |
|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2130        | Baloglu, E. et al., “Strategies to Prolong the Intravaginal Residence Time of Drug Delivery Systems,” <i>Journal of Pharmaceutical Science</i> , 12(3):312-336 (2009)                                                         |
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| 2132        | Cauci, S. et al., “Combination of vaginal pH with vaginal sialidase and prolidase activities for prediction of low birth weight and preterm birth,” <i>American Journal of Obstetrics and Gynecology</i> , 192:489-496 (2005) |
| 2133        | Flori, F. et al., “Menstrual cycle–related sialidase activity of the female cervical mucus is associated with exosome-like vesicles,” <i>Fertility and Sterility</i> , 88(Suppl 2):1212-1219 (October 2007)                   |
| 2134        | Mestecky, J. et al., “Antibody-mediated protection and the mucosal immune system of the genital tract: relevance to vaccine design,” <i>Journal of Reproductive Immunology</i> , 85:81-85 (2010)                              |
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| 2138        | Rhee, J. et al., “Mucosal vaccine adjuvants update,” <i>Clinical and Experimental Vaccine Research</i> , 1:50-63 (2012)                                                                                                       |
| 2139        | Lycke, N., “Recent progress in mucosal vaccine development: potential and limitations,” <i>Nature Review</i> , 12:592-605 (August 2012)                                                                                       |

| Exhibit No. | Description                                                                                                                                                                                                                                                |
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| 2140        | Rudin, A. et al., “Differential Kinetics and Distribution of Antibodies in Serum and Nasal and Vaginal Secretions after Nasal and Oral Vaccination of Humans,” <i>Infection and Immunity</i> , 66(7):3390-3396 (July 1998)                                 |
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| 2142        | Russell, M., “Immunization for Protection of the Reproductive Tract: A Review,” <i>American Journal of Reproductive Immunology</i> , 47:265-268 (2002)                                                                                                     |
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| 2144        | <i>Intentionally Left Blank</i>                                                                                                                                                                                                                            |
| 2145        | Gallichan, W. et al., “Specific secretory immune responses in the female genital tract following intranasal immunization with a recombinant adenovirus expressing glycoprotein B of herpes simplex virus,” <i>Vaccine</i> , 13(6):1589-1595 (1995)         |
| 2146        | Johansson, E. et al., “Antibodies and Antibody-Secreting Cells in the Female Genital Tract after Vaginal or Intranasal Immunization with Cholera Toxin B Subunit or Conjugates,” <i>Infection and Immunity</i> , 66(2):514-520 (February 1998)             |
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| Exhibit<br>No. | Description                                                                                                                                                                                                                            |
|----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2149           | Rhorer, J. et al., “Efficacy of live attenuated influenza vaccine in children: A meta-analysis of nine randomized clinical trials,” <i>Vaccine</i> , 27:1101-1110 (2009)                                                               |
| 2150           | Mielcarek, N., “Genital Antibody Responses in Mice after Intranasal Infection with an Attenuated Candidate Vector Strain of <i>Bordetella pertussis</i> ,” <i>Infection and Immunity</i> , 68(2):485-491 (February 2000)               |
| 2151           | Houghton, A., “Immune recognition of self in immunity against cancer,” <i>The Journal of Clinical Investigation</i> , 114(4):468-471 (August 2004)                                                                                     |
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| 2153           | Dieudé, M. et al., “Autoantibodies to heat shock protein 60 promote thrombus formation in a murine model of arterial thrombosis,” <i>Journal of Thrombosis and Haemostasis</i> , 7:710-719 (2009)                                      |
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| 2155           | Trentham, D. et al. “Autoimmunity to Type II Collagen: An Experimental Model of Arthritis,” <i>The Journal of Experimental Medicine</i> , 146:857-868 (1977)                                                                           |
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| 2157           | Tomita, M. et al., “Hybridoma technologies for antibody production,” <i>Immunotherapy</i> , 3(3):371-380 (2011)                                                                                                                        |

| Exhibit No. | Description                                                                                                                                                                                                                                                                                                               |
|-------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2158        | Excerpts from <i>Antibody Methods and Protocols</i> , Proetzel G. and Ebersbach H. eds., Humana Press (2012) (including Zhang, C., “Hybridoma Technology for the Generation of Monoclonal Antibodies,” Chapter 7; and Lee, E. et al., “The Application of Transgenic Mice for Therapeutic Antibody Discovery,” Chapter 8) |
| 2159        | Zeitlin, L. et al., “Topically Applied Human Recombinant Monoclonal IgG1 Antibody and Its Fab and F(ab') <sub>2</sub> Fragments Protect Mice from Vaginal Transmission of HSV-2,” <i>Virology</i> , 225:213-215 (1996)                                                                                                    |
| 2160        | Sherwood, J. et al., “Controlled release of antibodies for long-term topical passive immunoprotection of female mice against genital herpes,” <i>Nature Biotechnology</i> , 14:468-471 (April 1996)                                                                                                                       |
| 2161        | Veselinovic, M. et al., “Topical gel formulation of broadly neutralizing anti-HIV-1 monoclonal antibody VRC01 confers protection against HIV-1 vaginal challenge in a humanized mouse model,” <i>Virology</i> , 432:505-510 (2012)                                                                                        |
| 2162        | Schweitzer, M. et al., “Microscopic, chemical and molecular methods for examining fossil preservation,” <i>Comptes Rendus Palevol</i> , 7:159-184 (2008)                                                                                                                                                                  |
| 2163        | National Medal of Science in Medicine Citation for Gregory Petsko, 2022 (accessible at <a href="https://nationalmedals.org/laureate/gregory-petsko/?amp=1">https://nationalmedals.org/laureate/gregory-petsko/?amp=1</a> , last accessed September 19, 2025)                                                              |
| 2164        | Petsko, G., et al., <i>Protein Structure and Function</i> , New Science Press (2004)                                                                                                                                                                                                                                      |
| 2165        | U.S. Patent Application Publication No. 2010/0143457 A1 to Wei et al., published June 10, 2010                                                                                                                                                                                                                            |
| 2166        | Petsko Patent Analysis Data                                                                                                                                                                                                                                                                                               |

| <b>Exhibit No.</b> | <b>Description</b>                                                                                                                                                                                                                                                                                        |
|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>2167</b>        | Huang, C. et al., “ Effect of sublingual administration with a native or denatured protein allergen and adjuvant CpG oligodeoxynucleotides or cholera toxin on systemic TH2 immune responses and mucosal immunity in mice,” <i>Annals of Allergy, Asthma, and Immunology</i> , 99:443-452 (November 2007) |
| <b>2168</b>        | Profile of Gregory A. Petsko, American Academy of Arts and Sciences (accessible at <a href="https://www.amacad.org/person/gregory-petsko">https://www.amacad.org/person/gregory-petsko</a> , last accessed September 22, 2025)                                                                            |
| <b>2169</b>        | “BLAST Topics,” National Institutes of Health (accessible at <a href="https://blast.ncbi.nlm.nih.gov/doc/blast-topics">https://blast.ncbi.nlm.nih.gov/doc/blast-topics</a> , last accessed September 22, 2025)                                                                                            |
| <b>2170</b>        | Chain, E. et al., “Identity of Hyaluronidase and Spreading Factor,” <i>British Journal of Experimental Pathology</i> , 21(6):324-338 (1940)                                                                                                                                                               |
| <b>2171</b>        | Tollner, T. et al., “Macaque Sperm Release ESP13.2 and PSP94 During Capacitation: The Absence of ESP13.2 Is Linked to Sperm-Zona Recognition and Binding,” <i>Molecular Reproduction and Development</i> , 69:325-337 (2004)                                                                              |
| <b>2172</b>        | Yudin, A. et al., “Characterization of the active site of monkey sperm hyaluronidase,” <i>Reproduction</i> , 121:735-743 (2001)                                                                                                                                                                           |
| <b>2173</b>        | Yudin, A. et al., “PH-20 but Not Acrosin Is Involved in Sperm Penetration of the Macaque Zona Pellucida,” <i>Molecular Reproduction and Development</i> , 53:350-362 (1999)                                                                                                                               |
| <b>2174</b>        | Errata from Park Deposition (introduced during Park deposition and marked by court reporter as “Park 2068”)                                                                                                                                                                                               |
| <b>2175</b>        | Mutational Analysis Table, 2024-11-7, Native Excel File (introduced during Park deposition and marked by court reporter as “Park 2069”)                                                                                                                                                                   |
| <b>2176</b>        | Mutational Analysis Table, 2024-11-7, PDF File (introduced during Park deposition and marked by court reporter as “Park 2070”)                                                                                                                                                                            |

