

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,
Petitioner

v.

HALOZYME, INC.,
Patent Owner

Case PGR2025-00030
U.S. Patent No. 12,054,758

**SECOND DECLARATION OF BARBARA TRIGGS-RAINE, PH.D. IN
SUPPORT OF PATENT OWNER'S PRELIMINARY RESPONSE**

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Halozyme EX2055
Merck v. Halozyme
PGR2025-00030

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I, Barbara Triggs-Raine, Ph.D., hereby declare as follows.

I. INTRODUCTION

1. I am over the age of 18 and competent to make this declaration.

2. I have been retained as an expert witness on behalf of Patent Owner Halozyme, Inc. (“Patent Owner”) for the above-captioned post-grant review proceeding (PGR). I am being compensated for my time in connection with this PGR at my standard consulting rate, which is \$300 per hour.

3. I understand that this Declaration accompanies a Patent Owner’s Preliminary Response filed in this PGR involving U.S. Patent No. 12,054,758 (“the ’758 patent”) (EX1001), which resulted from U.S. Patent Application No. 18/066,960 (“the ’960 application”), filed on December 15, 2022.

4. I understand that the ’758 patent is related to the following U.S. Patent Applications:

- U.S. Patent Application No. 17/327,568 (“the ’568 application”), filed on May 21, 2021;
- U.S. Patent Application No. 16/912,590 (“the ’590 application”), filed on June 25, 2020; and
- U.S. Patent Application No. 16/824,572 (“the ’572 application”), filed on March 19, 2020;
- U.S. Patent Application No. 15/226,489 (“the ’489 application”),

filed on August 2, 2016; and

- U.S. Patent Application No. 13/694,731 (“the ’731 application”), filed on December 28, 2012. Dr. Hecht provided the ’731 application as EX1026.

5. I understand that the ’758 patent is also related to the following provisional applications:

- Provisional Application No. 61/796,208 (“the ’208 provisional application”), filed on November 1, 2012; and
- Provisional Application No. 61/631,313 (“the ’313 provisional application”), filed on December 30, 2011.

6. In addition to reviewing the ’758 patent and the ’731 application, I have reviewed a redline comparison of the specifications of the ’758 patent and the ’731 application (EX1045). The ’758 patent has substantively the same specification¹

¹ I understand that the specification of the ’758 patent includes its Figures and a narrative discussion, EX1001, pp. 15-184, including any documents that are “incorporated by reference,” as well as the patent’s sequence listing, EX2006.² Because the specification of the ’758 patent and the specification of the ’731 application share a common disclosure that is substantively the same, I may refer to them interchangeably.³ I understand that in assessing the ’731 application for written

as the '731 application filed on December 28, 2012. *Compare* EX1001, with EX1026, 14-370. Dr. Hecht agrees that the specifications of the '758 patent and the '731 application are substantively the same and share a “common disclosure.” EX1003, ¶18. Like Dr. Hecht, for convenience, I provide citations to the disclosure in the '758 patent and at times refer to the specification that is substantively shared by the '758 patent and the '731 application as the “common disclosure.”² Below, I

description and enablement, the application must be assessed as of the '731 application's filing date (December 28, 2012). I understand that the '758 patent is also related to two earlier-dated patent applications: the '208 provisional application filed on November 1, 2012, and the '313 provisional application filed on December 30, 2011. However, Drs. Hecht and Park did not assess the earlier-dated '208 and '313 provisional applications for written description or enablement, or even include them on their Exhibit Lists. EX1003, ¶¶123-124; EX1004, Appendix A.⁴ I declined these awards.⁵ Enzymes are a specific type of protein.

² Because the specification of the '758 patent and the specification of the '731 application share a common disclosure that is substantively the same, I may refer to them interchangeably.³ I understand that in assessing the '731 application for written description and enablement, the application must be assessed as of the '731 application's filing date (December 28, 2012). I understand that the '758 patent is

often refer to December 28, 2012, the filing date of the '731 application, as I have been asked to consider the '731 application in my analysis of written description and enablement.

7. In preparing this Declaration, I reviewed: (i) the '758 patent and its entire prosecution history, including the entire prosecution histories of the '568 application, the '590 application, the '572 application, the '489 application, the '731 application, the '208 provisional application, and the '313 provisional application and (ii) each of the documents cited in this declaration, in light of general knowledge in the art in the following timeframes referenced: In assessing written description and enablement, I refer to December 28, 2012—the filing date of the '731 application that is related to the '758 patent.³ In assessing obviousness

also related to two earlier-dated patent applications: the '208 provisional application filed on November 1, 2012, and the '313 provisional application filed on December 30, 2011. However, Drs. Hecht and Park did not assess the earlier-dated '208 and '313 provisional applications for written description or enablement, or even include them on their Exhibit Lists. EX1003, ¶¶123-124; EX1004, Appendix A.⁴ I declined these awards.⁵ Enzymes are a specific type of protein.

³ I understand that in assessing the '731 application for written description and enablement, the application must be assessed as of the '731 application's filing date

in response to Dr. Hecht's and Park's declarations, I refer to the same timeframe Dr. Hecht considered: before December 29, 2011. EX1003, ¶11.

8. In formulating my opinions, I relied upon my experience, education, and knowledge in the relevant art. In formulating my opinions, I also considered the viewpoint of a person of ordinary skill in the art ("POSA"), as defined below in § V, as of the timeframes discussed herein (e.g., paragraph 7), in light of general knowledge in the art.

II. MY BACKGROUND AND QUALIFICATIONS

9. I am a Professor in the Department of Biochemistry & Medical Genetics at the Rady Faculty of Health Sciences at the University of Manitoba. And I was the Head of the Department of Biochemistry & Medical Genetics from 2018-2025. I hold a Ph.D. in Microbial Genetics and B.Sc. in Microbiology, with First Class

(December 28, 2012). I understand that the '758 patent is also related to two earlier-dated patent applications: the '208 provisional application filed on November 1, 2012, and the '313 provisional application filed on December 30, 2011. However, Drs. Hecht and Park did not assess the earlier-dated '208 and '313 provisional applications for written description or enablement, or even include them on their Exhibit Lists. EX1003, ¶¶123-124; EX1004, Appendix A.⁴ I declined these awards.⁵

Enzymes are a specific type of protein.

Honors from the University of Manitoba. In addition, I am a board member of the International Society for Hyaluronan Sciences, a member of the American Society of Matrix Biology, and a member of the American Society for Biochemistry & Molecular Biology.

10. I have extensive experience in the fields of cellular and molecular biology, biochemistry (including protein biochemistry), glycobiology, and human genetics—including extensive practical experience researching hyaluronidases, which have been a focus of my research since 1995.

11. My *curriculum vitae* is submitted herewith as EX2002.

12. In 1983, I completed my B.Sc. at the University of Manitoba, during which I was awarded the Natural Sciences and Engineering Research Council of Canada (“NSERC”) Undergraduate University Summer Research Award and the NSERC Postgraduate Scholarship. In 1987, I completed my Ph.D. at the University of Manitoba (studying a gene encoding a bacterial enzyme and its regulation). I was also extended awards for the Medical Research Council Postgraduate Scholarship (in 1983)⁴ and the Sigma Xi Student Award for Excellence in Research and the NSERC Postdoctoral Fellowship (in 1987).

13. Prior to my postdoctoral work, I was a teaching assistant (sessional) in

⁴ I declined these awards.⁵ Enzymes are a specific type of protein.

the Dept. of Microbiology in the Faculty of Science, University of Manitoba from 1987–1988.

