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MERCK SHARP & DOHME LLC,
Petitioner

v.

HALOZYME INC.,
Patent Owner

Case PGR2025-00033
U.S. Patent No. 12,049,652

PATENT OWNER'S SUR-REPLY

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PATENT OWNER'S UPDATED EXHIBIT LIST

Exhibit No.	Description
2001	Declaration of Barbara Triggs-Raine, Ph.D. in support of Patent Owner Discretionary Denial Brief (WITHDRAWN)
2002	*Curriculum Vitae* of Barbara Triggs-Raine, Ph.D.
2003	Disclaimer in a Patent under 37 C.F.R. § 1.321(a), filed in U.S. Patent Application No. 18/064,886, June 13, 2025
2004	"Halozyme Therapeutics to Present Data on PEGPH20 at the Upcoming 2011 EORTC-NCIASCO Annual Meeting," Halozyme Therapeutics, Inc. Press Release, October 24, 2011
2005	LinkedIn profiles of Michael Shepard, Robert Connor, Ge (Gina) Wei, and Qiping Zhao
2006	Sequence listing of U.S. Patent Application No. 18/064,886
2007	Gifre, L., et al., "Trends in recombinant protein use in animal production," *Microb Cell Fact* 16:40 (2017)
2008	"Recombinant Drugs," Smithsonian Institution, accessible at https://www.si.edu/spotlight/birth-of-biotech/recombinant-drugs (last accessed February 27, 2025)
2009	Naz, R., "Antisperm Contraceptive Vaccines: Where We Are and Where We Are Going?," *American Journal of Reproductive Immunology* 66:5-12 (2011)
2010	Primakoff, P., et al., "Fully effective contraception in male and female guinea pigs immunized with the sperm protein PH-20," *Nature* 335:543-546 (October 6, 1988)
2011	Definition of "guinea pig," Merriam-Webster OnLine, archived by the Internet Archive on February 21, 2010, accessible at https://web.archive.org/web/20100221175034/http://www.merriam-webster.com/dictionary/guinea%20pig (last accessed February 27, 2025)

Exhibit No.	Description
2012	"A decade in numbers," *Nature Materials* 11:743-744 (September 2012)
2013	Lin, Y., *et al.*, "Molecular cloning of the human and monkey sperm surface protein PH-20," *Proc. Natl. Acad. Sci USA* 90:10071-10075 (November 1993)
2014	*Intentionally Left Blank*
2015	File History of U.S. Patent No. 7,872,107
2016	Pils, B., *et al.*, "Variation in structural location and amino acid conservation of functional sites in protein domain families," *BMC Bioinformatics* 6 (August 25, 2005)
2017	European Patent Application Publication No. 0953574 A1, published November 3, 1999
2018	Duterme, C., *et al.*, "Two Novel Functions of Hyaluronidase-2 (Hyal2) Are Formation of the Glycocalyx and Control of CD44-ERM Interactions," *The Journal of Biological Chemistry*, 284(48):33495-33508 (November 27, 2009)
2019	Atmuri, V., *et al.*, "Hyaluronidase 3 (*HYAL3*) knockout mice do not display evidence of hyaluronan accumulation," *Matrix Biology* 27 (2008)
2020	Hemming, R., *et al.*, "Mouse Hyal3 encodes a 45- to 56-kDa glycoprotein whose overexpression increases hyaluronidase 1 activity in cultured cells," *Glycobiology* 18(4):280-289 (2008)
2021	Miller, A., "Hyaluronidase 2 and its intriguing role as a cell-entry receptor for oncogenic sheep retroviruses," *Seminars in Cancer Biology* 18:296-301 (2008)

Exhibit No.	Description
2022	Kaneiwa, T. *et al.*, "Identification of human hyaluronidase-4 as a novel chondroitin sulfate hydrolase that preferentially cleaves the galactosaminidic linkage in the trisulfated tetrasaccharide sequence," *Glycobiology* 20(3):300-309 (March 2010)
2023	Petition for Post-Grant Review, *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. PGR2025-00004 (P.T.A.B.), November 26, 2024
2024	Petition for Post-Grant Review, *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. PGR2025-00003 (P.T.A.B.), November 12, 2024
2025	Petition for Post-Grant Review, *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. PGR2025-00009 (P.T.A.B.), December 27, 2024
2026	Petition for Post-Grant Review, *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. PGR2025-00006 (P.T.A.B.), December 10, 2024
2027	Petition for Post-Grant Review, *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. PGR2025-00030 (P.T.A.B.), February 4, 2025
2028	Petition for Post-Grant Review, *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. PGR2025-00024 (P.T.A.B.), February 21, 2025
2029	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. PGR2025-00004 (P.T.A.B.), November 26, 2024
2030	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. PGR2025-00003 (P.T.A.B.), November 12, 2024

Exhibit No.	Description
2031	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. PGR2025-00009 (P.T.A.B.), December 27, 2024
2032	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. PGR2025-00006 (P.T.A.B.), December 10, 2024
2033	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. PGR2025-00030 (P.T.A.B.), February 4, 2025
2034	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. PGR2025-00024 (P.T.A.B.), February 21, 2025
2035	Lokeshwar, V., *et al.*, "Regulation of Hyaluronidase Activity by Alternative mRNA Splicing," *The Journal of Biological Chemistry* 277(37):33654-33663 (2002)
2036	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. PGR2025-00017 (P.T.A.B.), January 17, 2025
2037	Petition for Post-Grant Review, *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. PGR2025-00017 (P.T.A.B.), January 17, 2025
2038	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. PGR2025-00039 (P.T.A.B.), March 28, 2025
2039	Petition for Post-Grant Review, *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. PGR2025-00039 (P.T.A.B.), March 28, 2025
2040-2044	*Intentionally Left Blank*

Exhibit No.	Description
2045	Declaration of Tyler C. Liu (originally served as Exhibit 2068) (*served not filed*)
2046	"2023 Pharma 50: The 50 largest pharma companies in the world," drugdiscoverytrends.com, accessible at https://www.drugdiscoverytrends.com/2023-pharma-50-largest-companies/ (last accessed April 28, 2025)
2047	"Merck Announces Fourth-Quarter and Full-Year 2024 Financial Results," Merck Press Release, February 4, 2025
2048	"Products list," Merck.com, accessible at https://www.merck.com/products/ (last accessed April 28, 2025)
2049	*Intentionally Left Blank*
2050	"Merck & Company, Inc. Common Stock (new) (MRK)," Nasdaq.com, accessible at https://www.nasdaq.com/market-activity/stocks/mrk (last accessed April 28, 2025)
2051	"Halozyme Therapeutics, Inc. Common Stock (HALO)," Nasdaq.com, accessible at https://www.nasdaq.com/market-activity/stocks/halo (last accessed April 28, 2025)
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 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 (last accessed April 28, 2025)
2053	"Commercial Products," Halozyme.com, accessible at https://halozyme.com/commercial-products/ (last accessed April 28, 2025)

