

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. IPR2026-00312
U.S. Patent No. 10,865,400

PETITIONER'S UPDATED EXHIBIT LIST

EXHIBIT LIST

<u>EXHIBIT #</u>	<u>REFERENCE NAME</u>
1001	U.S. Patent No. 10,865,400
1002	File History of U.S. Patent No. 10,865,400
1003	Declaration of Dr. James Naismith
1004	United States Patent Publication No. 2013/03032275
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., “Hyaluronidases: Their Genomics, Structures, and Mechanisms of Action,” Chem. Rev. 106:818-839 (2006)
1009	Jedzrejas 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 SWISSMODEL 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	Branden & Tooze, “Introduction to Protein Structure,” Second Ed., Chapters 1-6, 11-12, 17-18 (1999)

<u>EXHIBIT #</u>	<u>REFERENCE NAME</u>
1015	Table Associating Citations from the '400 Patent (EX1001) to Corresponding Citations in the '731 Application (EX1026) and US-275 (EX1004)
1016	Steipe, "Consensus-Based Engineering of Protein Stability: From Intrabodies to Thermostable Enzymes," Methods in Enzymology, 388:176-186 (2004)
1017	Green, "Computer Graphics, Homology Modeling, and Bioinformatics," Protein Eng'g & Design, 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," Curr. Opin. Biotechnol., (4):378-384 (2005)
1019	Hardy et al., "Assessment of contraceptive vaccines based on recombinant mouse sperm protein PH20," Reprod., 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," Am. J. Reprod. Immunol., (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," J. Biol. Chem., 277(33):30310-4 (2002)
1022	Primakoff et., "Reversible Contraceptive Effect of PH-20 Immunization In Male Guinea Pigs," Biol Reprod., 56(5): 1142-6 (1997)
1023	Tung et al., "Mechanism of Infertility in Male Guinea Pigs Immunized with Sperm PH-20," Biol. Reprod., 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," BioDrugs, 32(1):83-89 (2018)
1025	[Reserved]

<u>EXHIBIT #</u>	<u>REFERENCE NAME</u>
1026	U.S. Patent Application No. 13/694,731
1027	2024 Chemistry Nobel Prize Background
1028	Bordier, “Phase separation of integral membrane proteins in Triton X-114 solution.” J. Bio. Chem. 256 (4):1604-1607 (1981)
1029	Gmachl et al., “The human sperm protein PH-20 has hyaluronidase activity,” FEBS Letters, 3:545-548 (1993)
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)
1034	“Negative Results,” Nature: Editorials, 453:258 (2008)
1035	[Reserved]
1036	Hayden, “Chemistry: Designer Debacle,” Nature, 453:275-278 (2008)
1037-1038	[Reserved]
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)

<u>EXHIBIT #</u>	<u>REFERENCE NAME</u>
1042	Ruan et al., “Design and Characterization of a Protein Fold Switching Network,” Nature Comm., 14 (2023)
1043-1044	[Reserved]
1045	Redline Comparison of the '731 Application and '400 Patent 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)
1049-1050	[Reserved]
1051	U.S. Patent Application No. 61/631,313
1052	U.S. Patent Application No. 61/796,208
1053-1058	[Reserved]
1059	Leisola & Turunen, “Protein Engineering: Opportunities and Challenges,” Appl. Microbiol. Biotechnol. 75:1225-1232 (2007)
1060	[Reserved]
1061	Rosengren et al., “Clinical Immunogenicity of rHuPH20, a Hyaluronidase Enabling Subcutaneous Drug Administration,” AAPS J. 5:1144-56 (2015)
1062-1065	[Reserved]
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	[Reserved]

<u>EXHIBIT #</u>	<u>REFERENCE NAME</u>
1068	Declaration of Jeffrey P. Kushan
1069-1075	[Reserved]
1076 [NEW]	Declaration of Leif E. Peterson, II
1077-1078	[Reserved]
1079	Hunnicuttt 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	Goldberg, "Protein degradation and protection against misfolded or damaged proteins," Nature, 426:895-899 (2003)
1082-1086	[Reserved]
1087	Vembar & Brodsky, "One Step at a Time: Endoplasmic Reticulum-Associated Degradation," Nature, 9:944-958 (2008)
1088-1104	[Reserved]
1105	United States Patent Publication No. 2010/0143457
1106-1111	[Reserved]
1112	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)
1113 [NEW]	Declaration of Sue Wang
1114 [NEW]	Declaration of Brian M. Goldberg
1115	Declaration of Katherine A. Helm, Ph.D.

