

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyne Inc.,
Patent Owner.

Case No. PGR2025-00039
U.S. Patent No. 12,104,185

PETITIONER'S UPDATED EXHIBIT LIST

EXHIBIT LIST

No.	Exhibit Description
1001	U.S. Patent No. 12,104,185
1002	File History of U.S. Patent No. 12,104,185
1003	Declaration of Dr. Michael Hecht
1004	Declaration of Dr. Sheldon Park
1005	U.S. Patent No. 7,767,429
1006	Chao et al., "Structure of Human Hyaluronidase-1, a Hyaluronan Hydrolyzing Enzyme Involved in Tumor Growth and Angiogenesis," Biochemistry, 46:6911-6920 (2007)
1007	WO 2010/077297, published 8 July 2010
1008	Stern et al., "The Hyaluronidases: Their Genomics, Structures, and Mechanisms of Action," Chem. Rev. 106:818-839 (2006)
1009	Jedrzejewski et al., "Structures of Vertebrate Hyaluronidases and Their Unique Enzymatic Mechanism of Hydrolysis," Proteins: Structure, Function and Bioinformatics, 61:227-238 (2005)
1010	Zhang et al., "Hyaluronidase Activity of Human Hyal1 Requires Active Site Acidic and Tyrosine Residues," J. Biol. Chem., 284(14):9433-9442 (2009)
1011	Arming et al., "In vitro mutagenesis of PH-20 hyaluronidase from human sperm," Eur. J. Biochem., 247:810-814 (1997)
1012	Bordoli et al., "Protein structure homology modeling using SWISS-MODEL workspace," Nature Protocols, 4(1):1-13 (2008)
1013	Frost, "Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration," Expert Opinion on Drug Delivery, 4(4):427-440 (2007)
1014	Brandon & Tooze, "Introduction to Protein Structure," Second Ed., Chapters 1-6, 11-12, 17-18 (1999)
1015	Table Associating Citations from the '185 Patent (EX1001) to Corresponding Citations in the '731 Application (EX1026)

No.	Exhibit Description
1016	Steipe, “Consensus-Based Engineering of Protein Stability: From Intrabodies to Thermostable Enzymes,” <i>Methods in Enzymology</i> , 388:176-186 (2004)
1017	Green, “Computer Graphics, Homology Modeling, and Bioinformatics,” <i>Protein Eng’g & Design</i> , Ch. 10, 223-237 (2010)
1018	Chica et al., “Semi-rational approaches to engineering enzyme activity: combining the benefits of directed evolution and rational design,” <i>Curr. Opin. Biotechnol.</i> , (4):378-384 (2005)
1019	Hardy et al., “Assessment of contraceptive vaccines based on recombinant mouse sperm protein PH20,” <i>Reprod.</i> , 127:325-334 (2004)
1020	Pomering et al., “Restricted Entry of IgG into Male and Female Rabbit Reproductive Ducts Following Immunization with Recombinant Rabbit PH-20,” <i>Am. J. Reprod. Immunol.</i> , (3):174-82 (2002)
1021	Baba et al., “Mouse Sperm Lacking Cell Surface Hyaluronidase PH-20 Can Pass through the Layer of Cumulus Cells and Fertilize the Egg,” <i>J. Biol. Chem.</i> , 277(33):30310-4 (2002)
1022	Primakoff et al., “Reversible Contraceptive Effect of PH-20 Immunization in Male Guinea Pigs,” <i>Biol Reprod.</i> , 56(5):1142-6 (1997)
1023	Tung et al., “Mechanism of Infertility in Male Guinea Pigs Immunized with Sperm PH-20,” <i>Biol. Reprod.</i> , 56(5):1133-41 (1997)
1024	Rosengren et al., “Recombinant Human PH20: Baseline Analysis of the Reactive Antibody Prevalence in the General Population Using Healthy Subjects,” <i>BioDrugs</i> , 32(1):83-89 (2018)
1025	U.S. Patent No. 9,447,401
1026	U.S. Patent Application No. 13/694,731
1027	2024 Chemistry Nobel Prize Background
1028	[Reserved]
1029	Gmachl et al., “The human sperm protein PH-20 has hyaluronidase activity,” <i>FEBS Letters</i> , 3:545-548 (1993)