Exhibit No.	Description
2054	"About Us," Halozyme.com, accessible at https://halozyme.com/about-us/#our-focus (last accessed April 28, 2025)
2055	Second Declaration of Barbara Triggs-Raine, Ph.D. in Support of Patent Owner's Preliminary Response (WITHDRAWN)
2056	Petition for Post-Grant Review, *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. PGR2025-00042 (P.T.A.B.), April 15, 2025
2057	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. PGR2025-00042 (P.T.A.B.), April 15, 2025
2058	Complaint for Patent Infringement and Declaratory Judgment of Patent Infringement, *Halozyme, Inc. v. Merck Sharp & Dohme Corp.*, 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 https://www.alteogen.com/en/ir_1/?uid=2223&mod=document&pageid=1 (last accessed April 28, 2025)
2060	Petition for Post-Grant Review, *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. PGR2025-00046 (P.T.A.B.), April 29, 2025
2061	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. PGR2025-00046 (P.T.A.B.), April 29, 2025
2062	Petition for Post-Grant Review, *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. PGR2025-00050 (P.T.A.B.), May 7, 2025
2063	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. PGR2025-00050 (P.T.A.B.), May 7, 2025

Exhibit No.	Description
2064	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. PGR2025-00053 (P.T.A.B.), June 6, 2025
2065	Petition for Post-Grant Review, *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. PGR2025-00053 (P.T.A.B.), June 6, 2025
2066	Petition for Post-Grant Review, *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. PGR2025-00052 (P.T.A.B.), June 27, 2025
2067	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. PGR2025-00052 (P.T.A.B.), June 27, 2025
2068	Declaration of Melanie A. Simpson, Ph.D. in Support of Patent Owner's Response
2069	*Curriculum Vitae* of Melanie A. Simpson, Ph.D.
2070	Declaration of Gregory A. Petsko, Ph.D. in Support of Patent Owner's Response
2071	*Curriculum Vitae* of Gregory A. Petsko, Ph.D.
2072	Declaration of Gary N. Cherr, Ph.D. in Support of Patent Owner's Response
2073	*Curriculum Vitae* of Gary N. Cherr, Ph.D.
2074	Declaration of James J. Moon, Ph.D. in Support of Patent Owner's Response
2075	*Curriculum Vitae* of James J. Moon, Ph.D.
2076	Transcript of the Deposition of Michael Hecht, Ph.D., August 26, 2025
2077	Transcript of the Deposition of Dr. Sheldon Park, August 7, 2025

Exhibit No.	Description
2078	Transcript of the Deposition of Dr. Sheldon Park, August 21, 2025
2079	Koehl, P. et al., "Structure-based conformational preferences of amino acids," *PNAS*, 96(22):12524-12529 (October 26, 1999)
2080	Pommié, C. et al., "IMGT standardized criteria for statistical analysis of immunoglobulin V-REGION amino acid properties," *Journal of Molecular Recognition*, 17:17-32 (2004)
2081	*Intentionally Left Blank*
2082	Kyte, J. et al., "A Simple Method for Displaying the Hydropathic Character of a Protein,"*Journal of Molecular Biology*, 157:105-132 (1982)
2083	*Assay Guidance Manual*, Eli Lilly & Company and the National Center for Advancing Translational Sciences
2084	"The Central Role of Enzymes as Biological Catalysts," NCBI Bookshelf, National Institutes of Health (accessible at https://www.ncbi.nlm.nih.gov/books/NBK9921/, last accessed September 22, 2025)
2085	French, S. et al., "What is a Conservative Substitution?", *Journal of Molecular Evolution*, 19:171-175 (1983)
2086	El-Safory, N. et al., "Hyaluronidases, a group of glycosidases: Current and future perspectives," *Carbohydrate Polymers*, 81:165-181 (2010)
2087	Lu, J. et al., "Hyaluronidase: structure, mechanism of action, diseases and therapeutic targets," *Molecular Biomedicine*, 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," *FEBS Letters*, 336(3):545-548 (December 1993)

Exhibit No.	Description
2090	Gmachl, M. et al., "Bee venom hyaluronidase is homologous to a membrane protein of mammalian sperm," *PNAS USA*, 90:3569-3573 (April 1993)
2091	Davies, G. et al., "Structures and mechanisms of glycosyl hydrolases," *Current Biology*, 3:853-859 (1995)
2092	Marković-Housley, Z. et al., "Crystal Structure of Hyaluronidase, a Major Allergen of Bee Venom," *Structure*, 8:1025-1035 (October 2000)
2093	U.S. Patent No. 8,343,487 B2 to Baker et al., issued January 1, 2013
2094	Thermo Scientific Multidrop® 384 User Manual, Rev. 3.4, Thermo Fisher Scientific (October 2008)
2095	*Intentionally Left Blank*
2096	Frost, G. et al., "A Microtiter-Based Assay for Hyaluronidase Activity Not Requiring Specialized Reagents," *Analytical Biochemistry*, 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," *Analytical Biochemistry*, 229:35-41 (1995)
2099	Takahashi, T. et al., "A fluorimetric Morgan-Elson assay method for hyaluronidase activity," *Analytical Biochemistry*, 322:257-263 (2003)
2100	Vines, C.V. et al., "Identification of a Hyaluronic Acid (HA) Binding Domain in the PH-20 Protein That May Function in Cell Signaling," *Molecular Reproduction and Development*, 60:542-552 (2001)