| <b>Exhibit No.</b> | <b>Description</b>                          |
|--------------------|---------------------------------------------|
| <b>2177</b>        | E-mail Correspondence dated August 14, 2025 |
| <b>2178</b>        | 1LOH pdb file                               |
| <b>2179</b>        | 1FCV pdb file                               |
| <b>2180</b>        | 2PE4 pdb file                               |
| <b>2181</b>        | 8SMN pdb file                               |
| <b>2182</b>        | S312G Swiss Model                           |
| <b>2183</b>        | S312K Swiss Model                           |
| <b>2184</b>        | S312L Swiss Model                           |
| <b>2185</b>        | S312N Swiss Model                           |
| <b>2186</b>        | N47_N219A_S312T Swiss Model                 |
| <b>2187</b>        | N47A_N131A_S312T Swiss Model                |
| <b>2188</b>        | N47A_N313A_N219A_S312T Swiss Model          |
| <b>2189</b>        | N131A_N219A_S312T Swiss Model               |
| <b>2190</b>        | Orangutan S312T Swiss Model                 |
| <b>2191</b>        | PH20 Swiss Model                            |
| <b>2192</b>        | S312T Swiss Model                           |
| <b>2193</b>        | Chimpanzee S312N Swiss Model                |
| <b>2194</b>        | Gibbon S312N Swiss Model                    |
| <b>2195</b>        | Chimpanzee S312T Swiss Model                |
| <b>2196</b>        | Gibbon S312T Swiss Model                    |
| <b>2197</b>        | N47A_N219A_S312N Swiss Model                |

| <b>Exhibit No.</b> | <b>Description</b>                                                                                                                                                      |
|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>2198</b>        | N47A_N131A_S312N Swiss Model                                                                                                                                            |
| <b>2199</b>        | N47A_N131A_N219A_S312N Swiss Model                                                                                                                                      |
| <b>2200</b>        | N131A_N219A_S312N Swiss Model                                                                                                                                           |
| <b>2201</b>        | Orangutan S312N Swiss Model                                                                                                                                             |
| <b>2202-2213</b>   | <i>Intentionally Left Blank</i>                                                                                                                                         |
| <b>2214</b>        | Declaration of Zachariah Summers in Support of <i>Pro Hac Vice</i> Admission                                                                                            |
| <b>2215</b>        | Khurana, et al., “MF59 Adjuvant Enhances Diversity and Affinity of Antibody-Mediated Immune Response to Pandemic Influenza Vaccines,” Sci Transl Med. 3(85) (June 2011) |
| <b>2216-2299</b>   | <i>Intentionally Left Blank</i>                                                                                                                                         |
| <b>2300</b>        | Errata sheet for Declaration of James Naismith, Ph.D.                                                                                                                   |
| <b>2301</b>        | Transcript of the Deposition of James Naismith, Ph.D., February 6, 2026                                                                                                 |
| <b>2302</b>        | Transcript of the Deposition of Garnett H. Kelsoe, Ph.D., February 5, 2026                                                                                              |
| <b>2303-2399</b>   | <i>Intentionally Left Blank</i>                                                                                                                                         |
| <b>2400</b>        | Merck & Co., Inc. Form 10-Q, Securities and Exchange Commission, November 5, 2025                                                                                       |
| <b>2401</b>        | E-mail Correspondence between Counsel for Petitioner and Patent Owner, January 6, 2026 (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)                                       |

| <b>Exhibit No.</b> | <b>Description</b>                                                                                                                                                                                                                 |
|--------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>2402</b>        | MERCK_PGR00006 - 30November2023 Merck 031988 Master Agreement - executed 4932-6153-3216 1_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)                                                                                      |
| <b>2403</b>        | MERCK_PGR00056 - MSA - Term 4 - Dechert LLP_Signed_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)                                                                                                                             |
| <b>2404</b>        | MERCK_PGR00467 - Mark Stewart Offer Letter_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)                                                                                                                                     |
| <b>2405</b>        | MERCK_PGR00052 - Hecht Engagement Letter (7-19)_Signed (Redacted)_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)                                                                                                              |
| <b>2406</b>        | MERCK_PGR00086 - Park Engagement Letter with signature - sjp (redacted)_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)                                                                                                        |
| <b>2407</b>        | “Executive team,” MSD, accessible at <a href="http://www.msd.com/company-overview/leadership/executive-team/">http://www.msd.com/company-overview/leadership/executive-team/</a> (last accessed January 5, 2026)                   |
| <b>2408</b>        | “Executive team,” Merck, accessible at <a href="http://www.merck.com/company-overview/leadership/executive-team/">http://www.merck.com/company-overview/leadership/executive-team/</a> (last accessed January 5, 2026)             |
| <b>2409</b>        | “Board of directors,” MSD, accessible at <a href="http://www.msd.com/company-overview/leadership/board-of-directors/">http://www.msd.com/company-overview/leadership/board-of-directors/</a> (last accessed January 5, 2026)       |
| <b>2410</b>        | “Board of directors,” Merck, accessible at <a href="http://www.merck.com/company-overview/leadership/board-of-directors/">http://www.merck.com/company-overview/leadership/board-of-directors/</a> (last accessed January 5, 2026) |
| <b>2411</b>        | “Contact us,” MSD, accessible at <a href="http://www.msd.com/contact-us/">http://www.msd.com/contact-us/</a> (last accessed January 5, 2026)                                                                                       |

| Exhibit No. | Description                                                                                                                                                    |
|-------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2412        | “Contact us,” Merck, accessible at <a href="http://www.merck.com/contact-us/">http://www.merck.com/contact-us/</a> (last accessed January 5, 2026)             |
| 2413        | “Who we are,” MSD, accessible at <a href="http://www.msd.com/company-overview/">http://www.msd.com/company-overview/</a> (last accessed January 5, 2026)       |
| 2414        | “Who we are,” Merck, accessible at <a href="http://www.merck.com/company-overview/">http://www.merck.com/company-overview/</a> (last accessed January 5, 2026) |
| 2415        | Merck & Co., Inc. Form 10-K, Securities and Exchange Commission, February 25, 2025                                                                             |
| 2416        | USPTO OED Practitioner Search - Mark J. Stewart, October 30, 2025                                                                                              |
| 2417        | Petition for <i>Inter Partes</i> Review, <i>Merck Sharp &amp; Dohme LLC v. The Johns Hopkins University</i> , IPR2024-00240 (P.T.A.B.), November 30, 2023      |
| 2418        | Petition for <i>Inter Partes</i> Review, <i>Merck Sharp &amp; Dohme LLC v. The Johns Hopkins University</i> , IPR2024-00622 (P.T.A.B.), March 4, 2024          |
| 2419        | Petition for <i>Inter Partes</i> Review, <i>Merck Sharp &amp; Dohme LLC v. The Johns Hopkins University</i> , IPR2024-00623 (P.T.A.B.), March 4, 2024          |
| 2420        | Petition for <i>Inter Partes</i> Review, <i>Merck Sharp &amp; Dohme LLC v. The Johns Hopkins University</i> , IPR2024-00624 (P.T.A.B.), March 4, 2024          |
| 2421        | Petition for <i>Inter Partes</i> Review, <i>Merck Sharp &amp; Dohme LLC v. The Johns Hopkins University</i> , IPR2024-00625 (P.T.A.B.), March 4, 2024          |