14. From 1988–1989, I was a postdoctoral fellow at the Hospital for Sick Children, Toronto (studying the genetics of Tay-Sachs disease), during which I was awarded the Medical Research Council Postdoctoral Fellowship. From 1989–1991, I continued my postdoctoral training at the McGill University-Montreal Children’s Hospital, Montreal (studying the genetics of Tay-Sachs disease).

15. In 1991, I returned to the University of Manitoba, where I have held multiple roles until the present date, including: (i) at the Faculty of Medicine—Assistant Professor, Dept. Biochemistry & Medical Genetics (1991–1997); Assistant Professor, Dept. Human Genetics (1994–1997); Associate Professor, Dept. Biochemistry & Medical Genetics (1997–2003); and Associate Professor, Dept. Pediatrics & Child Health (2003–2006); (ii) at the Manitoba Institute of Child Health—Director of Research, Facilities and Space Development (2008–2010); and (iii) at the Rady Faculty of Health Sciences—Professor, Dept. Biochemistry & Medical Genetics (2004–present); Professor, Dept. Pediatrics & Child Health (2006–2021); Associate Head, Dept. Biochemistry & Medical Genetics (2011–2018); Scientific Director, Central Animal Core Facility (2015–2022); and Head, Dept. Biochemistry & Medical Genetics (2018–February 2025).

16. While at the University of Manitoba, I received multiple awards,

including: Manitoba Health Research Council Scholarship (1991–1992), Medical Research Council of Canada Scholarship (1992–1997), Rh Award in the Health Sciences (1995), Journal of Biological Chemistry: Best of 2012—Glycobiology and Extracellular Matrices (2012), Manitoba Medical Students’ Association Nomination for Best Teaching: Small Group Setting—Class of 2020 (2018), Bachelor of Science in Medicine Supervisor Mentorship Award (2018–2019), and Science Co-op Supervisor Recognition Award (2023).

17. Since 1995, a primary focus of my research has been researching and characterizing hyaluronidases. My research has led to over 80 peer-reviewed research publications and six book chapters, over 20 of which specifically relate to hyaluronidases. I have also received over 50 grants, over 10 of which specifically related to the characterization of hyaluronidases. Additionally, I have advised 6 doctoral students and 10 masters students, seven of whom specifically studied hyaluronidases for their dissertation.

18. I have also advised three postdoctoral fellows, two resident research projects, and over forty undergraduate students, and I have served on over 70 graduate student committees. I frequently peer review publications and have been an *ad hoc* reviewer for the publications *Nature Communications*, *American Journal of Human Genetics*, *American Journal of Medical Genetics*, *BMC Genetics*, *BMC Medical Genetics*, *Brain and Behavior*, *Canadian Journal of*

Physiology and Pharmacology, European Journal of Human Genetics, Gene, Gene Therapy, Glycobiology, Matrix Biology, Molecular Genetics and Metabolism, Molecular and Cellular Biochemistry, Mutation Research, Orphanet Journal of Rare Diseases, Plant Biotechnology Journal, PLOS One, Journal of Biological Chemistry, and Mutation Research. The publications I reviewed often related to hyaluronan or hyaluronidase biology.

19. In addition to my educational training and my professional and research experience, I have kept abreast of the fields of cellular and molecular biology, biochemistry (including protein biochemistry), glycobiology, and human genetics by reading scientific literature, conferring with colleagues in the field, and attending and presenting lectures at scientific conferences. I have given over 20 presentations and invited lectures, over half of which specifically related to hyaluronidases and/or hyaluronan degradation. I have provided abstracts to 100 scientific conferences, approximately 40 of which specifically related to hyaluronidases and/or hyaluronan. I have also taught undergraduate and graduate courses on genetics in biomedicine, glycobiology, human genetics, environmental microbiology, biological energy transductions, genetic counseling, and medical biochemistry—and I was the Symposium Program Chair at the 2018 Annual Glycomics Symposium. I was also a member of the organizing committee for the International Society of Hyaluronan Sciences biennial meeting in 2023 and 2025.

III. SUMMARY OF OPINIONS

20. I have been asked to consider whether a POSA would have found the subject matter of claims 1-2 and 6-30 of the '758 patent (i.e., the claimed invention) to be adequately described in the patent (Ground A), and whether it would have required undue experimentation for a POSA to practice the claimed invention, in light of the teachings in the common disclosure and general knowledge in the field (Ground B). In view of the state of the art as of December 28, 2012, and in light of the teachings in the common disclosure, a POSA would not have found the challenged claims to lack written description support or enablement. In particular, a POSA would have recognized that the claimed modified PH20 polypeptides all include common structural features, which are defined by amino acid sequence identity—not hyaluronidase activity; thus, Dr. Hecht's analysis of written description and enablement, which is predicated on requiring that the claimed modified PH20 polypeptides exhibit hyaluronidase activity, is erroneous.

21. I have also been asked to consider (1) whether all limitations of the challenged claims are found in Dr. Hecht's asserted prior art: Chao (EX1006) and the '429 patent (EX1005); (2) whether a POSA would have had a reason to combine the teachings of Chao (EX1006) and the '429 patent (EX1005) to make the claimed modified PH20 polypeptides that include an L317Q substitution,

including whether (i) bridging the gap between Chao, the '429 patent, and the claimed invention would have required more than ordinary creativity; and (ii) whether a POSA exercising ordinary creativity would have had a reasonable expectation of success in combining Chao and the '429 patent to arrive at the claimed invention (Ground C).

22. In view of the state of the art before December 29, 2011, a POSA would not have found the challenged claims to have been obvious.

IV. LIST OF DOCUMENTS CONSIDERED

In providing my testimony, I considered the documents cited in this Declaration and the documents listed in the table below.

Exhibit No.	Description
1001	U.S. Patent No. 12,054,758
1002	File History of U.S. Patent No. 12,054,758
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," <i>Biochemistry</i> , 46:6911-6920 (2007)
1008	Stern et al., "The Hyaluronidases: Their Genomics, Structures, and Mechanisms of Action," <i>Chem. Rev.</i> 106:818-839 (2006)

Exhibit No.	Description
1009	Jedzrejas et al., “Structures of Vertebrate Hyaluronidases and Their Unique Enzymatic Mechanism of Hydrolysis,” <i>PROTEINS: Structure, Function and Bioinformatics</i> , 61:227-238 (2005)
1010	Zhang et al., “Hyaluronidase Activity of Human Hyal1 Requires Active Site Acidic and Tyrosine Residues,” <i>J. Biol. Chem.</i> , 284(14):9433-9442 (2009)
1011	Arming et al., “In vitro mutagenesis of PH-20 hyaluronidase from human sperm,” <i>Eur. J. Biochem.</i> , 247:810-814 (1997)
1012	Bordoli et al., “Protein structure homology modeling using SWISS-MODEL workspace,” <i>Nature Protocols</i> , 4(1):1-13 (2008)
1013	Frost, “Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration,” <i>Expert Opinion on Drug Delivery</i> , 4(4):427-440 (2007)
1014	Brandon & Tooze, “Introduction to Protein Structure,” Second Ed., Chapters 1-6, 11-12, 17-18 (1999)
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)

Exhibit No.	Description
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)
1023	Tung et al., "Mechanism of Infertility in Male Guinea Pigs Immunized with Sperm PH-20," Biol. Reprod., 56(5):1133-41 (1997)
1029	Gmachl et al., "The human sperm protein PH-20 has hyaluronidase activity," FEBS Letters, 3:545-548 (1993)
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)
1035	Lins et al., "Analysis of Accessible Surface of Residues in Proteins," Protein Sci., 12:1406-1417 (2003)
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).