Exhibit No.	Description
2101	Wassarman, P. et al., "Structure and Function of the Mammalian Egg Zona Pellucida," *Journal of Experimental Zoology (Mol Dev Evol)*, 285:251-258 (1999)
2102	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," *Cell Tissue Res* 251:555-564 (1988)
2103	Tollner, T. et al., "Multifunctional glycoprotein DEFB126 – a curious story of defensin-clad spermatozoa," *Nature Reviews | Urology*, Vol. 9, pp. 365-375 (July 2012)
2104	Visconti, P. et al., "The Molecular Basis of Sperm Capacitation," *Journal of Andrology*, 19(2):242-248 (March/April 1998)
2105	Wassarman, P. et al., "A profile of fertilization in mammals," *Nature Cell Biology*, Vol. 3, pp. E59-E64 (February 2001)
2106	Bailey, J., "Factors Regulating Sperm Capacitation," *Systems Biology in Reproductive Medicine*, 56:334-348 (2010)
2107	Sabeur, K. et al., "The PH-20 Protein in Human Spermatozoa," *Journal of Andrology*, 18(2):151-158 (March/April 1997)
2108	Hunnicutt, 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," *Biology of Reproduction*, 55:80-86 (1996)
2109	Tollner, T. et al., "Beta-Defensin 126 on the Surface of Macaque Sperm Mediates Attachment of Sperm to Oviductal Epithelia," *Biology of Reproduction*, 78:400-412 (2008)
2110	Tollner, T. et al., "Release of DEFB126 From Macaque Sperm and Completion of Capacitation Are Triggered by Conditions That Simulate Periovulatory Oviductal Fluid," *Molecular Reproduction & Development*, 76:431-443 (2009)

Exhibit No.	Description
2111	Yudin, A. et al., "Beta-Defensin 126 on the Cell Surface Protects Sperm from Immunorecognition and Binding of Anti-Sperm Antibodies," *Biology of Reproduction*, 73:1243-1252 (2005)
2112	Yudin, A. et al., "The Carbohydrate Structure of DEFB126, the Major Component of the Cynomolgus Macaque Sperm Plasma Membrane Glycocalyx," *Journal of Membrane Biology*, 207:119-129 (2005)
2113	Tollner, T. et al., "A Common Mutation in the Defensin DEFB126 Causes Impaired Sperm Function and Subfertility," *Science Translational Medicine*, 3(92):1-9 (2011), with erratum
2114	Frayne, J. et al., "The potential use of sperm antigens as targets for immunocontraception; past, present and future," *Journal of Reproductive Immunology*, 43:1-33 (1999)
2115	Yanagimachi, R., "Acceleration of the Acrosome Reaction and Activation of Guinea Pig Spermatozoa by Detergents and Other Reagents," *Biology of Reproduction*, 13:519-526 (1975)
2116	Chamley, L. et al., "Antisperm antibodies and conception," *Seminars in Immunopathology*, 29:169-184 (2007)
2117	Kremer, J. et al., "The significance of antisperm antibodies for sperm-cervical mucus interaction," *Human Reproduction*, 7(6):781-784 (1992)
2118	Primakoff, P. et al., "A Map of the Guinea Pig Sperm Surface Constructed with Monoclonal Antibodies," *Developmental Biology*, 98:417-428 (1983)
2119	Myles, D. et al., "Localized Surface Antigens of Guinea Pig Sperm Migrate to New Regions Prior to Fertilization," *The Journal of Cell Biology*, 99:1634-1641 (1984)

Exhibit No.	Description
2120	Chan, C. et al., "Identification of Linear Surface Epitopes on the Guinea Pig Sperm Membrane Protein PH-20," *Life Sciences*, 64(22):1989-2000 (1999)
2121	Ganesan, R. et al., "Structural and mechanistic insight into how antibodies inhibit serine proteases," *Biochemistry Journal*,430:179-189 (2010)
2122	Mestecky, J. et al., "Mucosal Immune System of the Human Genital Tract," *The Journal of Infectious Diseases*, 179(Suppl 3):S470-S474 (1999)
2123	*Intentionally Left Blank*
2124	*Intentionally Left Blank*
2125	*Intentionally Left Blank*
2126	Suri, A., "Contraceptive vaccines targeting sperm," *Expert Opinion on Biological Therapy*, 5(3):381-392 (2005)
2127	Morrow, R. et al., "Sustained release of proteins from a modified vaginal ring device," *European Journal of Pharmaceutics and Biopharmaceutics*, 77:3-10 (2011)
2128	Hussain, A. et al., "The vagina as a route for systemic drug delivery," *Journal of Controlled Release*, 103:301-313 (2005)
2129	Veazey, R. et al., "Prevention of virus transmission to macaque monkeys by a vaginally applied monoclonal antibody to HIV-1 gp120," *Nature Medicine*, 9(3):343-346 (2003)
2130	Baloglu, E. et al., "Strategies to Prolong the Intravaginal Residence Time of Drug Delivery Systems," *Journal of Pharmaceutical Science*, 12(3):312-336 (2009)
2131	Suarez, S. et al., "Sperm transport in the female reproductive tract," *Human Reproduction Update*, 12(1):23-37 (2006)

Exhibit No.	Description
2132	Cauci, S. et al., "Combination of vaginal pH with vaginal sialidase and prolidase activities for prediction of low birth weight and preterm birth," *American Journal of Obstetrics and Gynecology*, 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," *Fertility and Sterility*, 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," *Journal of Reproductive Immunology*, 85:81-85 (2010)
2135	Kim, S. et al., "Antibody Engineering for the Development of Therapeutic Antibodies," *Molecules and Cells*, 20(1):17-29 (2005)
2136	Lardner, A., "The effects of extracellular pH on immune function," *Journal of Leukocyte Biology*, 69:522-530 (April 2001)
2137	Lipman, N. et al., "Monoclonal Versus Polyclonal Antibodies: Distinguishing Characteristics, Applications, and Information Resources," *ILAR Journal*, 46(3):258-268 (2005)
2138	Rhee, J. et al., "Mucosal vaccine adjuvants update," *Clinical and Experimental Vaccine Research*, 1:50-63 (2012)
2139	Lycke, N., "Recent progress in mucosal vaccine development: potential and limitations," *Nature Review*, 12:592-605 (August 2012)
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," *Infection and Immunity*, 66(7):3390-3396 (July 1998)
2141	Wu, H. et al., "Generation of Female Genital Tract Antibody Responses by Local or Central (Common) Mucosal Immunization," *Infection and Immunity*, 68(10):5539-5545 (October 2000)