| <b>Exhibit No.</b> | <b>Description</b>                                                                                                                                     |
|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>2422</b>        | Petition for <i>Inter Partes</i> Review, <i>Merck Sharp &amp; Dohme LLC v. The Johns Hopkins University</i> , IPR2024-00647 (P.T.A.B.), March 13, 2024 |
| <b>2423</b>        | Petition for <i>Inter Partes</i> Review, <i>Merck Sharp &amp; Dohme LLC v. The Johns Hopkins University</i> , IPR2024-00648 (P.T.A.B.), March 13, 2024 |
| <b>2424</b>        | Petition for <i>Inter Partes</i> Review, <i>Merck Sharp &amp; Dohme LLC v. The Johns Hopkins University</i> , IPR2024-00649 (P.T.A.B.), March 13, 2024 |
| <b>2425</b>        | Petition for <i>Inter Partes</i> Review, <i>Merck Sharp &amp; Dohme LLC v. The Johns Hopkins University</i> , IPR2024-00650 (P.T.A.B.), March 13, 2024 |
| <b>2426</b>        | MERCK_PGR00035 - 20250813 Payment Remittance_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)                                                       |
| <b>2427</b>        | MERCK_PGR00042 - Dechert T360 Halozyme - 202500327_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)                                                 |
| <b>2428</b>        | MERCK_PGR00045 - FW_Atnn_Accounts Receivable Dept - PAYMENT REMITTANCE DETAIL (Nov 2025)_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)           |
| <b>2429</b>        | MERCK_PGR00049 - Halozyme - 202000447 - Invoices 5_1_2024-12_22_2025_1 of 3_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)                        |
| <b>2430</b>        | MERCK_PGR00465 - Mark Stewart Payroll Statement for Dec 12 2025_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)                                    |
| <b>2431</b>        | MERCK_PGR00001 - Workday - Ginkel Organization Screen Shot (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)                                                  |

| <b>Exhibit No.</b> | <b>Description</b>                                                                                                                           |
|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| <b>2432</b>        | MERCK_PGR00002 - Workday - Lally Organization Screen Shot (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)                                         |
| <b>2433</b>        | MERCK_PGR00003 - Workday - Majchrzak Organization Screen Shot (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)                                     |
| <b>2434</b>        | MERCK_PGR00004 - Workday - Stewart Organization Screen Shot (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)                                       |
| <b>2435</b>        | MERCK_PGR00005 - Workday - Su Organization Screen Shot (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)                                            |
| <b>2436</b>        | MERCK_PGR00036 - 20250903 Payment Remittance_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)                                             |
| <b>2437</b>        | MERCK_PGR00037 - 20251001 Payment Remittance_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)                                             |
| <b>2438</b>        | MERCK_PGR00038 - 20251203 Payment Remittance_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)                                             |
| <b>2439</b>        | MERCK_PGR00040 - 20251215 Payment Remittance_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)                                             |
| <b>2440</b>        | MERCK_PGR00046 - FW_Atn_Accounts Receivable Dept - PAYMENT REMITTANCE DETAIL (Oct 2025)_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)  |
| <b>2441</b>        | MERCK_PGR00047 - FW_Atn_Accounts Receivable Dept - PAYMENT REMITTANCE DETAIL (Sept 2025)_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL) |
| <b>2442</b>        | MERCK_PGR00048 - Halozyme - 202000447 - Invoice IN00125072310 Review History (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)                      |
| <b>2443</b>        | MERCK_PGR00050 - Halozyme - 202000447 - Invoices 5_1_2024-12_22_2025_2 of 3_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)              |

| <b>Exhibit No.</b> | <b>Description</b>                                                                                                                                                                                                     |
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| <b>2444</b>        | MERCK_PGR00051 - Halozyme - 202000447 - Invoices 5_1_2024-12_22_2025_3 of 3_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)                                                                                        |
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## I. INTRODUCTION

The primary dispute between the parties is whether POSAs can predictably multiply mutate PH20 *when using the patent's mutagenesis data*. The overwhelming evidence of record shows that POSAs can do so without undue experimentation. Petitioner ignores the patent data and raises theoretical problems with no evidence they apply to PH20—including effects its own experts called “not very common.” Petitioner’s claim construction errors are similarly dispositive. Petitioner’s Grounds should be rejected.

## II. CLAIM CONSTRUCTION

### A. The Claims Are Structural, Not Functional

The claimed modified PH20 polypeptides are defined by their structure—a the S312 mutation and 91% sequence identity—not by their function. Petitioner’s expert, Dr. Kelsoe, admitted as much:

Q So you don’t read claim 1 to require any hyaluronidase activity, right?

A. To the best of my understanding, no.

EX2302, 41:6-12; 48:1-4. Whether a polypeptide falls within the claim depends entirely on what the polypeptide *is*, not what it *does*.

Originally, Petitioner read enzymatic activity into the claims, arguing that the term “modified PH20 polypeptide” was defined to require at least 40% activity. But Petitioner’s expert, Dr. Hecht, admitted at deposition that the term “modified

PH20 polypeptide” is used in the specification to refer to both active and inactive PH20s. EX2076, 189:1-194:12, 172:21-173:17, 213:1-215:19, 221:8-223:22. Dr. Hecht explained that he simply ignored this teaching because it was “contradictory” to his opinion. *Id.*, 190:2-191:11.

On Reply, Petitioner replaced Dr. Hecht with Dr. Naismith. This fixed nothing. Dr. Naismith admits that “the definition of ‘modified PH20 polypeptide’ in the common disclosure considered in isolation does not explicitly state that each modified PH20 polypeptide is enzymatically active.” EX1133, ¶109. Thus, while Petitioner for itself still claims 40% activity is required (Reply, 4, fn. 13), Dr. Naismith does not: he testified that PH20s with far less than 40% activity are within the claim’s scope. EX2301, 194:9-14, 197:10-21, 192:13-198:21.

Petitioner and Dr. Naismith do agree, however, that “PH20” in the phrase “modified PH20 polypeptide” means the claims cover only “properly folded” modified PH20s. Reply, 1-4; EX2301, 200:9-16. This argument, like Petitioner’s abandoned and contradicted arguments, similarly conflicts with the specification.

First, “PH20” is itself a defined term, and the definition does not mention proper folding: “As used herein, PH20 refers to a type of hyaluronidase that occurs in sperm and is neutral-active.” EX1001, 45:56-57. Second, like “modified PH20 polypeptide,” the specification uses “PH20” to refer to both active and inactive polypeptides, so Petitioner’s construction is inconsistent with the specification.

EX1001, 116:59-117:12; 79:27-29. Third, Petitioner contends that because wild type PH20, which is a membrane-bound sperm cell protein, is active and properly folded, “PH20” must be too. But the claims are directed to *modified* PH20 polypeptides which are C-terminally truncated and not membrane-bound or in sperm.

Petitioner’s new expert, Dr. Naismith, took things even further from the claims and specification. He testified that “properly” folded meant “stably” folded, which he said meant exhibiting activity at **8 hours**. EX2301, 138:6-141:19, 180:2-184:24, 190:9-19, 200:9-16, 250:17-25. Of course, the patent’s activity data was measured after 90 minutes. EX1001, Example 3.

**B. Petitioner And Its Experts Contradict Each Other**

Because there is no functional claim language, Petitioner and its experts disagree on what exact function is required, as shown above. The Board can treat these self-contradictory positions as dispositive. *Finesse*, 1227. At a minimum, the Board cannot ignore them when assessing credibility.