Exhibit No.	Description
1043	Sievers et al., “Fast, Scalable Generation of High-Quality Protein Multiple Sequence Alignments Using Clustal Omega,” <i>Molecular Sys. Biology</i> , 7.1 (2011)
1044	Mihel, “PSAIA – Protein Structure and Interaction Analyzer,” <i>BMC Structural Biology</i> , 8:21 (2008)
1045	Redline Comparison of the '731 and '758 Specifications
1046	Beasley & Hecht, “Protein Design: The Choice of de Novo Sequences,” <i>J. Biological Chemistry</i> , 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,” <i>PNAS</i> , 92: 6349-6353 (1995)
1050	Pace & Scholtz, “A Helix Propensity Scale Based on Experimental Studies of Peptides and Proteins,” <i>Biophysical J.</i> 75:422-427
1053	Hom_pre2011
1054	Hom_pre2011_header
1055	Hom_pre2011_header_clean
1056	Hom_pre2011.fasta
1057	Ph20_pre2011.aln-clustal_num
1058	Ph20_pre2011 Alignment html
1059	Leisola & Turunen, “Protein Engineering: Opportunities and Challenges,” <i>Appl. Microbiol. Biotechnol.</i> 75:1225-1232 (2007)
1061	Rosengren et al., “Clinical Immunogenicity of rHuPH20, a Hyaluronidase Enabling Subcutaneous Drug Administration,” <i>AAPS J.</i> , 17:1144-1156 (2015)

Exhibit No.	Description
1064	Collection of BLAST Webpages from the Internet Archive, navigable from: 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/
1069	Swiss Model Printout of PH20 Model
1070	Swiss Model Printout of PH20 Model with L317Q Mutation
1071	Swiss Model Printout of PH20 Model with L317R Mutation
1072	Swiss Model Printout of PH20 Model with L317M Mutation
1074	Swiss Model Printout of PH20 Model with L317I Mutation
2002	<i>Curriculum Vitae</i> 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. 18/066,960, June 13, 2025.
2004	“Halozyme Therapeutics to Present Data on PEGPH20 at the Upcoming 2011 EORTC-NCI-ASCO Annual Meeting,” Halozyme Therapeutics, Inc. Press Release, October 24, 2011
2005	LinkedIn profiles of Michael Shepard, Robert Connor, Ge (Gina) Wei, and Qiping Zhao

Exhibit No.	Description
2006	Sequence listing of U.S. Patent Application No. 18/066,960
2007	Gifre, L., et al., “Trends in recombinant protein use in animal production,” <i>Microb Cell Fact</i> 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?,” <i>American Journal of Reproductive Immunology</i> 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,” <i>Nature</i> 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)
2012	“A decade in numbers,” <i>Nature Materials</i> 11:743-744 (September 2012)
2013	Lin, Y., <i>et al.</i> , “Molecular cloning of the human and monkey sperm surface protein PH-20,” <i>Proc. Natl. Acad. Sci USA</i> 90:10071-10075 (November 1993)
2015	File History of U.S. Patent No. 7,872,107
2017	European Patent Application Publication No. 0953574 A1, published November 3, 1999
2018	Duterme, C., <i>et al.</i> , “Two Novel Functions of Hyaluronidase-2 (Hyal2) Are Formation of the Glycocalyx and Control of CD44-ERM Interactions,” <i>The Journal of Biological Chemistry</i> , 284(48):33495-33508 (November 27, 2009)

Exhibit No.	Description
2019	Atmuri, V., <i>et al.</i> , “Hyaluronidase 3 (<i>HYAL3</i>) knockout mice do not display evidence of hyaluronan accumulation,” <i>Matrix Biology</i> 27:653-660 (2008)
2020	Hemming, R., <i>et al.</i> , “Mouse Hyal3 encodes a 45- to 56-kDa glycoprotein whose overexpression increases hyaluronidase 1 activity in cultured cells,” <i>Glycobiology</i> 18(4):280-289 (2008)
2021	Miller, A., “Hyaluronidase 2 and its intriguing role as a cell-entry receptor for oncogenic sheep retroviruses,” <i>Seminars in Cancer Biology</i> 18:296-301 (2008)
2022	Kaneiwa, T. <i>et al.</i> , “Identification of human hyaluronidase-4 as a novel chondroitin sulfate hydrolase that preferentially cleaves the galactosaminidic linkage in the trisulfated tetrasaccharide sequence,” <i>Glycobiology</i> 20(3):300-309 (March 2010)
2029	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp & Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00004 (P.T.A.B.), November 26, 2024
2030	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp & Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00003 (P.T.A.B.), November 12, 2024
2031	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp & Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00009 (P.T.A.B.), December 27, 2024
2032	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp & Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00006 (P.T.A.B.), December 10, 2024
2033	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp & Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00017 (P.T.A.B.), January 17, 2025

Exhibit No.	Description
2034	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp & Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00024 (P.T.A.B.), February 21, 2025
2036	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp & Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00033 (P.T.A.B.), March 7, 2025
2038	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp & Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00039 (P.T.A.B.), March 28, 2025
2057	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp & Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00042 (P.T.A.B.), April 15, 2025
2061	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp & Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00046 (P.T.A.B.), April 29, 2025
2063	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp & Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00050 (P.T.A.B.), May 7, 2025
2064	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp & Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00053 (P.T.A.B.), June 6, 2025
2067	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp & Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00052 (P.T.A.B.), June 27, 2025

V. PERSON OF ORDINARY SKILL IN THE ART

23. As an expert, I have offered opinions throughout this declaration from the perspective of a person of ordinary skill in the art (“POSA”). I understand that

the level of ordinary skill in the art acts as a lens through which the prior art and claimed invention must be viewed. I further understand that an assessment of whether an invention is adequately described, enabled, or nonobvious is conducted from the viewpoint of a POSA.

24. I understand that a POSA is a hypothetical person who is presumed to be aware of all pertinent art, who thinks along conventional wisdom in the art, and is a person of ordinary creativity. I also understand that the following factors are pertinent to the determination of the level of ordinary skill: (1) the educational level of the inventor(s), (2) the type of problems encountered in the art, (3) the prior art solutions to those problems, (4) the rapidity with which innovations are made, (5) the sophistication of the technology, and (6) the educational level of active workers in the field.

25. Dr. Hecht opined that “a person of ordinary skill in the art . . . would have had an undergraduate degree, a Ph.D., and post-doctoral experience in scientific fields relevant to [the] study of protein structure and function (*e.g.*, chemistry, biochemistry, biology, biophysics) . . . [and] [f]rom training and experience, the person would have been familiar with factors influencing protein structure, folding and activity, production of modified proteins using recombinant DNA techniques, and use of biological assays to characterize protein function, as well with techniques and tools used to analyze protein structure (*i.e.*, sequence

searching and alignments, protein modeling software, etc.).” EX1003, ¶13.

26. I disagree with Dr. Hecht’s assessment of the level of skill of a POSA because he omits any practical experience with hyaluronidases and because a Ph.D. and/or post-doctoral experience is not required to make and use the claimed modified PH20 polypeptides. EX1003. As I discuss below, a POSA in the relevant field, or at least a member of their team, would have had experience working with hyaluronidases. **First**, general experience with non-hyaluronidase proteins or enzymes is inadequate because hyaluronidases differ from other proteins and enzymes.⁵ In particular, different hyaluronidases have different three-dimensional structures, which are linked to their different substrates and/or functions. EX2018, 33495, 33507; EX2019, 653, 658; EX2020, 286; EX2021, 296; EX1008, 825; EX2022, 6-7; EX1001, 72:44-47, 166:62-67, 226:6-9; EX1008, 825; EX2022, 6-7; EX1006, 6911-6916; EX1004, ¶36. The ’758 patent explains, for example, that hyaluronan is a natural PH20 hyaluronidase substrate and inhibitor and specifically states that “[o]ne of skill in the art is familiar with *various classes of hyaluronidase inhibitors*.” EX1001, 159:61-62 (emphasis added). Neither Dr. Hecht nor Dr. Park, according to their *curriculum vitae* and Background and Qualifications, have any experience with hyaluronidases, let alone PH20. EX1003, ¶¶1-9 and Appendix B.