Exhibit No.	Description
2142	Russell, M., "Immunization for Protection of the Reproductive Tract: A Review," *American Journal of Reproductive Immunology*, 47:265-268 (2002)
2143	Uppada, S. et al., "Enhanced humoral and mucosal immune responses after intranasal immunization with chimeric multiple antigen peptide of LcrV antigen epitopes of Yersinia pestis coupled to palmitate in mice," *Vaccine*, 29:9352-9360 (2011)
2144	*Intentionally Left Blank*
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," *Vaccine*, 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," *Infection and Immunity*, 66(2):514-520 (February 1998)
2147	Bergquist, C. et al., "Intranasal Vaccination of Humans with Recombinant Cholera Toxin B Subunit Induces Systemic and Local Antibody Responses in the Upper Respiratory Tract and the Vagina," *Infection and Immunity*, 65(7):2676-2684 (July 1997)
2148	Neto, H. et al., "Efficacy and Safety of 1 and 2 Doses of Live Attenuated Influenza Vaccine in Vaccine-Naive Children," *The Pediatric Infectious Disease Journal*, 28(5):365-371 (May 2009)
2149	Rhorer, J. et al., "Efficacy of live attenuated influenza vaccine in children: A meta-analysis of nine randomized clinical trials," *Vaccine*, 27:1101-1110 (2009)
2150	Mielcarek, N., "Genital Antibody Responses in Mice after Intranasal Infection with an Attenuated Candidate Vector Strain of *Bordetella pertussis*," *Infection and Immunity*, 68(2):485-491 (February 2000)

Exhibit No.	Description
2151	Houghton, A., "Immune recognition of self in immunity against cancer," *The Journal of Clinical Investigation*, 114(4):468-471 (August 2004)
2152	Wan, Y. et al., "Prepared and screened a modified TNF-a molecule as TNF-α autovaccine to treat LPS induced endotoxic shock and TNF-α induced cachexia in mouse," *Cellular Immunology*, 246:55-64 (2007)
2153	Dieudé, M. et al., "Autoantibodies to heat shock protein 60 promote thrombus formation in a murine model of arterial thrombosis," *Journal of Thrombosis and Haemostasis*, 7:710-719 (2009)
2154	Oliver, A. et al., "Rat and Human Myelin Oligodendrocyte Glycoproteins Induce Experimental Autoimmune Encephalomyelitis by Different Mechanisms in C57BL/6 Mice," *The Journal of Immunology*, 171(1):462-468 (2003)
2155	Trentham, D. et al. "Autoimmunity to Type II Collagen: An Experimental Model of Arthritis," *The Journal of Experimental Medicine*, 146:857-868 (1977)
2156	Courtenay, J. et al., "Immunisation against heterologous type II collagen induces arthritis in mice," *Nature*, 283:666-668 (1980)
2157	Tomita, M. et al., "Hybridoma technologies for antibody production," *Immunotherapy*, 3(3):371-380 (2011)
2158	Excerpts from *Antibody Methods and Protocols*, 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 $F(ab')_2$ Fragments Protect Mice from Vaginal Transmission of HSV-2," *Virology*, 225:213-215 (1996)

Exhibit No.	Description
2160	Sherwood, J. et al., "Controlled release of antibodies for long-term topical passive immunoprotection of female mice against genital herpes," *Nature Biotechnology*, 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," *Virology*, 432:505-510 (2012)
2162	Schweitzer, M. et al., "Microscopic, chemical and molecular methods for examining fossil preservation," *Comptes Rendus Palevol*, 7:159-184 (2008)
2163	National Medal of Science in Medicine Citation for Gregory Petsko, 2022 (accessible at https://nationalmedals.org/laureate/gregory-petsko/?amp=1, last accessed September 19, 2025)
2164	Petsko, G., et al., *Protein Structure and Function*, 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
2167	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," *Annals of Allergy, Asthma, and Immunology*, 99:443-452 (November 2007)
2168	Profile of Gregory A. Petsko, American Academy of Arts and Sciences (accessible at https://www.amacad.org/person/gregory-petsko, last accessed September 22, 2025)
2169	"BLAST Topics," National Institutes of Health (accessible at https://blast.ncbi.nlm.nih.gov/doc/blast-topics, last accessed September 22, 2025)

Exhibit No.	Description
2170	Chain, E. et al., "Identity of Hyaluronidase and Spreading Factor," *British Journal of Experimental Pathology*, 21(6):324-338 (1940)
2171	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," *Molecular Reproduction and Development*, 69:325-337 (2004)
2172	Yudin, A. et al., "Characterization of the active site of monkey sperm hyaluronidase," *Reproduction*, 121:735-743 (2001)
2173	Yudin, A. et al., "PH-20 but Not Acrosin Is Involved in Sperm Penetration of the Macaque Zona Pellucida," *Molecular Reproduction and Development*, 53:350-362 (1999)
2174	Errata from Park Deposition (introduced during Park deposition and marked by court reporter as "Park 2068")
2175	Mutational Analysis Table, 2024-11-7, Native Excel File (introduced during Park deposition and marked by court reporter as "Park 2069")
2176	Mutational Analysis Table, 2024-11-7, PDF File (introduced during Park deposition and marked by court reporter as "Park 2070")
2177	E-mail Correspondence dated August 14, 2025
2178	1LOH pdb file
2179	1FCV pdb file
2180	2PE4 pdb file
2181	8SMN pdb file
2182	D320H Swiss Model
2183	D320K Swiss Model
2184	D320R Swiss Model

Exhibit No.	Description
2185	D320S Swiss Model
2186	N47_N219A_D320K Swiss Model
2187	N47A_N131A_D320K Swiss Model
2188	N47A_N131A_N219A_D320K Swiss Model
2189	N131A_N219A_D320K Swiss Model
2190	Orangutan_D320K Swiss Model
2191	PH20 Swiss Model
2192	N47_N219A_D320S Swiss Model
2193	N47A_N131A_D320S Swiss Model
2194	N47A_N131A_N219A_D320S Swiss Model
2195	N131A_N219A_D320S Swiss Model
2196	Orangutan_D320S Swiss Model
2197	Chimpanzee_D320K Swiss Model
2198	Chimpanzee_D320S Swiss Model
2199	Gibbon_D320K Swiss Model
2200	Gibbon_D320S Swiss Model
2201-2213	*Intentionally Left Blank*
2214	Declaration of Zachariah Summers in Support of *Pro Hac Vice* Admission
2215	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)