No.	Exhibit Description
1030	Sills, “Retraction,” Science, 319:569 (2008)
1031	Yue et al., “Loss of Protein Structure Stability as a Major Causative Factor in Monogenic Disease,” J. Mol. Biol., 353:459-473 (2005)
1032	Wang & Moulton, “SNPs, Protein Structure, and Disease,” Hum. Mutation, 17:263-270 (2001)
1033	Marković-Housley et al., “Crystal Structure of Hyaluronidase, a Major Allergen of Bee Venom,” Structure, 8:1025-1035 (2000)
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1035	Lins et al., “Analysis of Accessible Surface of Residues in Proteins,” Protein Sci., 12:1406-1417 (2003)
1036	Hayden, “Chemistry: Designer Debacle,” Nature, 453:275-278 (2008)
1037	Benkert et al., “Toward the Estimation of the Absolute Quality of Individual Protein Structure Models,” Bioinformatics, 27:343-350 (2010)
1038	Schwede et al., “SWISS-MODEL: An Automated Protein Homology-Modeling Server,” Nucleic Acids Res., 31:3381-3385 (2003)
1039	Alberts, “Molecular Biology of the Cell,” Fifth Edition, Chapter 3 (2007).
1040	He et al., “NMR Structures of Two Designed Proteins with High Sequence Identity but Different Fold and Function,” PNAS, 105:14412-14417 (2008)
1041	Alexander et al., “A Minimal Sequence Code for Switching Protein Structure and Function,” PNAS, 106:21149-21154 (2009)
1042	Ruan et al., “Design and Characterization of a Protein Fold Switching Network,” Nature Comm., 14 (2023)
1043	Sievers et al., “Fast, Scalable Generation of High-Quality Protein Multiple Sequence Alignments Using Clustal Omega,” Molecular Sys. Biology, 7.1 (2011)
1044	Mihel, “PSAIA – Protein Structure and Interaction Analyzer,” BMC Structural Biology, 8:21 (2008)

No.	Exhibit Description
1045	Redline Comparison of the '731 and '185 Specifications
1046	Beasley & Hecht, "Protein Design: The Choice of <i>de Novo</i> Sequences," J. Biological Chemistry, 272:2031-2034 (1997)
1047	Xiong et al., "Periodicity of Polar and Nonpolar Amino Acids is the Major Determinant of Secondary Structure in Self-Assembling Oligomeric Peptides," PNAS, 92: 6349-6353 (1995)
1048	Hayden, "Key Protein-Design Papers Challenged," Nature, 461:859 (2009)
1049	KEGG, <i>DRUG: Hyaluronidase (human recombinant)</i> , available at: https://www.genome.jp/entry/D06604
1050	Pace & Scholtz, "A Helix Propensity Scale Based on Experimental Studies of Peptides and Proteins," Biophysical J. 75:422-427 (1998)
1051	U.S. Patent Application No. 61/631,313
1052	U.S. Patent Application No. 61/796,208
1053	Hom_pre2011
1054	Hom_pre2011_header
1055	Hom_pre2011_header_clean
1056	Hom_pre2011.fasta
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1058	Ph20_pre2011 Alignment html
1059	Leisola & Turunen, "Protein Engineering: Opportunities and Challenges," Appl. Microbiol. Biotechnol. 75:1225-1232 (2007)
1060	Hecht et al., "De Novo Proteins from Designed Combinatorial Libraries," Protein Sci., 13:1711-1723 (2004)
1061	Rosengren et al., "Clinical Immunogenicity of rHuPH20, a Hyaluronidase Enabling Subcutaneous Drug Administration," AAPS J., 17:1144-1156 (2015)
1062-1063	[Reserved]
1064	Collection of BLAST Webpages from the Internet Archive, navigable from:

No.	Exhibit Description
	https://web.archive.org/web/20111022151531/http://www.clustal.org/omega/
1065	Collection of Clustal Omega Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20111022151531/http://www.clustal.org/omega/
1066	Collection of SWISS-MODEL Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20110519141121/http://swissmodel.expasy.org/?pid=smh01&uid=&token=
1067	Collection of PyMol Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20110701072314/http://pymol.org/
1068	Declaration of Jeffrey P. Kushan
1069	Swiss Model Printout of PH20 Model
1070	Swiss Model Printout of PH20 Model with D320K Mutation
1071	Swiss Model Printout of PH20 Model with D320H Mutation
1072	Swiss Model Printout of PH20 Model with D320R Mutation
1073	Swiss Model Printout of PH20 Model with D320S Mutation
1074-1075	[Reserved]
1076	Declaration of Leif E. Peterson, II
1077-1078	[Reserved]
1079	Hunnicut 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,” Biol. Reprod., 55(1):80-86 (1996)
1080	Bookbinder et al., “A Recombinant Human Enzyme for Enhanced Interstitial Transport of Therapeutics,” J. Controlled Release, 114:230-241 (2006)
1081	[Reserved]
1082	United States District Court – National Judicial Caseload Profile, navigable from: https://www.uscourts.gov/data-