⁵ Enzymes are a specific type of protein.

And Dr. Hecht's published works, as listed in his *curriculum vitae*, indicate that he has minimal experience with enzymes generally. EX1003, 232-237. Only ~four of Dr. Hecht's published works relate to enzymes, none of which exist in nature because they were designed *de novo*. EX1003, 236-237. Thus, these ~four published works do not demonstrate a general understanding of natural enzymes, much less hyaluronidases. And the remaining proteins referenced in Dr. Hecht's published works, as listed in his *curriculum vitae*, are also *de novo* proteins or proteins of bacterial origin—unlike the modified PH20 polypeptides of the '758 patent, which are of mammalian, specifically human, origin. EX1001, 69:7-9; EX1003, 232-237. This lack of hyaluronidase experience is relevant because, in Dr. Hecht's obviousness analysis, as I explain in Section X, he relies on an 88-sequence alignment (prepared by Dr. Park) that contains 70 non-PH20 hyaluronidases, including, e.g., Hyal-1, Hyal-2, Hyal-3, Hyal-4, Hyal-5, and Hyal-6—and only 18 PH20 sequences. EX1004, ¶27; EX1056. But a POSA having hyaluronidase experience (or a POSA working with a team member having hyaluronidase experience) would have been aware of the differences between PH20 and other hyaluronidase proteins, including, but not limited to, their: structures, substrates (or lack thereof), biological origins, functions (*e.g.*, enzymatic activity, cell-signaling activity), and/or optimal pH; therefore, they would not have aligned these 88 different hyaluronidases in seeking to modify

PH20 as Drs. Hecht and Park propose. This lack of hyaluronidase experience is also relevant because, as I discuss in Section IX, Dr. Hecht dismisses PH20's well-known contraceptive utility, even though, before 2011, a POSA would have been well-aware of the data demonstrating that PH20 was 100% effective as a contraceptive in guinea pigs. Section IX; EX1003, ¶109; EX1023, Abstract; EX2010, 1, Abstract. Moreover, the '758 patent discusses various problems encountered in the art and contemplated solutions to those problems, which require familiarity with hyaluronidases, as discussed further below. And as also discussed below, while the hyaluronidase assays described in the common disclosure do not require extensive experience to employ, they do require familiarity with hyaluronidases.

27. The '758 patent's specification and its cited references are further informative to factors 2-4. The '758 patent contains significant description regarding hyaluronidases, and the '758 patent cites numerous references relating to hyaluronidases. For example, more than 80 references cited plainly relate to hyaluronidase according to their title. EX1001, 3-13 (containing more than 80 references mentioning hyaluronidase and/or its substrate hyaluronan in their titles); EX1001, page 5 ("Hyaluronidase and its substrate hyaluronan: biochemistry, biological activities and therapeutic uses"). Additionally, *both* of the references that Dr. Hecht relies upon for his obviousness analysis (the '429 patent and Chao)

relate to hyaluronidases. EX1003; EX1005, 1 (“Soluble hyaluronidase glycoprotein (sHASEGP), process for preparing the same, uses and pharmaceutical compositions comprising thereof”); EX1006, 6911 (“Structure of Human Hyaluronidase-1, a Hyaluronan Hydrolyzing Enzyme Involved in Tumor Growth and Angiogenesis”). Moreover, *over 20* references cited in Dr. Hecht’s declaration relate to hyaluronidases, including: EX1001 (the ’758 patent), EX1004-EX1011, EX1013, EX1019-EX1026, EX1029, EX1033, EX1049, EX1051-EX1052, EX1061, and EX1069. EX1003, 146-47.

28. The ’758 patent also states that the field of the invention relates to modified PH20 hyaluronidase peptides. EX1001, 4:16-19. And the background of the invention discusses hyaluronan and “hyaluronan-degrading enzymes (e.g., hyaluronidases)” EX1001, 4:21-50.

29. The background of the invention also discusses the therapeutic use of hyaluronidases. For Example: EX1001, 4:41-46 (“Various hyaluronidases have been used therapeutically (e.g., hyaluronidase sold under the trademarks Hydase® (bovine testicular hyaluronidase), Vitrase® (ovine hyaluronidase), and Wydase® (bovine hyaluronidase))”). Throughout, the specification relates to modified PH20 polypeptides, as do the claims.

30. Furthermore, Halozyme, the owner of (and original applicant for) the ’758 patent, was known in December 2011 for developing and commercializing

products involving hyaluronidases. EX1002, 20 (listing Halozyme, Inc. as applicant); EX2004, 1.⁶ And I understand that each of the inventors, or at least one or more members of the team of inventors, had at least two years of experience working with hyaluronidases in December 2011. EX2005, 1-14.⁷

31. In addition, I understand that each of the inventors was employed by

⁶ On February 27, 2025, I retrieved EX2004 online from Fierce Pharma Biopharma News & Insights and generated a PDF from the online webpage. EX2004 is true and accurate to the best of my knowledge. I consider EX2004 to be a reliable source of information containing the type of information upon which an expert in the field would typically rely. Accordingly, I rely on EX2004 here.

⁷ On December 18, 2024, I retrieved the LinkedIn profiles of Michael Shepard, Robert Conner, Ge Wei, and Qiping Zhao from LinkedIn and generated PDFs from the corresponding online webpages. I combined these PDFs into a single document to create EX2005. EX2005 is true and accurate to the best of my knowledge. I consider EX2005 to be a reliable source of information containing the type of information upon which an expert in the field would typically rely. Accordingly, I rely on EX2005 here.⁸ *I.e.*, (ii) the type of problems encountered in the art, (iii) the prior art solutions to those problems, (iv) the rapidity with which innovations are made, and (v) the sophistication of the technology.

Halozyme, Inc. (the owner of, and original applicant for, the '758 patent) in December 2011; therefore, their experience working with hyaluronidases would have been examples of active workers in the field of the invention at this time. EX1002, 20; EX2005, 1-14.

32. In view of the above, and in accordance with the first and sixth factors referenced above in paragraph 24, a POSA in this field or a member of a team that includes the POSA would have at least two years of practical experience with hyaluronidases. The practical experience with hyaluronidases would need to come from either the POSA's own experience or through collaborations with a team having experience studying and characterizing hyaluronidases.

33. A POSA for the '758 patent would also typically have a degree such as a B.S., M.S., or a Ph.D., with at least two years of experience and training in cellular and molecular biology and protein biochemistry. This experience and training could come from a POSA's undergraduate or graduate studies or employment.

34. Regarding the educational level of the inventors of the '758 patent, I understand that (i) in December 2011, Michael Shepard had a B.S. in Zoology (Cellular and Developmental Biology) and a Ph.D. in Cellular and Developmental Biology & Genetics; (ii) in December 2011, Robert Conner had a B.A. in Biochemistry and Molecular Biology and a Ph.D. in Biological Chemistry; and (iii) in December 2011, Ge Wei had a B.S. in Biochemistry, an M.S. in Biochemistry,

and a Ph.D. in Biochemistry and Molecular Genetics. EX2005, 1-14. Therefore, I understand that at least 3 of the 4 inventors held a degree such as a B.S., M.S., or a Ph.D., with at least two years of experience and training in (i) cellular and molecular biology and (ii) protein biochemistry from their undergraduate or graduate studies and/or employment. EX2005, 1-14.