Exhibit No.	Description
2215-2299	*Intentionally Left Blank*
2300	Errata sheet for Declaration of James Naismith, Ph.D.
2301	Transcript of the Deposition of James Naismith, Ph.D., February 6, 2026
2302	Transcript of the Deposition of Garnett H. Kelsoe, Ph.D., February 5, 2026
2303	Declaration of Naismith (Exhibit 1133), *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. PGR2025-00046 (P.T.A.B.), May 4, 2026
2304-2399	*Intentionally Left Blank*
2400	Merck & Co., Inc. Form 10-Q, Securities and Exchange Commission, November 5, 2025
2401	E-mail Correspondence between Counsel for Petitioner and Patent Owner, January 6, 2026 (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2402	MERCK_PGR00006 - 30November2023 Merck 031988 Master Agreement - executed 4932-6153-3216 1_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2403	MERCK_PGR00056 - MSA - Term 4 - Dechert LLP_Signed_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2404	MERCK_PGR00467 - Mark Stewart Offer Letter_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2405	MERCK_PGR00052 - Hecht Engagement Letter (7-19)_Signed (Redacted)_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)

Exhibit No.	Description
2406	MERCK_PGR00086 - Park Engagement Letter with signature - sjp (redacted)_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2407	"Executive team," MSD, accessible at http://www.msd.com/company-overview/leadership/executive- team/ (last accessed January 5, 2026)
2408	"Executive team," Merck, accessible at http://www.merck.com/company-overview/leadership/executive-team/ (last accessed January 5, 2026)
2409	"Board of directors," MSD, accessible at http://www.msd.com/company-overview/leadership/board-of-directors/ (last accessed January 5, 2026)
2410	"Board of directors," Merck, accessible at http://www.merck.com/company-overview/leadership/board-of-directors/ (last accessed January 5, 2026)
2411	"Contact us," MSD, accessible at http://www.msd.com/contact-us/ (last accessed January 5, 2026)
2412	"Contact us," Merck, accessible at http://www.merck.com/contact-us/ (last accessed January 5, 2026)
2413	"Who we are," MSD, accessible at http://www.msd.com/company-overview/ (last accessed January 5, 2026)
2414	Who we are," Merck, accessible at http://www.merck.com/company-overview/ (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

Exhibit No.	Description
2417	Petition for *Inter Partes* Review, *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, IPR2024-00240 (P.T.A.B.), November 30, 2023
2418	Petition for *Inter Partes* Review, *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, IPR2024-00622 (P.T.A.B.), March 4, 2024
2419	Petition for *Inter Partes* Review, *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, IPR2024-00623 (P.T.A.B.), March 4, 2024
2420	Petition for *Inter Partes* Review, *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, IPR2024-00624 (P.T.A.B.), March 4, 2024
2421	Petition for *Inter Partes* Review, *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, IPR2024-00625 (P.T.A.B.), March 4, 2024
2422	Petition for *Inter Partes* Review, *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, IPR2024-00647 (P.T.A.B.), March 13, 2024
2423	Petition for *Inter Partes* Review, *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, IPR2024-00648 (P.T.A.B.), March 13, 2024
2424	Petition for *Inter Partes* Review, *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, IPR2024-00649 (P.T.A.B.), March 13, 2024
2425	Petition for *Inter Partes* Review, *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, IPR2024-00650 (P.T.A.B.), March 13, 2024
2426	MERCK_PGR00035 - 20250813 Payment Remittance_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)

Exhibit No.	Description
2427	MERCK_PGR00042 - Dechert T360 Halozyme - 202500327_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2428	MERCK_PGR00045 - FW_ Attn_ Accounts Receivable Dept - PAYMENT REMITTANCE DETAIL (Nov 2025)_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2429	MERCK_PGR00049 - Halozyme - 202000447 - Invoices 5_1_2024-12_22_2025_1 of 3_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2430	MERCK_PGR00465 - Mark Stewart Payroll Statement for Dec 12 2025_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2431	MERCK_PGR00001 - Workday - Ginkel Organization Screen Shot (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2432	MERCK_PGR00002 - Workday - Lally Organization Screen Shot (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2433	MERCK_PGR00003 - Workday - Majchrzak Organization Screen Shot (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2434	MERCK_PGR00004 - Workday - Stewart Organization Screen Shot (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2435	MERCK_PGR00005 - Workday - Su Organization Screen Shot (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2436	MERCK_PGR00036 - 20250903 Payment Remittance_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2437	MERCK_PGR00037 - 20251001 Payment Remittance_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)

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2438	MERCK_PGR00038 - 20251203 Payment Remittance_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2439	MERCK_PGR00040 - 20251215 Payment Remittance_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2440	MERCK_PGR00046 - FW_ Attn_ Accounts Receivable Dept - PAYMENT REMITTANCE DETAIL (Oct 2025)_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2441	MERCK_PGR00047 - FW_ Attn_ Accounts Receivable Dept - PAYMENT REMITTANCE DETAIL (Sept 2025)_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2442	MERCK_PGR00048 - Halozyme - 202000447 - Invoice IN00125072310 Review History (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2443	MERCK_PGR00050 - Halozyme - 202000447 - Invoices 5_1_2024-12_22_2025_2 of 3_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2444	MERCK_PGR00051 - Halozyme - 202000447 - Invoices 5_1_2024-12_22_2025_3 of 3_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2445	By-Laws of Merck & Co., Inc., Effective as of November 19, 2024
2446	U.S. Supreme Court Amicus Curiae Brief by the Intellectual Property Owners Association, *Jack Daniel's Properties, Inc. v. VIP Products LLC*, Case No. 22-148
2447	Board of Directors – Intellectual Property Owners Association, accessible at https://ipo.org/index.php/board-of-directors (last accessed February 15, 2026)
2448	ChIPs Speaker Bio Information

Exhibit No.	Description
2449	LinkedIn Profile Page
2450	Form PTO-158, Office of Enrollment and Discipline, United States Patent & Trademark Office
2451	Jennifer Zachary's March 16, 2018 Job Offer Letter
2452	Form 13F Cover Page, Merck & Co., Inc., September 2025
2453	Form 13F Cover Page, Merck Sharp & Dohme LLC, September 2025
2454	Form 10-Q, Merck & Co. Inc., Quarterly Report for Quarter Ended June 30, 2025
2455	*Intentionally Left Blank*
2456	Exhibit 24.1 to Merck & Co. Inc.'s Form 10-K for the Fiscal Year Ended December 31, 2024
2457	Sarbanes-Oxley Act of 2002
2458	Jennifer Zachary Biography, Merck.com
2459	Rules of Professional Conduct of the New Jersey Bar
2460	Jennifer Zachary Biography, MSD.com
2461	USPTO Office of Enrollment and Discipline Practitioner Search for Mark J. Stewart, February 13, 2026
2462	Schedule 13D, Harpoon Therapeutics, Inc., January 17, 2024
2463	Schedule 14A Proxy Statement, Merck & Co., Inc., 2025
2464	Form 13F, Information Required of Institutional Investment Managers Pursuant to Section 13(f) of the Securities Exchange Act of 1934 and Rules Thereunder, accessible at https://www.sec.gov/pdf/form13f.pdf (last accessed February 15, 2026)