No.	Exhibit Description
	news/reports/statistical-reports/federal-court-management-statistics/federal-court-management-statistics-december-2024
1083	Table Showing Outcomes of Disputed Motions to Stay Pending IPRs in DNJ
1084	News Release: “Halozyme Raises 2025 Financial Guidance Ranges and Reports Strong First Quarter 2025 Results,” navigable from: https://www.prnewswire.com/news-releases/halozyme-raises-2025-financial-guidance-ranges-and-reports-strong-first-quarter-2025-results-302447541.html
1085	News Release: “Merck Breaks Ground on New \$1 Billion Biologics Center of Excellence in Wilmington, Delaware,” navigable from: https://www.merck.com/news/merck-breaks-ground-on-new-1-billion-biologics-center-of-excellence-in-wilmington-delaware/
1086	Halozyme Therapeutics, Inc. Q1 2025 Earnings Call Transcript (May 6, 2025)
1087-1112	[Reserved]
1113	Declaration of Sue Wang
1114	Declaration of Brian M. Goldberg
1115	Declaration of Katherine A. Helm
1116-1124	[Reserved]
1125	Emails re: AutoDock Vina (Sept. 9, 2025 - Oct. 27, 2025)
1126	Im, S. et al., “Cryo-EM Structure of Human Hyaluronidase PH-20,” Proteins: Structure, Function, and Bioinformatics 93:1067-1073 (2025)
1127-1129	[Reserved]
1130	Melanie Ann Simpson, Ph.D. Deposition Transcript
1131	Gregory Petsko, Ph.D. Deposition Transcript
1132	[Reserved]
1133	Declaration of James Naismith, Ph.D.
1134	[Reserved]
1135	Dr. Naismith Analysis Spreadsheet

No.	Exhibit Description
1136	Dobson, “Principles of protein folding, misfolding and aggregation” <i>Semin. Cell. Dev. Biol.</i> 15(1):3-16 (2004)
1137	Dobson, “Protein folding and misfolding” <i>Nature</i> . 18;426(6968):884-90 (2003)
1138	Dobson, “Experimental investigation of protein folding and misfolding” <i>Methods</i> 34(1):4-14 (2004)
1139	Chiti & Dobson, “Protein Misfolding, Functional Amyloid, and Human Disease” <i>Annu. Rev. Biochem.</i> 75:333–66 (2006)
1140	Dobson, “Protein misfolding, evolution and Disease” <i>Trends Biochem. Sci.</i> (9):329-32 (1999)
1141	Goldsmith & Tawfik, “Directed enzyme evolution: beyond the low-hanging fruit” <i>Curr. Opin. Struct. Biol.</i> 22(4):406-12 (2012)
1142	Farber & Petsko, “The evolution of alpha/beta barrel enzymes” <i>Trends Biochem. Sci.</i> 15(6):228-34 (1990)
1143	Nagano et al., “One Fold with Many Functions: The Evolutionary Relationships between TIM Barrel Families Based on their Sequences, Structures and Functions” <i>J. Mol. Biol.</i> 30;321(5):741-65 (2002)
1144	Ochoa-Levya et al., “Protein Design through Systematic Catalytic Loop Exchange in the (beta/alpha) ₈ Fold” <i>J. Mol. Biol.</i> 10 387(4):949-64 (2009)
1145	AutoDock Vina Tutorial 2011
1146	Pal et al., “Comprehensive and Quantitative Mapping of Energy Landscapes for Protein-Protein Interactions by Rapid Combinatorial Scanning” <i>J. Biol. Chem.</i> 4;281(31):22378-22385 (2006)
1147	Van Rossum et al., “Reporter-based screening and selection of enzymes” <i>FEBS J.</i> 280:2979-96 (2013)
1148	Reed et al., “Use of Coefficient of Variation in Assessing Variability of Quantitative Assays” <i>Clin. Diagn. Lab Immunol.</i> 9(6):1235-9 (2002)