35. And, as mentioned above, I understand that each of the inventors was employed by Halozyme, Inc. (the owner of, and original applicant for, the '758 patent) in December 2011; therefore, their educational background and experience and training in cellular and molecular biology and protein biochemistry would have been examples of active workers in the field of the invention at this time. EX1002, 20; EX2005, 1-14.

36. In view of the above, and in accordance with the first and sixth factors referenced above in paragraph 24, a POSA for the '758 patent would typically have a degree such as a B.S., M.S., or a Ph.D., and the POSA or a team member would have at least two years of experience and training in cellular and molecular biology and protein biochemistry.

37. The second through fifth factors referenced above in paragraph 24⁸ also

⁸ *I.e.*, (ii) the type of problems encountered in the art, (iii) the prior art solutions to those problems, (iv) the rapidity with which innovations are made, and

support a POSA definition requiring at least two years of practical experience with hyaluronidases from either the POSA or a member of a multi-disciplinary team that includes the POSA because, as discussed above, the field and background of the invention relate to hyaluronidases. EX1001, 4:15-50.

38. Additionally, the '758 patent discusses various problems encountered in the art and contemplated solutions to those problems, which require familiarity with hyaluronidases. For Example: EX1001, 106:6-9 (“PH20 hyaluronidase, such as rHuPH20, rapidly loses activity in the presence of preservatives”), 106:37-41 (“The modified PH20 polypeptides provided herein that exhibit increased stability in the presence of phenolic preservatives exhibit more than 15% enzymatic activity in the presence of at least one phenolic preservative”); EX1001, 115:14 (“PH20 denatures in the presence of low salt or no salt.”); and 118:47-51 (“Provided herein are modified PH20 polypeptides that exhibit increased stability in the presence of low concentrations of salt”).

39. Regarding the sophistication of the technology, while the hyaluronidase assays described in the common disclosure do not require extensive experience to employ, they do require familiarity with hyaluronidases. For example: EX1001, 126:59-62 (“Provided herein are methods for identifying a modified or variant

(v) the sophistication of the technology.

hyaluronan-degrading enzyme, such as a modified hyaluronidase or modified PH20 polypeptide.”), 129:10-135:26; 170:48-172:38 (describing hyaluronidase assays), 170:49-52 (“assays can be used to assess the hyaluronidase activity of the PH20 polypeptide”). Furthermore, the ’758 patent describes the role of PH20 in contraception, and comprehending the role of PH20 in contraception is relevant to understanding a contraceptive utility (i.e., use) for the claimed modified PH20 polypeptides. EX1001, 187:41-51 (“PH20 plays a role in fertilization by facilitating entry of the sperm through the cumulus layer surrounding the unfertilized egg. PH20 also is able to bind to hyaluronic acid (HA) on the zona pellucida during early phases of fertilization. This binding also initiates intracellular signaling that aids in the acrosome reaction. Immunization with PH20 has been shown to be an effective contraceptive in male guinea pigs.”), 187:41-51 (“Modified PH20 polypeptides provided herein can be used as vaccines in contraceptive applications.”).

40. As I will discuss in Section IX, without support in the scientific literature, Dr. Hecht dismisses a well-established contraceptive utility for PH20 hyaluronidases, which would have been known by a POSA in December 2011. And as I will discuss in Section X, Drs. Hecht and Park base their obviousness analysis on a sequence alignment of evolutionarily distant hyaluronidase sequences, many of which are not even from humans; but a POSA having

hyaluronidase experience would have understood that the inclusion of such sequences would undermine the conclusions they draw from the alignment.

41. Accordingly, the second through fifth factors referenced above in paragraph 24 also support requiring at least two years of practical experience with hyaluronidases from either the POSA or a member of a team that includes the POSA.

42. The second through fifth factors referenced above in paragraph 24⁹ also support a POSA definition where the POSA would have had at least two years of experience and training in cellular and molecular biology and protein biochemistry from their undergraduate or graduate studies or employment.

43. The '758 patent extensively describes methods for producing the claimed modified PH20 polypeptides. EX1001, 135:28-39 ("Polypeptides of a modified PH20 polypeptide set forth herein can be obtained by methods well known in the art for protein purification and recombinant protein expression. Polypeptides also can be synthesized chemically. Modified or variant, including truncated, forms can be engineered from a wild[-]type polypeptide using standard

⁹ *I.e.*, (ii) the type of problems encountered in the art, (iii) the prior art solutions to those problems, (iv) the rapidity with which innovations are made, and (v) the sophistication of the technology.

recombinant DNA methods. For example, modified PH20 polypeptides can be engineered from a wild[-]type polypeptide, such as by site-directed mutagenesis.”), 135:28-149:54, 188:35-225:9 (further detailing methods for producing modified PH20 polypeptides). Recombinant DNA methods, site-directed mutagenesis, recombinant protein expression, chemical protein synthesis, and protein purification methods are routine cellular and molecular biology and protein biochemistry methods and/or techniques that a POSA equipped with the ’758 patent specification’s guidance could have used to make the claimed modified PH20 polypeptides. EX1001, 135:28-39.

44. In view of the above, and in accordance with the second through fifth factors referenced above in paragraph 24, a POSA for the ’758 patent would typically have a degree such as a B.S., M.S., or a Ph.D., with at least two years of experience and training in cellular and molecular biology and protein biochemistry.

45. Altogether, in view of the six factors referenced above in paragraph 24, a POSA in this field or a member of a multi-disciplinary team that includes the POSA would have also had at least two years of practical experience with hyaluronidases. The practical experience with hyaluronidases would need to come from either the POSA’s own experience or through collaboration with a member of a multi-disciplinary team having experience studying and characterizing hyaluronidases. Additionally, a POSA for the ’758 patent would also typically

have a degree such as a B.S., M.S., or a Ph.D., with at least two years of experience and training in cellular and molecular biology and protein biochemistry. The experience and training in cellular and molecular biology and protein biochemistry could come from the POSA's experience and training during their undergraduate or graduate studies or employment.

46. Considering my ample practical experience with hyaluronidases as described in my background and qualifications, I am more experienced than a POSA under both my own definition and Dr. Hecht's.

VI. LEGAL BASIS FOR MY ANALYSIS

47. My understanding regarding the legal principles relating to the definition of a POSA is provided in Section V above. In formulating my further opinions set forth in this Declaration, I also applied the following legal principles:

A. Claim Construction

48. I understand that in a post-grant review ("PGR"), patent claim terms are given their ordinary and customary meaning as understood by a POSA at the time of the invention, in view of the patent's specification and its prosecution history—unless the patent explicitly defines the claim term. I also understand that when a patent explicitly defines a claim term in the specification, the patent's definition controls. I also understand that no two claims in the same patent should be interpreted to be the same invention, *i.e.*, I understand that every claim is presumed

to be distinct. I also understand that the scope of a dependent claim is presumed to be narrower than the scope of the claim(s) from which it/they depends.