Exhibit No.	Description
2465	USPTO Office of Enrollment and Discipline Practitioner Search for "Merck," February 15, 2026
2466	Form 8-K, Merck & Co. Inc., February 3, 2026
2467	Exhibit 99.1 to Form 8-K, Merck & Co. Inc., February 3, 2026
2468	Exhibit 99.2 to Form 8-K, Merck & Co. Inc., February 3, 2026

TABLE OF AUTHORITIES

Cases

Ajinomoto Co. v. Int'l Trade Comm'n,
932 F.3d 1342 (Fed. Cir. 2019) 10, 17, 22, 23

Ariad Pharms., Inc. v. Eli Lilly & Co.,
598 F.3d 1336 (Fed. Cir. 2010) 23

Boehringer Ingelheim Animal Health USA Inc. v. Kansas State Univ. Res. Foundation,
PGR2022-00021, Paper 13 (P.T.A.B. Mar. 22, 2023) 5

In re Brana,
51 F.3d 1560 (Fed. Cir. 1995) 27

Cephalon, Inc. v. Watson Pharmaceuticals, Inc.,
707 F.3d 1330 (Fed. Cir. 2013) 17, 18

Finesse Wireless LLC v. AT&T Mobility,
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In re Gardner,
475 F.2d 1389 (C.C.P.A. 1973).....27

Invitrogen Corp. v. Clontech Lab'ys, Inc.,
429 F.3d 1052 (Fed. Cir. 2005) 13

Johns Hopkins Univ. v. CellPro, Inc.,
152 F.3d 1342 (Fed. Cir. 1998) 13, 17, 18

Martek v. Nutrinova,
579 F.3d 1363 (Fed. Cir. 2009) 3

PPG Industries, Inc. v. Guardian Industries Corp.,
75 F.3d 1558 (Fed. Cir. 1996) 17, 18

In re Wands,
858 F.2d 731 (Fed. Cir. 1988) 10, 16, 17, 18

Zoltek Corp. v. United States,
815 F.3d 1302 (Fed. Cir. 2016) 22

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—an D320H, D320K, D320R, or D320S 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 ignored this teaching because it was "contradictory" to his opinion. *Id*., 190:2-191:11.

On Reply, 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. 12), Dr. Naismith does not: he testified that PH20s with far less than 40% activity are within the claim's scope.[1] 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. *First*, this construction is incorrect because "modified PH20 polypeptide" is itself defined solely in the **first sentence**—introduced under the Definitions section and using "refers to"—as a purely structural term while subsequent sentences, which use permissive language such as "can have," provide non-limiting examples that do not impose any

[1] In a related proceeding, Dr. Naismith abandoned any activity requirement and opined that the claims require only "proper folding." EX2303, ¶¶43, 104.

functional requirements. *Alnylam v. Moderna*, 138 F.4th 1326, 1333 (Fed. Cir. 2025). *Second*, Petitioner improperly imports the constituent term "PH20" into the separately defined "modified PH20 polypeptide," contrary to Federal Circuit precedent. As *Martek v. Nutrinova* holds, "the patentee's definition controls." 579 F.3d 1363, 1380-81 (Fed. Cir. 2009). As in *Martek*, there is no basis to narrow the express definition. An express definition controls absent "words or expressions of manifest exclusion or restriction," and the court refused to narrow the term where the patentee used no language "that manifestly exclude[d]" the broader scope. *Id*. Here, too, the specification contains no language of manifest exclusion or restriction limiting "modified PH20 polypeptide" to enzymatically active embodiments. Accordingly, the Board must apply the definition, and the claims should not be limited to active modified PH20s.

Third, even if Merck were correct to read the definition of "PH20" into "modified PH20 polypeptide," (it is not), Petitioner's argument still fails. The PH20 definition imposes no "properly folded" or any folding requirement. Petitioner thus has no basis to import that limitation into the claims. *Fourth*, 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, 115:58-116:8; 79:27-29. *Finally*, Petitioner contends that because wildtype 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, §112 is satisfied. POR, 44-82. But a proper claim construction is essential for a proper

§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. POPR, 19-25; 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, ¶¶208-213).

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 cites, 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, 102-109;

EX1004, ¶¶36, 104-167; EX2077, 176:2-5; EX1130, 97:14-99:10; EX2070, ¶¶112-230, 343-432; EX2068, ¶¶95-157.

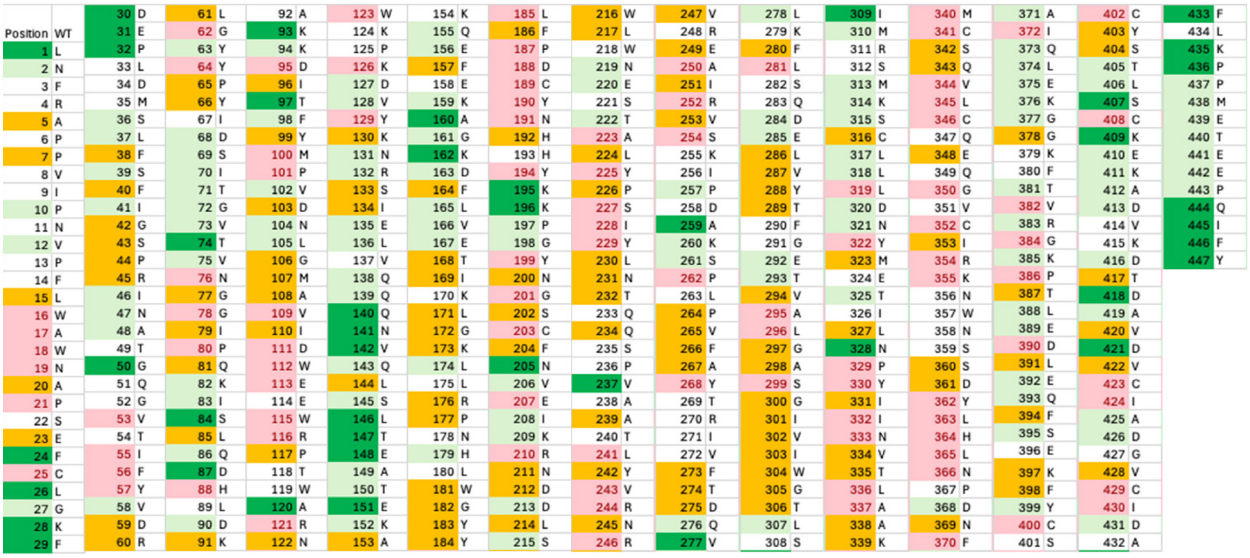
With this information, Dr. Simpson, a PH20 expert, and Dr. Petsko explained how POSAs could, ***using the patent's disclosure***, visualize and recognize the genus and predictably practice the full scope of the claims.