**C. When Properly Construed, There Is No Dispute the Claims Meet Section 112**

Petitioner mistakenly contends that claim construction is irrelevant to patentability based on a mischaracterization of PO’s position. Reply, 2. That is not the case.

As PO explained, under either its proposed construction or the Board’s

preliminary construction, which requires “some” hyaluronidase activity, Section 112 is satisfied. POR, 44-82. But a proper claim construction is essential for a proper Section 112 analysis. That is because PO need not enable or describe unclaimed features.

Here, as in *Boehringer II*, although the claims encompass a subset of functional species, the claimed genus is not limited to polypeptides with a specific function. PO Preliminary Response, 18-22; POR, 43-44. When the claims are properly construed, Petitioner admits that the POSA can distinguish the claimed sequences in the genus (EX2301, 225:22-226:7; EX2076, 203:18-204:18), and that it is routine to make and use the claimed polypeptides (EX1003, ¶¶198-203).

### **III. THE PATENT’S MUTAGENESIS DATA MAKES MODIFYING PH20 PREDICTABLE**

Beyond claim construction, the parties’ primary dispute is whether the patent data could be used to predict the effects of multiple changes in the PH20 sequence such that the POSA could visualize and recognize the claimed genus and practice the full scope of the claims without undue experimentation.

The evidence shows a POSA could do so.

Drs. Petsko and Simpson detail what was known about PH20 *before* disclosure of the patent’s vast mutagenesis study, including the location of catalytic and substrate binding residues, essential glycosylation sites, and effect of C-terminal truncations on activity. EX2070, ¶¶112-230; EX2068, ¶¶110-157.

Additionally, all parties agree that an accurate homology model of PH20's structure, showing the distorted PH20 alpha-beta barrel fold and location of each amino acid in the structure, was available to a POSA. Pet., 11-15, 74, 101-108; EX1004, ¶¶36, 104-149; EX2077, 176:2-5; EX1130, 97:14-99:10; EX2070, ¶¶112-230, 343-434; EX2068, ¶¶95-157.

With this information, Dr. Simpson, a PH20 expert, and Dr. Petsko explained how POSAs could, *using the patent's disclosure*, visualize and recognize the genus and predictably practice the full scope of the claims.

**A. What the Disclosure Shows**

The patent teaches the results of a systematic mutagenesis study in which each of 447 positions on PH20 was changed to up to 18 amino acids. EX2068, ¶ 196. Dr. Petsko imported the mutagenesis data into a spreadsheet (EX2166) and color coded it to show positions that tolerated:

- all tested substitutions (43 positions/9%/dark green);
- no tested substitutions (94 positions/21%/red);
- 60% or more (115 positions/26%/light green);
- 30% or less (120 positions/27%/orange).

The results are below:

|          |    |      |      |       |       |       |       |       |       |       |       |       |       |       |       |
|----------|----|------|------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
|          |    | 30 D | 61 L | 92 A  | 123 W | 154 K | 185 L | 216 W | 247 V | 278 L | 309 I | 340 M | 371 A | 402 C | 433 F |
| Position | WT | 31 E | 62 G | 93 K  | 124 K | 155 Q | 186 F | 217 L | 248 R | 279 K | 310 M | 341 C | 372 I | 403 Y | 434 L |
| 1        | L  | 32 P | 63 Y | 94 K  | 125 P | 156 E | 187 P | 218 W | 249 E | 280 F | 311 R | 342 S | 373 Q | 404 S | 435 K |
| 2        | N  | 33 L | 64 Y | 95 D  | 126 K | 157 F | 188 D | 219 N | 250 A | 281 L | 312 S | 343 Q | 374 L | 405 T | 436 P |
| 3        | F  | 34 D | 65 P | 96 I  | 127 D | 158 E | 189 C | 220 E | 251 I | 282 S | 313 M | 344 V | 375 E | 406 L | 437 P |
| 4        | R  | 35 M | 66 Y | 97 T  | 128 V | 159 K | 190 Y | 221 S | 252 R | 283 Q | 314 K | 345 L | 376 K | 407 S | 438 M |
| 5        | A  | 36 S | 67 I | 98 F  | 129 Y | 160 A | 191 N | 222 T | 253 V | 284 D | 315 S | 346 C | 377 G | 408 C | 439 E |
| 6        | P  | 37 L | 68 D | 99 Y  | 130 K | 161 G | 192 H | 223 A | 254 S | 285 E | 316 C | 347 Q | 378 G | 409 K | 440 T |
| 7        | P  | 38 F | 69 S | 100 M | 131 N | 162 K | 193 H | 224 L | 255 K | 286 L | 317 L | 348 E | 379 K | 410 E | 441 E |
| 8        | V  | 39 S | 70 I | 101 P | 132 R | 163 D | 194 Y | 225 Y | 256 I | 287 V | 318 L | 349 Q | 380 F | 411 K | 442 E |
| 9        | I  | 40 F | 71 T | 102 V | 133 S | 164 F | 195 K | 226 P | 257 P | 288 Y | 319 L | 350 G | 381 T | 412 A | 443 P |
| 10       | P  | 41 I | 72 G | 103 D | 134 I | 165 L | 196 K | 227 S | 258 D | 289 T | 320 D | 351 V | 382 V | 413 D | 444 Q |
| 11       | N  | 42 G | 73 V | 104 N | 135 E | 166 V | 197 P | 228 I | 259 A | 290 F | 321 N | 352 C | 383 R | 414 V | 445 I |
| 12       | V  | 43 S | 74 T | 105 L | 136 L | 167 E | 198 G | 229 Y | 260 K | 291 G | 322 Y | 353 I | 384 G | 415 K | 446 F |
| 13       | P  | 44 P | 75 V | 106 G | 137 V | 168 T | 199 Y | 230 L | 261 S | 292 E | 323 M | 354 R | 385 K | 416 D | 447 Y |
| 14       | F  | 45 R | 76 N | 107 M | 138 Q | 169 I | 200 N | 231 N | 262 P | 293 T | 324 E | 355 K | 386 P | 417 T |       |
| 15       | L  | 46 I | 77 G | 108 A | 139 Q | 170 K | 201 G | 232 T | 263 L | 294 V | 325 T | 356 N | 387 T | 418 D |       |
| 16       | W  | 47 N | 78 G | 109 V | 140 Q | 171 L | 202 S | 233 Q | 264 P | 295 A | 326 I | 357 W | 388 L | 419 A |       |
| 17       | A  | 48 A | 79 I | 110 I | 141 N | 172 G | 203 C | 234 Q | 265 V | 296 L | 327 L | 358 N | 389 E | 420 V |       |
| 18       | W  | 49 T | 80 P | 111 D | 142 V | 173 K | 204 F | 235 S | 266 F | 297 G | 328 N | 359 S | 390 D | 421 D |       |
| 19       | N  | 50 G | 81 Q | 112 W | 143 Q | 174 L | 205 N | 236 P | 267 A | 298 A | 329 P | 360 S | 391 L | 422 V |       |
| 20       | A  | 51 Q | 82 K | 113 E | 144 L | 175 L | 206 V | 237 V | 268 Y | 299 S | 330 Y | 361 D | 392 E | 423 C |       |
| 21       | P  | 52 G | 83 I | 114 E | 145 S | 176 R | 207 E | 238 A | 269 T | 300 G | 331 I | 362 Y | 393 Q | 424 I |       |
| 22       | S  | 53 V | 84 S | 115 W | 146 L | 177 P | 208 I | 239 A | 270 R | 301 I | 332 I | 363 L | 394 F | 425 A |       |
| 23       | E  | 54 T | 85 L | 116 R | 147 T | 178 N | 209 K | 240 T | 271 I | 302 V | 333 N | 364 H | 395 S | 426 D |       |
| 24       | F  | 55 I | 86 Q | 117 P | 148 E | 179 H | 210 R | 241 L | 272 V | 303 I | 334 V | 365 L | 396 E | 427 G |       |
| 25       | C  | 56 F | 87 D | 118 T | 149 A | 180 L | 211 N | 242 Y | 273 F | 304 W | 335 T | 366 N | 397 K | 428 V |       |
| 26       | L  | 57 Y | 88 H | 119 W | 150 T | 181 W | 212 D | 243 V | 274 T | 305 G | 336 L | 367 P | 398 F | 429 C |       |
| 27       | G  | 58 V | 89 L | 120 A | 151 E | 182 G | 213 D | 244 R | 275 D | 306 T | 337 A | 368 D | 399 Y | 430 I |       |
| 28       | K  | 59 D | 90 D | 121 R | 152 K | 183 Y | 214 L | 245 N | 276 Q | 307 L | 338 A | 369 N | 400 C | 431 D |       |
| 29       | F  | 60 R | 91 K | 122 N | 153 A | 184 Y | 215 S | 246 R | 277 V | 308 S | 339 K | 370 F | 401 S | 432 A |       |

The patent’s disclosure provides a granular structure/function correlation that teaches, on a position-by-position basis, the effect on activity of substituting different amino acids into every position within the primary structure.