49. I understand that claim 1 is the sole independent claim in the '758 patent and that claims 2 and 6-30 are dependent claims (depending directly or indirectly from claim 1). I understand that a dependent claim contains all limitations (i.e., elements) of the claim(s) from which it depends. Thus, I understand that claims 2 and 6-30 contain all limitations of claim 1, as well as those of any additional claims from which they depend. The copy of the '758 patent provided as Exhibit 1001 also lists claims 3-5 and 31-40, but I understand that Patent Owner Halozyme, Inc. statutorily disclaimed claims 3-5 and 31-40 on May 7, 2025. EX2003. Thus, I understand that the disclaimed claims 3-5 and 31-40 are not currently part of this post-grant review proceeding.¹⁰

B. Written Description

50. I understand that the written description provided by a patent specification must convey clearly to a POSA that the applicant was in possession¹¹

¹⁰ I understand that a statutory disclaimer means that, effectively, the only challenged claims are claims 1-2 and 6-30.

¹¹ I understand possession does not mean physical possession and does not require making or testing the invention.

of the claimed invention as of the patent's filing date or as of the filing date of a related earlier-filed application if the patent owner would like to receive the benefit of that earlier date (here, I have been asked to assess the '758 patent's written description as of the filing date of the earlier '731 related application: December 28, 2012). And I understand that this involves an objective inquiry into the disclosure provided in the specification from the perspective of a POSA as of December 28, 2012.

51. I further understand that this written description requirement must be assessed in view of the state of the knowledge of a POSA in the art. In addition, I understand that a patent specification is written for a POSA and that such a hypothetical person presumably has all of the knowledge of the state of the art as of the patent's filing date, in addition to the knowledge provided by the patent specification itself.

52. I understand that there is sufficient (*i.e.*, adequate) written description support when a POSA can visualize or recognize the full scope of the claimed subject matter and that the claimed subject matter need not be provided verbatim in a specification. I also understand that a skilled artisan comes to the patent with knowledge in the art, therefore, it is unnecessary to spell out every detail of the invention in the specification for a skilled artisan to conclude that there is written description support.

53. I understand that assessing whether there is written description support for a genus¹² claim involves consideration of a number of factors, including (i) the nature and scope of the claims; (ii) existing knowledge in the particular field and extent and content of the prior art; (iii) maturity of the science of technology and scientific and technologic knowledge already in existence; (iv) predictability of the aspect at issue; and (v) scope of the invention at issue.

54. I also understand that some genus claims are referred to as “functional” genus claims because they describe the claimed invention in terms of what it *does*—rather than defining the claimed invention by its structural components. By contrast, I understand that “structural” genus claims define the claimed invention by its *structural* components.

¹² I understand a genus to be a group that covers multiple “species” and that “species” are sometimes referred to as “embodiments.”¹³ I note that Dr. Hecht nonetheless argues that “[a] skilled artisan would have understood the claims to necessarily cover modified PH20 polypeptides that are active mutants, and would not view them as including inactive mutants.” EX1003, ¶134 (emphasis added). I note also that Dr. Park omits any mention of the concept of claim construction in his declaration; in particular, Dr. Park does not cite the ’758 patent in his declaration. EX1004.

55. I further understand that a sufficient description of a genus may be provided by the disclosure of either (i) a representative number of species falling within the scope of the genus or (ii) structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus. Additionally, I understand that an adequate written description requires a precise definition, such as by structure, formula, chemical name, physical properties, or other properties, of species falling within the genus sufficient to distinguish the claimed genus from other materials.

C. Enablement

56. I understand that a patent application specification that provides an enabling disclosure must allow a POSA to make and use the full scope of the claimed invention without undue experimentation as of that application's filing date. Here, I have been asked to consider whether the '731 application provides an enabling disclosure for the challenged patent claims of the '758 patent, which I understand is a consideration in determining whether the '758 patent is entitled to be treated as though it were effectively filed as of the '731 application's December 28, 2012 filing date. I understand that the following factors can be used to determine whether undue experimentation would have been needed (the so-called *Wands* factors): (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of

predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

57. I understand that the determination that “undue experimentation” would have been needed to make and use the claimed invention is a conclusion reached by weighing the above-noted factual considerations. I understand that whether some experimentation is necessary does not necessarily make such experimentation undue and that even a considerable amount of experimentation is not undue, if it is merely routine. Furthermore, I understand that evidence of a pharmaceutical property in any standard experimental animal is sufficient to establish utility (*i.e.*, usefulness).

D. Obviousness

58. I understand that an obviousness analysis involves comparing a claim with the prior art to determine whether the claimed subject matter would have been obvious to a POSA in view of the asserted prior art and the general knowledge in the background art. I understand that obviousness must be assessed from the viewpoint of a POSA at the time of the invention. In assessing obviousness, I have been asked to consider the timeframe before December 29, 2011, the same timeframe Dr. Hecht considered. EX1003, ¶¶11, 194. I further understand that to establish obviousness, a party seeking to establish obviousness must perform the

following factual inquiries: (a) determining the scope and content of the prior art; (b) ascertaining the differences between the claimed invention and the prior art; and (c) resolving the level of skill in the art. I understand that, in determining the scope and content of the prior art and ascertaining the differences between the claimed invention, a patent challenger may (1) specify where each element of the claim is found in the prior art or (2) explain why a POSA exercising ordinary creativity would bridge any gaps (*i.e.*, missing elements) between the prior art and the claimed invention to produce the claimed invention.

59. I understand that one way of showing obviousness is by establishing that a POSA would have had both (i) a reason to modify or combine the teachings of the prior art to achieve the claimed invention and (ii) a reasonable expectation of success in doing so. I understand that the reason to combine prior-art references can come from a variety of sources, not just the prior art itself or the specific problem the patentee was trying to solve. And I understand that the references themselves need not provide a specific hint or suggestion of the alteration needed to arrive at the claimed invention; the analysis may include recourse to logic, judgment, and common sense available to a person of ordinary skill that does not need to be explicit in any reference. Moreover, I understand that evidence showing that lack of motivation to combine may support a conclusion that the claimed invention was nonobvious.

60. I understand that a “reasonable expectation of success” is assessed in view of the prior art and general knowledge in the art from the viewpoint of a POSA before the relevant date (Dr. Hecht considered the timeframe before December 29, 2011, and I have been asked to consider the same timeframe). Furthermore, I understand that the expectation of success need only be *reasonable*, not absolute. I understand that this rationale, if not explicitly provided by the prior art, may be implicitly provided by the prior art. Moreover, I understand that evidence showing that there was no reasonable expectation of success may support a conclusion that the claimed invention was nonobvious.

61. I also understand that, before reaching a conclusion that the claimed invention would have been obvious, one must consider any objective evidence of non-obviousness if it is available. The objective evidence of non-obviousness can include evidence of commercial success attributable to the claimed invention, evidence of industry praise for the claimed invention, evidence of a long-felt need that was solved by the claimed subject matter, evidence that others copied the claimed subject matter, or evidence that the claimed subject matter achieved an unexpected, superior result relative to the closest prior art. I understand that such evidence must have a nexus, or causal relationship, to the claimed subject matter beyond what was available in the prior art, and must be commensurate in scope with the patent claim(s) at issue.

62. Finally, I understand that the patent examiner is charged with assessing all pending claims for compliance with certain requirements under the patent laws, including the requirement that the specification provide an adequate written description for the invention and that the claims be non-obvious.

VII. CLAIMS 1-2 AND 6-30 DO NOT REQUIRE HYALURONIDASE ACTIVITY

63. Although Dr. Hecht omits any mention of the concept of claim construction¹³, I have considered how a POSA would have construed the claimed invention: claims 1-2 and 6-30—in view of the principles of claim construction I summarized in Section VI.A.