No.	Exhibit Description
1149	Ten Have et al., “Cloning and characterization of the cDNA encoding the PH20 protein in the European red fox <i>Vulpes vulpes</i> ” <i>Reprod. Fertil. Dev.</i> 10(2):165-72 (1998)
1150	Chowpongpan et al., “Cloning and characterization of the bovine testicular PH-20 hyaluronidase core domain” <i>Biotechnol. Lett.</i> 26(15):1247-52 (2004)
1151	Fowler et al., “High-resolution mapping of protein sequence-function relationships” <i>Nature Methods</i> 7, 741–746 (2010)
1152	Ringe & Petsko, “Q&A: What are pharmacological chaperones and why are they interesting?” <i>J. Biol.</i> 8:80 (2009)
1153	Petsko, “Herding CATS” <i>Sci. Transl. Med.</i> 24;3(97):97 (2011)
1154	Second Table Associating Citations from the '185 Patent (EX1001) to Corresponding Citations in the '731 Application (EX1026)
1155	Calloni et al., “Investigating the Effects of Mutations on Protein Aggregation in the Cell” <i>J. Biol. Chem.</i> 10607-13 (2005)
1156	Chiti et al., “Studies of aggregation of mutant proteins in vitro provided insights into genetics of amyloid diseases” <i>PNAS</i> 99:16419-26 (2002)
1157	Chiti et al., “Rationalization of the effects of mutations on peptide and protein aggregation rates” <i>Nature</i> , 424:805-808 (2003)
1158	Wang et al., “Immunogenicity of protein aggregates-Concerns and Realities” <i>Int. J. Pharmaceutics</i> 431:1-11, (2012)
1159	Brachmann et al., “Genetic selection of intragenic suppressor mutations that reverse the effect of common p53 cancer mutations” <i>EMBO Journal</i> 17:1847–59 (1998)
1160	Poelwijk, Frank J., et al., “Empirical fitness landscapes reveal accessible evolutionary paths” <i>Nature</i> 445.7126 (2007): 383-386
1161-1163	[Reserved]
1164	MERCK_PGR00355 - PTAB-PGR2021-00036-1 Merck-Genentech PGR
1165	MERCK_PGR00458 - PTAB-PGR2021-00036-16 Merck-Genentech PGR

No.	Exhibit Description
1166	MERCK_PGR00462 - RE_2_25-cv-03179-ES-JRA_ HALOZYME, INC. v. MERCK SHARP & DOHME CORP.
1167	MERCK_PGR00094 - DNJ-2-25-cv-03179 Stipulation to Substitute Parties
1168	MERCK_PGR00090 - DNJ-2-25-cv-03179 2025-07-14 [019] Corporate Disclosure Statement
1169	Declaration of Jeffrey P. Kushan (Petitioner's Reply)
1170-1223	[Reserved]
1224	Declaration of Kelly Grez – Protective Order Material
1225	Transcript of the Deposition of Kelly Grez, March 26, 2026
1226	Kelly Grez Deposition Transcript Errata
1227-1233	[Reserved]
1234	MSD Netherlands Capital B.V., Preliminary Prospectus Supplement (May 14, 2024)
1235	Merck & Co., Inc., Form 8-K (Nov. 4, 2009)
1236	Jennifer_Zachary WD_Redacted – Protective Order Material
1237	Merck & Co., Inc. Subsidiaries (Dec. 31, 2024)
1238	State of New Jersey, Certificate of Long Form Standing with Officers and Directors, Merck & Co., Inc. (Feb. 18, 2026)
1239	Press Release: “Merck and Schering-Plough to Merge” (Mar. 9, 2009)
1240	State of New Jersey, Certificate of Long Form Standing with Officers and Directors, Merck Sharp & Dohme LLC (Feb. 18, 2026)

No.	Exhibit Description
1241	Company Statement: “Merck Sues Merck KGaA, Darmstadt, Germany for Improper Use of “Merck”” (Jan. 15, 2016)
1242	ZacharyJennifer ADP_Redacted – Protective Order Material
1243	Table Comparing the Boards of Directors for Merck & Co., Inc. and Merck Sharp & Dohme LLC
1244	Merck & Co., Inc., Form 851 – Affiliations Schedule for Tax Year Ending Dec. 31, 2024
1245-1277	[Reserved]
1278 [NEW]	Petitioner’s Demonstratives

Dated: July 20, 2026

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on this 20th day of July, 2026, I caused to be served a true and correct copy of the foregoing and any accompanying exhibits by e-mail on the following counsel of record for Patent Owner:

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