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:



Position	WT	30	61	92	123	154	185	216	247	278	309	340	371	402	433
1	L	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
2	N	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
3	F	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
4	R	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
5	A	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
6	P	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
7	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
8	V	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
9	I	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
10	P	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
11	N	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
12	V	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
13	P	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
14	F	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
15	L	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	
16	W	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	
17	A	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	
18	W	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	
19	N	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	
20	A	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	
21	P	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	
22	S	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	
23	E	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	
24	F	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	
25	C	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	
26	L	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	
27	G	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	
28	K	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	
29	F	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	
		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.

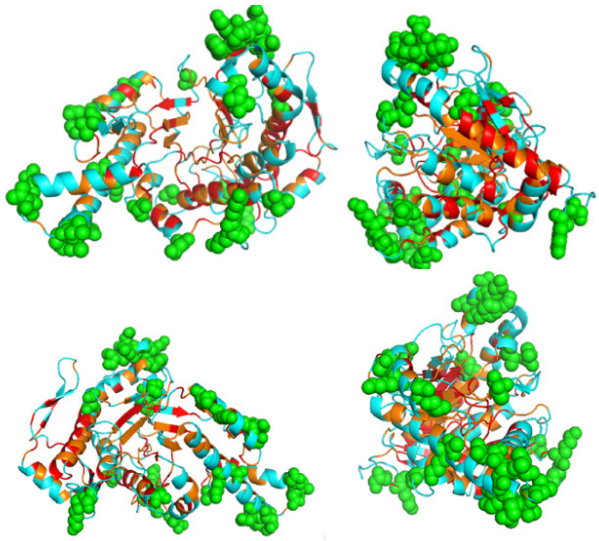
B. How a POSA Would Visualize and Use the Disclosure

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., 102-109. Indeed, Petitioner admits this method can be used to predict the effects of up to five modifications, ***without the patent data***. EX1003, ¶161; EX1004, ¶162; EX1133, ¶258, fn. 292 (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.

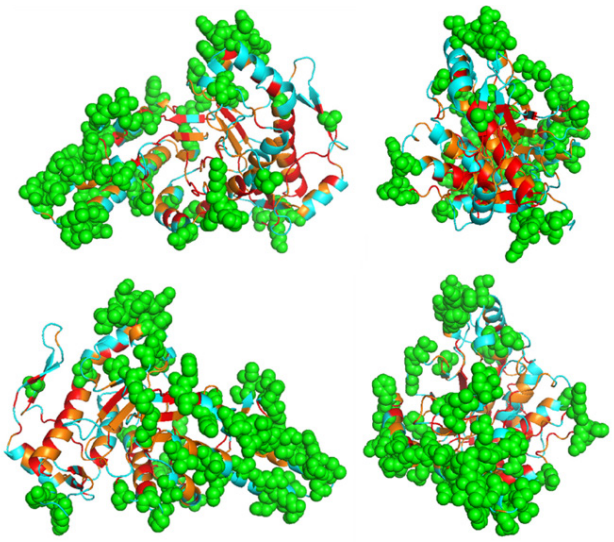
As Petitioner's expert, Dr. Park, explained, generating a homology model for a protein structure "allows you to look at the molecule, as opposed to imagining it in your head" and can also "help you evaluate the impact of a substitution." EX2077, 53:15-54:5.

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 the 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 could "visualize the species within the claim" and had sufficient information to "choose … the 95% identical polypeptide that would meet those criteria," including selecting variants based on whether activity retention was desired**.** 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 on the protein using the data in the '652 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, 343-432. As Dr. Petsko explained, a POSA can do that "for any member of the 10^49 sequences that they wish to examine." EX1131, 114:17-24. And, as Dr. Petsko confirmed, ***the patent's mutagenesis data are critical*** for this method. *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 "information content" of the disclosed 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 '652 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, 32-34. 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. §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, 35), and thus that Drs. Petsko and Simpson contradict the common disclosure by using the same "prevalent" method used by Petitioner's experts. Pet., 100-109; Reply, 7-9. 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 §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. 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 are "not very common."

EX2077, 200:14-201:13. He further admitted that, because the effect is uncommon, POSAs can "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.

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 epistastic effects. EX1131, 157:5-25; EX2070, ¶¶334-

342.

Indeed, Petitioner's 112 challenge fails because it identifies no prior art or post-filing evidence showing that combining mutations, including through epistasis or otherwise, renders visualizing, making, and using multiply-mutated PH20s unpredictable in light of 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 satisfy its §112 burden with theoretical concerns alone, particularly where PO's experts show that, in light of the patent's extensive mutagenesis data, a POSA could predictably make multiple substitutions.

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, it is routine for a POSA to make and test the desired

polypeptides to confirm its properties. EX2070, ¶348; EX2068, ¶¶360-361, 378-390. Confirmatory testing is routine because the patent's vast disclosure allows 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 occurred in the *Idenix* and *Amgen* cases. Unlike those cases where the specification failed to provide "meaningful guidance" regarding which embodiments would function, thereby forcing a POSA to engage in "iterative, trial-and-error" screening, the specification here provides extensive, position-by-position mutagenesis data and a detailed structure–function correlation. That guidance enables a POSA to identify tolerated substitutions and predictably make and use singly or multiply mutated PH20 variants without resorting to blind screening or undue experimentation. *Idenix*, 1161-1162.