A. A POSA Would Have Understood That a “modified PH20 polypeptide” Means “a PH20 polypeptide that contains at least one amino acid modification compared to a reference unmodified PH20 polypeptide”

64. A POSA interpreting claims 1-2 and 6-30 of the '758 patent would have

¹³ I note that Dr. Hecht nonetheless argues that “[a] skilled artisan would have understood the claims to necessarily cover modified PH20 polypeptides that are active mutants, and would not view them as including inactive mutants.” EX1003, ¶134 (emphasis added). I note also that Dr. Park omits any mention of the concept of claim construction in his declaration; in particular, Dr. Park does not cite the '758 patent in his declaration. EX1004.

deemed it necessary to interpret the meaning of “modified PH20 polypeptide” because the term “modified PH20 polypeptide” appears either explicitly or via incorporation in each of claims 1-2 and 6-30 and is fundamental to interpreting the claims. EX1001, Claims 1-2 and 6-30.

65. Claim 1, for example, states:

A^[14] *modified PH20 polypeptide*, comprising one or more amino acid modifications in an unmodified PH20 polypeptide, wherein: the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of *SEQ ID NOs: 3, 7 and 32-66*; amino acid modifications are selected from the group consisting of amino acid replacements(s), deletion(s), and/or insertion(s); the modified PH20 polypeptide comprises an amino acid replacement at a position corresponding to *residue 317*, with reference to amino acid positions set forth in *SEQ ID NO:3*; the replacement at the position corresponding to residue 317 is *selected from the group consisting of A, I, K, M, Q, and R*; corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the amino acid sequence of *SEQ ID NO:3*; and the modified PH20 polypeptide has *at least 91% sequence identity* to a polypeptide having the amino acid sequence selected from the group consisting of *SEQ ID NOs: 3, 7 and 32-66*.

EX1001, Claim 1 (emphasis added). The modified PH20 polypeptide of Claim 1 is

¹⁴ I understand the term “a” to mean one or more.

thus defined by the following common features: (i) the modified PH20 polypeptide of claim 1 shares “at least 91%” of the structure of the disclosed sequences (SEQ ID NO: 3, 7 and 32-66), implicitly limiting any sequence variation to 9%, and (ii) that the modified PH20 polypeptide of claim 1 contains one amino acid modification (selected from A, I, K, M, Q, and R) at position 317 (with reference to amino acid positions set forth in SEQ ID NO: 3). EX1001, Claim 1. Claim 1, therefore, is defined purely by structure, and not by any function. EX1001, Claim 1.

66. Specifically, I understand that claim 1, which explicitly recites the term “modified PH20 polypeptide,” is the only independent claim in the ’758 patent. And I understand that dependent claims contains all limitations (*i.e.*, all distinct claim components) of the claim(s) from which they depend. Section VII.A. Claims 2 and 6-30 depend from and thus incorporate every element of claim 1; therefore, the term “modified PH20 polypeptide” also appears via incorporation in each of claims 2 and 6-30. EX1001, Claims 2 and 6-30. Thus, I explain the meaning of “modified PH20 polypeptide” below.

67. **First**, I understand that when a patent explicitly defines a claim term in the specification, the patent’s definition controls. Section VII.A. The term “modified PH20 polypeptide” is expressly defined in the specification of the ’758 patent, as follows:

As used herein, “modified PH20 polypeptide” or “variant PH20 polypeptide” refers to a PH20 polypeptide that contains at least one amino acid modification, such as at least one amino acid replacement as described herein, in its sequence of amino acids compared to a reference unmodified PH20 polypeptide.^[15]

The specification then provides a non-limiting example:

A modified PH20 polypeptide can have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity. Typically, a modified PH20 polypeptide contains 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 amino acid replacements. It is understood that a modified PH20 polypeptide also can include any one or more other modifications, in addition to at least one amino acid replacement as described herein.

EX1001, 48:38-53 (emphasis added). The express definition of “modified PH20 polypeptide” does not encompass any function because it describes only structural components: (i) a sequence of amino acids (ii) with at least one amino acid modification (iii) relative to a reference sequence. EX1001, 48:38-43.

68. The term “modified PH20 polypeptide,” therefore, has a purely structural meaning in the context of the specification, and a POSA applying its

¹⁵ The express definition is underlined.

express definition would have understood that the term “modified PH20 polypeptide” is defined by a sequence of amino acids and not by any particular function. EX1001, 48:38-43. This structural definition—explicitly and solely described by a sequence of amino acids—does not *require* hyaluronidase activity. EX1001, 48:38-43.

69. **Second**, I understand that claim terms are given their ordinary and customary meaning as understood by a POSA at the time of the invention in view of the patent’s specification and its prosecution history—unless the patent explicitly defines the claim term. Section VII.A, above. As discussed above, “modified PH20 polypeptide” is explicitly defined; I do not separately analyze any ordinary and customary meaning of “modified PH20 polypeptide.”

70. **Third**, I understand per Section VII.A that claims are to be interpreted in view of the entirety of the patent’s specification, including the entirety of the claims, and the entirety of the ’758 patent’s specification clearly explains that “modified PH20 polypeptide” also refers to polypeptides (including hyaluronidases) that do not exhibit hyaluronidase activity.

71. A POSA interpreting claim 1 in view of the other dependent claims would find further support indicating that the term “modified PH20 polypeptide” does not require hyaluronidase activity. Dependent claims 17-18, for example, specify further modifications to the modified PH20 polypeptide of claim 1,

including glycosylation. Claim 18 specifically recites, “The modified PH20 polypeptide of claim 17, wherein the post-translational modification is *glycosylation*.” EX1001, Claim 18 (emphasis added).

72. Dr. Hecht states, “PH20 enzymes must be glycosylated to exhibit their catalytic activity.” EX1003, ¶197. The ’758 patent also states that glycosylation “is required for PH20 hyaluronidase activity” and that “at least N-linked glycosylation sites corresponding to amino acid residues N200, N333 and N358 are required for secretion and/or *activity* of the enzyme.” EX1001, 70:60-71:4 (emphasis added).

73. Because the modified PH20 polypeptide of dependent claim 18 must be glycosylated, claim 1 must cover *both* glycosylated and unglycosylated modified PH20 polypeptides; otherwise, the scope of claims 1 and 18 would be identical. EX1001, Claims 1 and 18. As discussed above, I understand that the scope of dependent claims are presumed to be distinct because the scope of a dependent claim should be narrower than the independent and dependent claims preceding it. Section VI.A.

74. Accordingly, a POSA would have understood that claim 1 necessarily encompasses unglycosylated modified PH20 polypeptides—and because the ’758 patent states that glycosylation “is required for PH20 hyaluronidase activity,” a POSA would have understood claim 1 to encompass modified PH20 polypeptides

that *lack* PH20 hyaluronidase activity.¹⁶

75. Reviewing the claims in view of other descriptions in the common disclosure further supports the understanding that the claims do not require hyaluronidase activity. EX1001, 75:60-63, 115:53-116:67, 187:56-58, 261:60-262:25, and Tables 5 and 10. For example, the specification explicitly explains that some modified PH20 polypeptides are *inactive*. In particular, the specification defines inactive mutants as modified PH20 polypeptides:

Inactive Mutants: Provided herein are *modified PH20 polypeptides* that contain one or more amino acid replacements in a PH20 polypeptide and that are *inactive, whereby the polypeptides do not exhibit*

¹⁶ Dependent claims 2-35 are likewise consistent with the understanding that claim 1 does not require hyaluronidase activity. I understand that claims 3-5 and 31-40 have been disclaimed; however, I have assessed them insofar as they would have informed the meaning of claim 1 to a POSA and do not interpret them as suggesting that claim 1 requires hyaluronidase activity. For example, I do not interpret the term “increased” to support the notion that claim 1 *requires* hyaluronidase activity because this term relates to the activity of the modified PH20 polypeptides of claim 4 relative to the hyaluronidase activity of the polypeptide set forth in SEQ ID NO: 3, an *unmodified* PH20 polypeptide. EX1001, Claim 4.

hyaluronidase activity or exhibit low or diminished hyaluronidase activity.