<u>EXHIBIT #</u>	<u>REFERENCE NAME</u>
[NEW]	
1116 [NEW]	Declaration of Christine M. Engen
1117 [NEW]	Declaration of Amit Bhatla
1118-1125	[Reserved]
1126	Im, S. et al., “Cryo-EM Structure of Human Hyaluronidase PH20,” Proteins: Structure, Function, and Bioinformatics 93:10671073 (2025)
1127-1129	[Reserved]
1130	Melanie Ann Simpson, Ph.D. Deposition Transcript
1131	Gregory Petsko, Ph.D. Deposition Transcript
1132-1134	[Reserved]
1135	Dr. Naismith Disclosure Analysis Spreadsheet
1136	Dobson, “Principles of protein folding, misfolding and aggregation” Semin. Cell. Dev. Biol. 15(1):3-16 (2004)
1137	Dobson, “Protein folding and misfolding” Nature. 18;426(6968):884-90 (2003)
1138	Dobson, “Experimental investigation of protein folding and misfolding” Methods 34(1):4-14 (2004)
1139	Chiti & Dobson, “Protein Misfolding, Functional Amyloid, and Human Disease” Annu. Rev. Biochem. 75:333–66 (2006)
1140	Dobson, “Protein misfolding, evolution and Disease” Trends Biochem. Sci. (9):329-32 (1999)
1141	Goldsmith & Tawfik, “Directed enzyme evolution: beyond the low-hanging fruit” Curr. Opin. Struct. Biol. 22(4):406-12 (2012)

<u>EXHIBIT #</u>	<u>REFERENCE NAME</u>
1142-1143	[Reserved]
1044	Ochoa-Leyva et al., “Protein Design through Systematic Catalytic Loop Exchange in the (beta/alpha) ₈ Fold” J. Mol. Biol. 387(4):949-64 (2009)
1045	[Reserved]
1146	Pal et al., “Comprehensive and Quantitative Mapping of Energy Landscapes for Protein-Protein Interactions by Rapid Combinatorial Scanning” J. Biol. Chem. 4;281(31):22378-22385 (2006)
1147	van Rossum et al., “Reporter-based screening and selection of enzymes” FEBS J. 280:2979-96 (2013)
1148	Reed et al., “Use of Coefficient of Variation in Assessing Variability of Quantitative Assays” Clin. Diagn. Lab Immunol. 9(6):1235-9 (2002)
1149	Ten Have et al., “Cloning and characterization of the cDNA encoding the PH20 protein in the European red fox Vulpes” Reprod. Fertil. Dev. 10(2):165-72 (1998)
1150	Chowpongpan et al., “Cloning and characterization of the bovine testicular PH-20 hyaluronidase core domain” Biotechnol. Lett. 26(15):1247-52 (2004)
1151	Fowler et al., “High-resolution mapping of protein sequence function relationships” Nature Methods 7, 741–746 (2010)
1152	Ringe & Petsko, “Q&A: What are pharmacological chaperones and why are they interesting?” J. Biol. 8:80 (2009)
1153-1154	[Reserved]
1155	Calloni et al., “Investigating the Effects of Mutations on Protein Aggregation in the Cell” J. Biol. Chem. 10607-13 (2005)
1156	Chiti et al., “Studies of aggregation of mutant proteins in vitro provided insights into genetics of amyloid diseases” PNAS

<u>EXHIBIT #</u>	<u>REFERENCE NAME</u>
	99:16419-26 (2002)
1157	Chiti et al., “Rationalization of the effects of mutations on peptide and protein aggregation rates” Nature, 424:805-808 (2003)
1158	Wang et al., “Immunogenicity of protein aggregates-Concerns and Realities” Int. J. Pharmaceutics 431:1-11, (2012)
1159	[Reserved]
1160	Poelwijk, Frank J., et al., “Empirical fitness landscapes reveal accessible evolutionary paths” Nature 445.7126 (2007): 383-386
1161-1188	[Reserved]
1189	Martin-Deleon, P., “Epididymal SPAM1 and its Impact on Sperm Function,” Molecular and Cellular Endocrinology 250:114-121 (2006)
1190-1199	[Reserved]
1200	US-275 Activity Data and ‘400 Patent Claims Comparison Spreadsheet
1201-1205	[Reserved]
1206	U.S. Food and Drug Administration, Medical Review: Hylenex, App. No. 21-859 (2005)
1207	[Reserved]
1208	Redline of the ’731 App. and US-275 Publication
1209	Petsko & Ringe, Protein Structure and Function, New Science Press (2004)
1210	Nelson & Cox, Lehninger Principles of Biochemistry, W.H. Freeman, 4th ed. (2005)
1211	Halozyme Therapeutics, Inc., Hylenex Label, U.S. Food and Drug Administration; AccessData (2005)

<u>EXHIBIT #</u>	<u>REFERENCE NAME</u>
-	Declaration of Gregory A. Petsko, PGR2025-00003 (U.S. Patent No. 11,952,600), EX2070 (Sept. 22, 2025)

Dated: April 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 April, 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

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