A POSA armed with the patent's 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 fails as a matter of law. As *Wands* makes clear, the enablement inquiry "is not merely quantitative," and "a considerable amount of experimentation is permissible" where the experimentation is routine or guided. If the number of potential embodiments were dispositive, any claim encompassing a range and therefore effectively infinite embodiments would be categorically invalid. The law is to the contrary: the question is whether the specification provides sufficient guidance such that a POSA can practice the invention without undue experimentation. *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 a POSA could "reliably predict" actives and practice the claims without "undue" experimentation.

G. Petitioner's Experts Refused to Consider the Data And Provide No Evidence Contradicting It

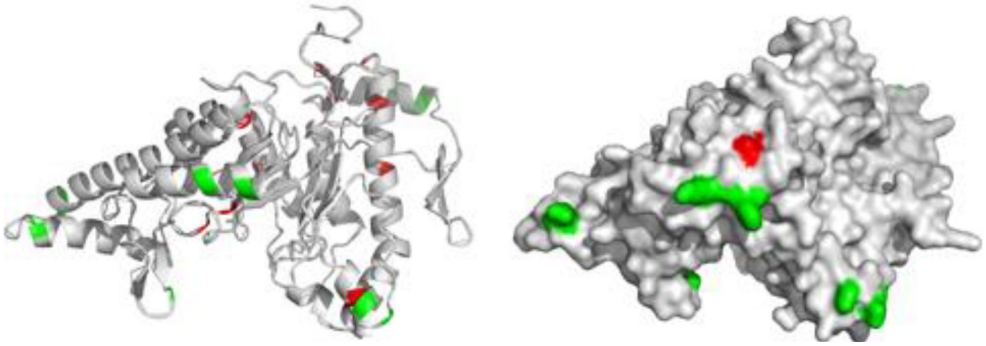
Despite Petitioner's changing claim construction positions and invalidity theories, Petitioner has been steadfast in one thing: its refusal to actually consider the patent data.

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, ¶¶141-203. 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 the 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 D320H, D320K, D320R, and D320S mutations;
- 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, 6) 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. 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, ¶¶149-160, 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 never meaningfully engages with PO's showing that the specification's extensive mutagenesis data, considered as a whole, identifies the "general quality" required under *Amgen* to reliably enable a POSA to make and use the claimed invention. POR, 65-66.

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's arguments misapply enablement law, as the specification's disclosed contraceptive use readily satisfy the low threshold required. Despite previously arguing that contraceptive utility was "not scientifically credible," Petitioner now pivots to asserting that "contraceptive utility requires near 100% effectiveness." Reply, 39-40. That argument fails both legally and factually. The claimed modified PH20 polypeptides possess a specific, substantial, and credible contraceptive utility across the claimed genus, and the law does not require near-perfect efficacy to satisfy the applicable utility standard. The relevant inquiry is whether the invention has real, operable utility, which the record shows.

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, 41-42; EX1134, ¶¶108-109; EX2302, 26:11-33:13.

Petitioner's assertion that PH20-based contraception failed in every species save guinea pigs is misplaced and legally insufficient. Petitioner relies on a single sentence in EX1189 referencing a "personal communication" to suggest a lack of sterility in macaques. But the underlying published study cited for the macaque model—Deng (2002)—reports that immunization produced "significant immune responses," including antibodies that successfully recognized sperm-surface PH20. EX1189, 119. Petitioner's reliance on an unsupported anecdote cannot overcome published evidence of contraceptive activity in macaques. EX1189, 119.

Moreover, as Dr. Cherr explained, it was well known that anti-sperm antibodies could impair fertility through non-specific binding mechanisms, independent of any reproduction-specific epitope. EX2072, ¶¶32-43; EX2074, ¶23. The record also shows that routine methods for enhancing contraceptive efficacy—including mucosal administration, adjuvants, booster immunizations, and sialidase administration—were known techniques for improving antigen-specific antibody responses. POR, 77–80. Unlike Dr. Cherr, Petitioner's expert admitted he was unaware of literature showing that anti-sperm antibodies can provide a contraceptive effect. EX2302, 113:18–123:20. And Petitioner's argument that anti-PH20 antibodies are unclaimed misses the point: the claims are directed to modified PH20 polypeptides possessing antigenic and immunogenic properties capable of eliciting such contraceptive antibodies.

VII. THE CHALLENGED CLAIMS ARE NOT OBVIOUS

Petitioner abandons any articulated motivation by asserting—without support—that all ~750 positions Dr. Park identifies for substitution would have been obvious candidates for substitution. But the claims require substitution ***at position 320***, and "there must be some reason to select a species from the genus." Petitioner offers none beyond impermissible, attorney-driven hindsight. Reply, 42-44; ID, 56-57; POR, 83-85.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX PLLC

/Eldora L. Ellison/

Eldora L. Ellison, Ph.D.
Registration No. 39,967
Lead Attorney for Patent Owner

Date: June 15, 2026

1101 K Street, NW, 10th Floor
Washington, DC 20005
(202) 371-2600

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,

STERNE, KESSLER, GOLDSTEIN & FOX PLLC

/Eldora L. Ellison/

Eldora L. Ellison, Ph.D.
Registration No. 39,967
Lead Attorney for Patent Owner

Date: June 15, 2026

1101 K Street, NW, 10th Floor
Washington, DC 20005
(202) 371-2600

Case PGR2025-00033
U.S. Patent No. 12,049,652

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 2300-2303 were served in their entireties on June 15, 2026, upon the following parties via electronic mail:

Jeffrey P. Kushan (Lead Counsel)	jkushan@sidley.com
Leif Peterson (Back-up Counsel)	leif.peterson@sidley.com
Sue Wang (Back-up Counsel)	sue.wang@sidley.com
Katherine A. Helm (Back-up Counsel)	khelm@dechert.com
Amy Mahan (Back-up Counsel)	Amy.mahan@sidley.com
Blaine Hackman (Back-up Counsel)	Blaine.Hackman@dechert.com
Christine M. Engen (Back-up Counsel)	christine.engen@sidley.com
Amit Bhatla (Back-up Counsel)	abhatla@sidley.com
Brian M. Goldberg (Back-up Counsel)	Brian.Goldberg@dechert.com
Mark Stewart (Back-up Counsel)	mark.stewart@merck.com
HalozymePGRs@sidley.com	
Merck-Halozyme-Dechert@dechert.com	

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX PLLC

/Eldora L. Ellison/

Eldora L. Ellison, Ph.D.
Registration No. 39,967
Lead Attorney for Patent Owner

Date: June 15, 2026

1101 K Street, NW, 10th Floor
Washington, DC 20005
(202) 371-2600