## B. How a POSA Would Visualize and Use the Disclosure

To evaluate written description and enablement, Drs. Petsko and Simpson used the same “visualization-based assessment” technique that Petitioner admits was “prevalent in 2011” and “provid[es] a consistent, objective and unbiased evaluation of substitutions.” Pet., 102-107. Indeed, Petitioner admits this method can be used to predict the effects of up to five modifications, *without the patent data*. EX1003, ¶158; EX1004, ¶144; EX1133, ¶258, fn. 289 (citing Hecht, Park for same).

Specifically, they overlayed the tolerance data onto the same prior art PH20 model used by Petitioner’s expert in order to visualize the data, as a POSA would.

As Petitioner's expert, Dr. Park, explained:

Q. So what's the purpose of generating a homology model for a protein structure?

**A. It allows you to look at the molecule, as opposed to imagining it in your head.**

Q. And it's useful to be able to look at the molecule, right?

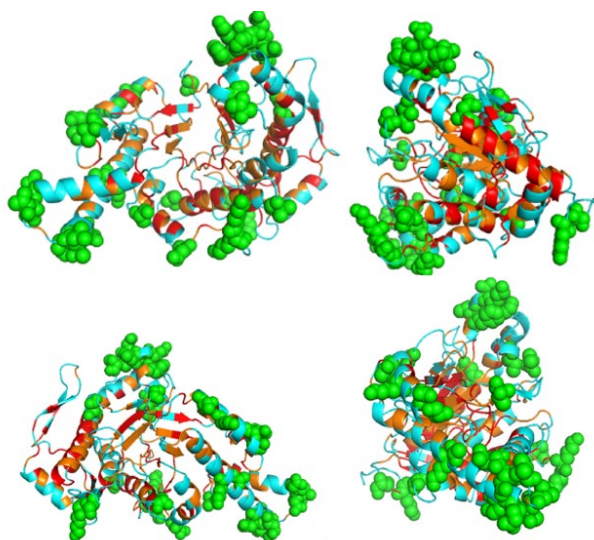
A. Absolutely.

Q. And you can use homology modeling to predict the impact of substitutions in a protein?

**A. A homology model can help you to evaluate the impact of a substitution. Yes.**

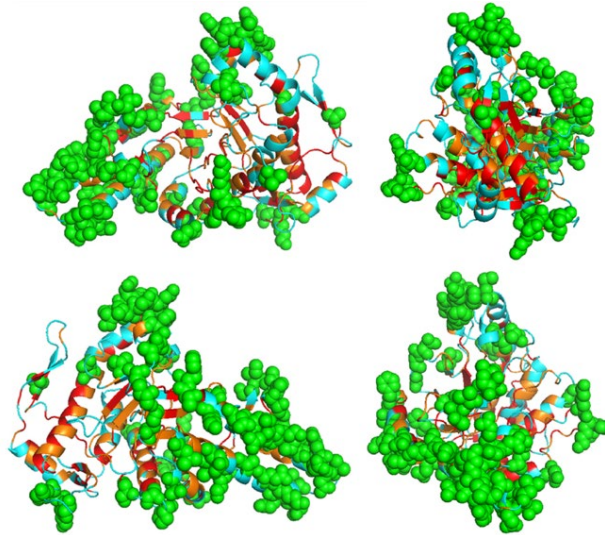
EX2077, 53:15-54:5.

Using this routine method, Dr. Petsko showed how a POSA would visualize, for instance, "those positions that tolerate all of the tested changes in green in the 'sphere' format":



EX2070, ¶320.

Similarly, Dr. Petsko generated figures showing positions that tolerated 90% or more of the tested changes:



EX2070, ¶321.

As Dr. Petsko testified, “[t]aken together, these figures show that there are many positions that are very tolerant of substitution on the surface of PH20 that can be targeted by a POSA seeking to generate a modified PH20 that retains hyaluronidase activity.” EX2070, ¶322. As he testified at deposition based on the patent data:

Q. So your opinion is that a POSA could use the data from testing single mutants in the patent to select 15 or 20 substitutions in the PH20 sequence, and you would be able to predict whether that mutated 15 or 20 residue-mutated PH20 will exhibit the activity that you are hoping to get?

**A. My opinion is that you could do so....**

\*\*\*

**A POSA would have the capability of both visualizing and practicing the full scope of the claims if they needed to.** They could -- that is to say, they could look at any particular type of variant that fit the claim and they could make that variant and they would be able to predict beforehand what that variant might do with a -- in many cases, on a high degree of confidence.

EX1131, 111:9-19, 114:5-16; EX2070, ¶355.

Similarly, as Dr. Simpson testified:

**[A] POSA would have had the information to choose to make a set of PH20 polypeptides that fit the criteria of the claim, and to be able to use them in the manner they intended. They would be able to visualize the species within the claim.**

\*\*\*

The POSA could then use [the mutagenesis data] to choose, depending on whether their goal was to have the protein remain active or whether they did not care about having activity retained...**They would have information that would allow them to make the 95% identical polypeptide that would meet those criteria for them.**

EX1130, 95:5-10, 97:14-98:10; EX2068, ¶¶31-45.

Put succinctly: “A POSA could select 23 residues to change and reasonably expect to obtain an active PH20 as those changes were based on the data in the patent.” EX2070, ¶359; *see Ajinomoto*, 1358-61; *see Wands*, 737.

Moreover, Drs. Petsko and Simpson testified that a POSA’s ability to practice the claims was not limited to independent changes at highly tolerated

positions. Instead, POSAs could evaluate additional substitutions or “make informed decisions about making several changes close together in the protein using the data in the ’035 patent regarding which substitutions were tested and the results for each, combined with an assessment of the local environment of the residues in question.” EX2070, ¶324; EX1130, 97:14-98:10, 101:21-102:21, 190:12-195:25.

Notably, Dr. Park made just such an assessment of the local environment as part of an evaluation that Petitioner characterized as “prevalent.” And Dr. Hecht admitted that using this visualization technique “you look at [a change] in the context of its physical chemical environment in the protein and in the context of its homologous environment sequence space, then you’re better able to come up with an assessment of the properties of a potential mutation.” EX2076, 72:15-73:6. He referred to this as a “more informed analysis of what would be the impact of such changes.” EX2076, 75:10-17. It is undisputed that POSAs understand the characteristics of amino acids, such as their charge/size/polarity and propensity to be present in secondary structures, and could evaluate their replacement using routine techniques, including visualizing interactions at the atomic level. EX2070, ¶¶61-67, 343-434. As Dr. Petsko explained:

Q. And they could do that for  $10^{49}$  – a number that -- I'm sorry.  
They can do that for a number of modified PH20 polypeptides that approaches  $10^{49}$  different sequences?

**A. They can do that for any member of the  $10^{49}$  sequences that they wish to examine. Okay? A person of skill in the art would do it that way.**

EX1131, 114:17-24. And, as Dr. Petsko confirmed, *the patent data are critical* for this method:

Q. So is it fair to say that you could not have formed those opinions about the tolerability of individual positions in PH20 to modification without the mutagenesis data in the common disclosure?

A. I could not have formed that opinion for most of the residues in the protein without the mutagenesis data.

*Id.*, 148:1-8; *see also* 148:9-20.

This routine method allows a POSA to reliably predict the effect of mutations based on the examples in the patent, without making and testing all of them as Petitioner contends is necessary. That is because, as Dr. Petsko explains, the “informational content” of knowing the effect of so many substitutions across the full sequence is “enormous”:

Q. So if you look at the entire genus that it has a set of changes that can include up to 21 or 22 mutations, the portion of the genus that is reflected in the dataset is a tiny, tiny fraction of that genus, right?

A. So the -- what is reflected in the patent is a subset. Okay. Which has a particular number of mutations. A few thousand. Sounds about

right. **The real question is: What about the information content?**

**The information content of that particular set of substitutions is enormous. And when combined with the structural information from modeling the PH20 structure, it allows you to visualize and make predictions about much more of the dataset than just what you see here.**

EX1131, 113:2-18.

Relatedly, and as importantly, with the patent data in hand, the POSA can avoid the billions of PH20s that will be inactivated by changes identified in the patent. Petitioner makes much of Dr. Petsko's testimony in this regard, but it mistakes its import entirely. There is no dispute that PH20s with the inactivating changes identified in the patent will stay inactive, even if further mutations are made, absent intentional "rescue" mutations. As Dr. Hecht testified, if you break a PH20, it will remain broken. EX2076, 228:1-9.

As Dr. Petsko explains, the number of inactivating mutations "does not mean PH20 is unpredictable or that making and using the claimed modified polypeptides is unpredictable." EX2070, ¶293. It means "[t]he '035 patent renders modifying PH20 predictable by identifying these areas that are particularly intolerant to mutation" while also teaching "where to make mutations to likely retain activity." *Id.*

Petitioner contends that the data on inactivating mutations should be ignored because those data do not differentiate proteins that failed to fold from those that

folded but lacked activity. Reply, 31-34. This ignores structural knowledge of PH20 regarding positions essential to folding. And it does not detract from the value of these data in showing which mutations inactivate the protein.

Petitioner also contends that because Dr. Petsko could not give a precise number of properly folded active modified PH20s satisfying the claims, the claims are invalid. Reply, 7-8. Section 112 imposes no such requirement.

**C. Drs. Petsko and Simpson Did Not Contradict the Specification**

Petitioner contends that the patent mandates a random screening approach to making multiply mutated PH20s (Reply, 34), and thus that Drs. Petsko and Simpson contradict the common disclosure by using the same “prevalent” method used by Petitioner’s experts. Pet., 99-107; Reply, 8-9. But Petitioner misunderstands the specification. The experiment that Petitioner identifies involves testing for stability—not activity—and that approach is called out as exemplary only. EX1026, 47:11-18, 141:7-33; 150:1-26. The patent in no way mandates it.

Patentee’s experts admitted it was “*very common and expected* for a POSA to generate a model and consider the substitution in that structural context,” as Patentee’s experts did. EX2077, 176:2-5; EX2076, 75:10-17. Petitioner had the burden of showing that all modes are insufficient to enable the claims, and it has failed. *CellPro*, 1361; *Invitrogen*, 1071.

**D. Petitioner's Theoretical Concerns About Unpredictability  
Contradict the Record and Are Unsupported**

Petitioner insists that introducing multiple mutations into PH20 is unpredictable, raising on Reply various theoretical problems concerning protein folding, aggregation and the specter of “epistasis.” But both parties’ experts agree these effects are “rare” and “not very common.” EX2077, 199:20-201:13. And Petitioner, unlike in other Section 112 cases, has a complete failure of proof in this regard: it does not point to a single example of a modified PH20 that contradicts what a POSA would predict using the data in the patent.

Petitioner’s arguments about misfolding rest on teachings about the possible conformations of *any* amino acid sequence. But here, the claim specifies a small range of sequences highly similar to mature PH20, and Petitioner’s expert admitted that if active, *they would fold to the PH20 alpha-beta barrel fold*. EX2301, 213:10-18, 85:19-86:595:9-20, 96:16-98:20, 99:13-18, 101:11-20, 159:13-25. Similarly, when asked whether a mutation will cause a modified PH20 to adopt a different structure, Dr. Petsko responded “[t]hat would not be the case for PH20.” EX1131, 41:22-42:7. Dr. Petsko further explained that misfolding due to mutation is “usually not the case for most mutations,” and “it is rare.” EX1131, 40:18-24; 197:6-15. When asked about the potential for mutations to cause aggregation, Dr. Petsko explained that is “not a common consequence,” and more specifically, “[i]f I make, typically, 100 mutations in a protein, okay, one or two might do that. None

of them might do that.” *Id.*, 48:23-49:8.

Petitioner also emphasizes the alleged potential for unpredictable effects resulting from epistasis. First, Petitioner argues that, though one can investigate the local environment, sometimes residues far apart in the structure can affect each other surprisingly. But Dr. Park testified that such effects “not very common”: “Distant residues are known to be coupled in some cases, ***but they’re not very common.***” EX2077, 200:14-201:13. He further admitted that, because the effect is uncommon, POSAs can estimate the combined effect of mutations: “So if you introduce a mutation that are far apart from each other, then each mutation can be treated independently and evaluated independently, and one may be able to estimate the combined effect of the two or more mutations, if necessary, and include whether the mutant would be better or worse than wild-type.” *Id.*, 201:7-13.

Similarly, Dr. Petsko explained that if two mutations “are separated from each other in the structure there is a high degree of likelihood that they will operate independently.” EX1131, 195:5-10. Moreover, even for this “not very common” phenomenon, Petitioner points to ***nothing*** that suggests the effect will abrogate activity entirely—*i.e.*, the evidence shows a predicted active PH20 will retain some hyaluronidase activity.

Moreover, Dr. Naismith admitted at deposition that epistasis simply refers to

the fact that multiple mutations will not necessarily be “additive” (EX2301, 129:17-130:18)—that is, that a POSA could not necessarily predict the precise activity level when combining mutations by looking at the effect on activity from individual mutations. But an exact prediction of activity level is not at issue here—particularly because Petitioner’s 40% activity construction must be rejected.

Petitioner suggests the patent’s disclosure shows the effect of epistasis is prevalent, pointing to the number of inactivating mutations. But as Dr. Petsko explains, the intolerant positions (and the tolerant positions) are not randomly scattered throughout the protein but rather are clustered, reflecting structural features rather than random epistatic effects. EX1131, 157:5-25; EX2070, ¶¶334-342.

Indeed, this strikes at the heart of why Petitioner’s 112 challenge fails: it has not shown any evidence, from prior art or post-filing, that cumulative effects of combining mutations (whether through epistasis or otherwise) renders visualizing, making, and using multiply-mutated PH20s unpredictable *when actually considering the mutagenesis data*. If modifying PH20 is so unpredictable, it should have been utterly trivial for them to do so. With Drs. Simpson’s and Dr. Petsko’s tolerance data and mappings in hand, if the patent data were as useless as Petitioner claims, Petitioner should have easily been able show multiple examples of sequences within the scope of the claims that produced results that were not

predicted by the patent's disclosure of tolerance data. Instead, *they did not submit a single example* that contradicts what the specification's disclosure teaches.

This is a complete failure of evidence. Petitioner cannot carry its burden on 112 with theoretical concerns in the face of PO showing, through its experts, how and why a POSA would have found making multiple substitutions to PH20 predictable in view of the patent's extraordinary disclosure of mutagenesis data.

**E. Testing to Confirm Active/Inactives Is Routine**

Once a POSA has used the patent's data to select and design a modified PH20, any confirmatory testing, if necessary, is routine. *Wands*, 736–37. As Drs. Petsko and Simpson explain, a “POSA would then make and test the desired polypeptide... to confirm desired properties. That is routine... It is routine experimentation.” EX2070, ¶348; EX2068, ¶¶360-361, 378-390. Confirmatory testing is routine because the patent's vast disclosure allow a POSA to select variants with high expectations about activity (or lack thereof). To the extent any results differ from those expectations, those instances would be rare, and the experimentation is not undue. *Wands*, 737-740; *CellPro*, 1360; *Cephalon*, 1336; *PPG*, 1564.

Contrary to Petitioner's argument, a POSA would not “ignore the information in the patent, generate an enormous library, and then screen billions of sequences,” (EX2070, ¶349), as in the *Idenix* and *Amgen* cases on which Petitioner

relies. Such screening is only necessary where a POSA lacks knowledge of the structure and lacks a predictable, routine method of practicing the invention.

Neither is present here.

The patent's extensive mutagenesis data transforms what would otherwise be exploratory work into routine experimentation. A POSA armed with this data does not guess; the POSA predicts, then confirms. Thus POSAs could "reliably predict" activity (*Ajinomoto*) and experimentation would not be "undue" (*Wands*). Section 112 is met.

**F. Numerosity Is Not a Basis for Invalidity Under § 112**

Petitioner avers, without support, that "experimentation for the size of the sequence space is impossible" because of the number of possible sequences. Reply, 9.

First, Petitioner's argument is mistaken as a matter of law. As *Wands* instructs, "[t]he test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Wands*, 737. If sheer numerosity were grounds for invalidity under 112, virtually any patent claim reciting a range—a formulation patent with excipient ranges, for instance—would be invalid. Such claims necessarily contain an infinite number of embodiments. That is plainly not

the law. *See Cellpro*, 1360 (no undue experimentation “where the experiments involve repetition of known or commonly used techniques.”); *Cephalon*, 1330 (same); *PPG*, 1558.

Second, Petitioner’s argument rests on its mistaken rejection of the patent data and belief that mutating PH20 is unpredictable and thus a POSA allegedly would start on a vast screening project. But a POSA would not, as Petitioner proposes, “start by calculating the theoretical maximum number of sequences” and screening. EX1130, 98:11-99:10, 97:14-23, 98:7-10. As Dr. Petsko testified: “the POSA would not start that way at all. They would start with a much more focused program making use of the data in the patent,” as set out above. EX1131, 106:21-25, 107:1-17, 113:20-114:24. That is because POSA could “reliably predict” actives and practice the claims without “undue” experimentation.

**G. Petitioner’s Experts Refused to Consider the Data But Provide No Evidence Contradicting It**

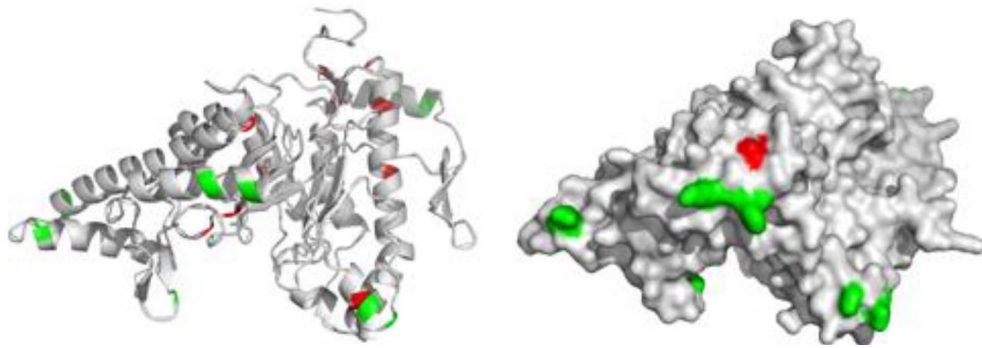
Despite Petitioner’s changing claim construction positions and invalidity theories, Petitioner has been steadfast in one thing: its refusal to actually consider the patent data.

Petitioner did not provide the patent data to Dr. Park at all.

Petitioner’s expert, Dr. Hecht, then characterized the data to the Board as a scattershot experiment with random changes and randomly selected positions, concluding it was of no use to a POSA. EX1003, ¶¶138-193. When he learned at

deposition the data was for every position in PH20, Dr. Hecht admitted that the patent data would in fact be useful in predicting changes in PH20. EX2076, 262:7-22, 253:9-254:12.

Petitioner then replaced Dr. Hecht with Dr. Naismith, who admitted that he had not heard of PH20 before this case. EX2301, 60:22-24. Dr. Naismith criticized assays that are common in the art, yet with which he has no familiarity (EX1133, ¶¶291-299; EX2301, 22:7-23), and dismissed the majority of the patent data by applying arbitrarily selected criteria. Thus, despite the disclosure of data for substitutions at all 447 positions in SEQ ID No. 3, he considered the data for *only 33 of those positions*, as shown below:



EX1133, ¶¶320, 305, 316, Appendix B-3.

Dr. Naismith provides no scientific basis for the limits he applied. And he admitted at deposition that his position that the activity data is unreliable rested on his misunderstanding of a *different assay*. EX2301, 308:2-19; 284:11-285:2, 277:7-278:4.

Evaluating written description and enablement requires evaluating the patent's actual disclosure. Petitioner has failed to offer *any* testimony to the Board doing so.

#### **IV. WRITTEN DESCRIPTION**

##### **A. The Specification Discloses Common Structural Features**

The record developed since Institution establishes that specification discloses the common structural features based on that primary structure and the related mutagenesis data:

- 91% sequence identity to the primary structure of the recited SEQ IDs;
- The S312 mutation;
- And for actives:
  - A PH20 alpha-beta barrel fold, with known catalytic and binding sites.
  - Lack of the inactivating changes identified in the disclosure.

Petitioner's primary response to this record is to argue that amino acid sequence is not in fact a structural feature. But Dr. Naismith admitted at deposition that both amino acid sequence and a particular recited residue are in fact structural features. EX2301, 57:9-60:10. Notably, under PO's claim construction, nothing more is required for written description: those features distinguish the polypeptides

that satisfy the claim from those that do not.

Beyond primary structure, Petitioner contends that the alpha-beta barrel motif is not a common structural feature shared by actives. But Dr. Naismith admitted at deposition that active PH20s within the scope of the claim will share the same PH20 alpha-beta barrel fold. EX2301, 213:10-18, 85:19-99:18, 101:11-20, 159:13-25.

Petitioner contends that the claimed genus is “structurally heterogeneous” (Reply, 7) because there can be variations in secondary structural features between actives. But the common structural features test does not require exactly identical structures. Dr. Naismith admitted that active modified PH20s will share the same alpha-beta barrel fold (EX2301, 213:10-18, 85:19-99:18, 101:11-20, 159:13-25), so any variation in structure amongst actives would not impact the fold or activity.

Petitioner makes much of the similarity in structure between human hyaluronidases, despite functional differences, to argue the PH20 alpha-beta barrel “can be ignored” as irrelevant to distinguishing actives. Reply, 21-22. But the common structural features must be considered *together*. While human hyaluronidases share an alpha-beta barrel fold, they are *not* 91% identical to PH20. EX2301, 215:19-217:2; EX2068, ¶¶105, 294-296. It is thus not surprising that while they share a common fold, some are not active.

Petitioner also argues that the specification does not disclose the PH20

alpha-beta barrel fold structure. But it is an inherent feature of the actives, and Petitioner acknowledges it was known in the art. EX2077, 175:18-176:5, 53:22-54:5; EX1004, ¶¶131-142, 33-52, 88-101. “[A] patentee may rely on information that is ‘well-known in the art’ for purposes of meeting the written description requirement, because the specification is viewed from the perspective of one of skill” in the relevant art. *Ajinomoto*, 1359; *Zoltek*, 1308. A POSA would use the prior art structure to easily visualize the actives based on the other common features, as Petitioner’s experts testified.

Finally, Petitioner makes much of a “hyal-EGF” domain,” which Petitioner acknowledges is common structural feature shared by actives. Petitioner contends the hyal-EGF domain is not identified by name in the specification. But the patent need not identify common structural features using Petitioner’s preferred terminology (particularly given the Hyal-EGF is a misnomer). The patent expressly reports the import of this region (“amino acid residues corresponding to positions 36-464... is the minimal sequence required for hyaluronidase activity”) and incorporates by reference Arming, which Petitioner itself says “proves” the region was essential based on its teaching that a C-terminal truncation mutant ending at position 340 was not secreted or active. EX1001, 69:66-70:14.

## **B. Representative Species**

As to representative species, Petitioner again relies on the numerosity, but

the law is clear this is not sufficient: “[No] bright-line rules govern[ ] ... the number of species that must be disclosed to describe a genus claim, as this number necessarily changes with each invention, and it changes with progress in a field.” *Ariad*, 1351; *Ajinomoto*, 1359.

There is no dispute that there are several highly active representative species disclosed in the specification. Moreover, Petitioner’s new expert admitted that all actives within the genus fold to the same PH20 alpha-beta barrel fold with catalytic and binding residues properly positioned, just as in the representative species. EX2301, 213:10-18, 85:19-99:18, 101:11-20, 159:13-25.

Petitioner thus only contests the reliability of the patent’s disclosure of structure/function correlation that makes the disclosed variants representative of further the sub-variants. PO addressed this issue in Section III.G above, and Petitioner’s attempt to disregard the mutagenesis data or diminish its predictive value should be rejected for the same reasons.

## **V.    ENABLEMENT**

The specification provides a detailed structure-function correlation that enables POSAs to predictably generate claimed PH20 variants with single or multiple amino acid substitutions and test them for activity using routine techniques.

Petitioner challenges only the predictability of determining active modified PH20s with five or more changes—not the routine nature of making and testing them. For the same reasons addressed in Section III, these challenges fail. But PO addresses the new arguments Petitioner raises below.

First, Petitioner focuses on the size of the “sequence space” encompassed by the claims. But, as set out above, this is not a case where a POSA would need to engage in a massive screening exercise to find, for instance, proteins capable of binding to a target. As Dr. Simpson explained at deposition, POSAs would be able to practice the full scope of the claims despite Petitioner’s “sequence space”: “no POSA would start with the theoretical maximum number of potential sequence variants as a starting point for making a comparative analysis of what amino acids would retain activity in a PH20 polypeptide.” EX1130, 93:20-24.

Instead, using the method Petitioner acknowledged was “prevalent” and used by Drs. Simpson and Petsko, “a POSA could determine...using the information in the disclosure, what would be reasonable locations... to make mutations such that the POSA would be able to narrow down the set of variant PH20 polypeptides to a manageable set that was fully accessible to them experimentally.” EX1030, 94:18-25.

In other words, POSAs would “be able to identify residues that would likely maintain the activity of the enzyme. And that would significantly narrow the scope

down from 10 to the 49th to a very small number of reasonable polypeptides that would fit that criterion.” EX1030, 92:25-93:7.

Second, Petitioner also contends that a POSA cannot identify the actives using the data in the disclosure because “most single mutations were deleterious.” Reply, 27. But, as addressed above, this mistakes the value of the disclosure of inactivating mutations. The patent discloses mutations at every position, including those positions essential for folding and activity. As Dr. Park explained, the importance of this data is knowing what to avoid:

Q. Would you expect that if you tried to introduce a mutation into a position known to be important for folding, that the -- that the protein would not be able to fold correctly?

A. I would expect that; **therefore, I would not try that.**  
EX2077, 106:12-17.

Third, Petitioner claims that the common PH20 alpha-beta barrel fold does not add to stability or predictability. But the 2009 paper (EX1144) Petitioner cites in this regard proves the opposite. In that paper, the authors intentionally *chose* areas most likely to disrupt the activity of the protein (not a PH20)—those near the catalytic domain. *Id.*, 949. The authors still found the fold “surprising[ly]” robust. Here, POSAs know far more.

Fourth, as addressed in Section III.G, Petitioner also criticizes the variability

of the patent data. But Dr. Simpson, who has experience with the patent's assays, explained why variability does not undermine reliability and is consistent with a POSA's expectation. EX2068, ¶¶202-203, 223-226, 182-183, 186. Petitioner, on the other hand, intentionally selected experts with absolutely *no prior experience* with hyaluronidases or PH20s. EX2301, 21:19-22:23; EX2077, 15:1-16:10; EX2076, 64:3-13; EX2302, 28:13-29:3.

Fifth, Dr. Naismith criticizes Dr. Petsko for evaluating what he termed “unreliable” positions on PH20. EX1133, ¶¶243-251, 284. But Dr. Park, whose analysis Dr. Naismith agreed with, considered those exact same positions in his analysis. EX2175; EX2176; EX2301, 267:7-18.

## **VI. THE SPECIFICATION ENABLES CREDIBLE CONTRACEPTIVE USE**

Petitioner initially dismissed the contraceptive utility of inactive PH20 variants as “not scientifically credible.” Pet., 80. In its Reply, Petitioner no longer disputes that inactive PH20 variants could have some contraceptive utility. Reply, 38-39. Petitioner instead argues that “contraceptive utility requires near 100% effectiveness.” *Id.* Petitioner's argument fails on the law and the facts.

As a matter of law, an invention that is at least partially successful in achieving a useful result still has credible utility. *Brana*; *Gardner*. Factually, Petitioner's expert agrees that no known human contraceptives achieve 100% effectiveness and substantially lower efficacy would still “have an important and

valuable” application. EX2302, 134:5-135:3. Additionally, Dr. Kelsoe—who, unlike Dr. Cherr, has no experience in reproductive biology or PH20—also erroneously assumed that binding to epitopes “relevant to reproduction” would be required. Reply, 40-41; EX1134, ¶¶108-109; EX2302, 26:11-33:13. But as Dr. Cherr explained, non-specific binding of anti-sperm antibodies was known to block fertility, independent of any reproduction-specific epitope. EX2072, ¶¶32-43; EX2074, ¶23. Petitioner’s expert admitted he was not familiar with literature showing that “allosteric effects” achieved by non-specific binding can provide contraceptive effect. EX2302, 113:18-123:20.

## **VII. THE CHALLENGED CLAIMS ARE NOT OBVIOUS**

Rather than offering any explanation for why position 312 would be targeted for substitution, Petitioner abandons the motivation requirement altogether and makes the sweeping—and unsupported—claim that *all* ~750 amino acid residues Dr. Park identifies as available for substitution would have been obvious under *KSR*. Reply, 42-43. That is plainly wrong: “there must be some reason to select a species from the genus.” ID, 55-56. Petitioner has not even attempted to identify a reason for selecting position 312 – other than attorney direction based on knowledge of the claimed invention. POR, 83-85.

Respectfully submitted,

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

1. This Patent Owner Sur-Reply complies with the type-volume limitation of 5,600 words, comprising 5,594 words, excluding the parts exempted by 37 C.F.R. § 42.24(a)(1).
2. This Patent Owner Sur-Reply complies with the general format requirements of 37 C.F.R. § 42.6(a) and has been prepared using Microsoft® Word in 14-point Times New Roman font.

Respectfully submitted,

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**CERTIFICATE OF SERVICE (37 C.F.R. § 42.6(e))**

I certify that the above-captioned **PATENT OWNER'S SUR-REPLY** and Exhibits 2215 and 2300-2302 were served in their entireties on February 18, 2026, upon the following parties via electronic mail:

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