EX1001, 115:52-58 (emphasis added). The specification then provides multiple non-limiting examples:

The *modified PH20 polypeptides* provided herein that are inactive *generally exhibit less than 20%*, such as less than 10%, of the hyaluronidase activity of a wildtype or reference PH20 polypeptide, such as the polypeptide set forth in SEQ ID NO: 3 or 7. For example, modified PH20 polypeptides herein that are inactive exhibit less than 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, ... 0.05% or less of the hyaluronidase activity....

EX1001, 115:52-122:67 (emphasis added). Numerous additional descriptions in the specification describe that modified PH20 polypeptides can be *inactive*.

EX1001, 261:62-65 (emphasis added) (“The other mutants that exhibited less than 20% hyaluronidase activity of wildtype PH20, in at least one of the duplicates, were rescreened to confirm that the dead mutants are *inactive*”); EX1001, 75:60-63 (emphasis added) (“Also provided are modified PH20 polypeptides that are *inactive*, and that can be used, for example, as antigens in contraception vaccines”); EX1001, 115:53-116:67 (emphasis added) (“For example, provided herein are PH20 polypeptides that are *inactive* and that are modified, for example by amino acid replacement or substitution, compared to a wildtype or reference

PH20 polypeptide”); EX1001, 116:53-60 (emphasis added) (“The amino acid replacement(s) can be at the corresponding position in a PH20 polypeptide as set forth in any of SEQ ID NOs: ... 3, 6-66 ... or a variant thereof having at least ... 91% ... or more sequence identity thereto, so long as the resulting modified PH20 polypeptide is *inactive*.”); EX1001, 187:57-58 (emphasis added) (“the modified PH20 polypeptides can be *inactive* enzymes”); EX1001, 261:60-262:25 (describing a modified assay that is intended to specifically detect inactive mutants); EX1001, Table 5 (providing replacements identified as corresponding to inactive mutants); EX1001, Table 10 (providing numerous examples of inactive mutants).

76. The specification also states that “[i]ncluded among the modified PH20 polypeptides provided herein are PH20 polypeptide that are active mutants....” EX1001, 75:51-53 (emphasis added). Because the specification states that active mutants are “included among” the “the modified PH20 polypeptides provided herein,” the specification clearly contemplates that the modified PH20 polypeptides are not limited to active mutants even beyond the explicit descriptions of inactive mutants referenced above. EX1001, 75:51-53.

77. I note that the specification states that a modified PH20 polypeptide can have “150 amino acid replacements, so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity”; however, this description is not part of the express definition of “modified PH20 polypeptide”; therefore a POSA would

not have interpreted this statement to mean that the term “modified PH20 polypeptide” requires hyaluronidase activity. EX1001, 48:38-46.

78. A POSA would also have understood that this statement merely describes an *upper limit* for the number of modifications possibly allowing a modified PH20 polypeptide to exhibit enzymatic activity. EX1001, 48:38-46.

79. And moreover, a POSA would have understood that the claims do not encompass a modified PH20 polypeptide having 150 amino acid replacements because a modified PH20 polypeptide having 150 amino acid replacements would exhibit a lower percent identity than the “at least 91%” structural identity required by the claims. EX1001, 48:38-46 and Claims 1-2 and 6-30; EX2006. SEQ ID No. 3, for example, contains 447 amino acids. EX2006. If 150 amino acid replacements were made to SEQ ID NO. 3, the resulting polypeptide would have only ~66% structural identity to SEQ ID NO. 3. EX2006. Likewise, the shortest amino acid sequence of SEQ ID Nos. 32-66—SEQ ID No. 32, has 430 amino acid residues; and the longest amino acid sequence of SEQ ID Nos. 32-66—SEQ ID No. 66, has 465 amino acid residues. EX2006. If 150 amino acid replacements were made to SEQ ID Nos. 32 and 66, the resulting polypeptides would have only ~65% and ~68% structural identity to SEQ ID Nos. 32 and 66, respectively.¹⁷ In any event, a

¹⁷ These values were calculated as follows: [(total amino acid residues—

150 amino acid replacement would result in significantly less than the “at least 91%” structural identity required by the claims. EX1001, 48:38-46, Claims 1-4, 8-21; EX2006.

80. In view of the above, therefore, the specification clearly does not restrict “modified PH20 polypeptide” to active enzymes nor contradict nor modify the specification’s explicit definition of modified PH20 polypeptide.

81. **Finally**, I reviewed the prosecution history for the ’758 patent (EX1002), but I did not find in it any discussion that contradicts or modifies the specification’s explicit definition of modified PH20 polypeptide.

82. In sum, a POSA interpreting “modified PH20 polypeptide” according to the express definition in view of the specification and prosecution history would have understood that “modified PH20 polypeptide” simply means “a PH20 polypeptide that contains at least one amino acid modification, such as at least one amino acid replacement as described [in the patent], in its sequence of amino acids compared to a reference unmodified PH20 polypeptide.” In other words, “modified PH20 polypeptide” is a purely *structural* term (defined by an amino acid sequence) that does not require hyaluronidase activity (i.e., a particular function).

150)/total amino acid residues]*100, *i.e.*: [(447–150)/447]*100 = 66; [(430–150)/430]*100 = 65; [(465–150)/465]*100 = 68.

B. A POSA Would Not Have Interpreted Claims 1-2 and 6-30 as Being Limited to Enzymatically Active Mutant PH20 Polypeptides

83. As discussed, a POSA would not have interpreted “modified PH20 polypeptide” to require any hyaluronidase activity. Section VII.A. Rather, as discussed, a POSA would have understood that “modified PH20 polypeptide” is a purely structural term defined by an amino acid sequence. Section VII.A.

84. Furthermore, because nothing in the remainder of the claims, specification, or prosecution history would have otherwise indicated to a POSA that the claims should be limited to modified PH20 polypeptides having hyaluronidase activity, *e.g.*, “active mutants,” a POSA would not have interpreted Claims 1-2 and 6-30 as requiring hyaluronidase activity.

85. Dr. Hecht acknowledges that the '758 patent contemplates both active and inactive mutants. EX1003, III.A, ¶98. Nevertheless, he argues that the claims would be understood to concern active mutant PH20 modified polypeptides. EX1003, IV.B. Dr. Hecht provides two primary reasons for this assertion—(1) that “a skilled artisan reading the common disclosure would have understood it to be describing two, mutually exclusive types of modified PH20 polypeptides: (i) active mutants are those with significant levels of hyaluronidase activity (*i.e.*, above 40% of the activity of unmodified PH20), and (ii) inactive mutants, which do not exhibit significant hyaluronidase activity (*i.e.*, less than 20% of the activity of the

unmodified PH20),” EX1003, ¶107—and (2) that “[t]he brief suggestion in the common disclosure about possibly using inactive mutant forms of PH20 as the immunogen of a contraceptive vaccine does not seem credible....” EX1003, ¶112.

86. **First**, a POSA would not have understood the claims to encompass only “active mutants.” As Dr. Hecht acknowledges, both active and inactive mutants are contemplated in the specification. EX1003, III.A, ¶98. Dr. Hecht argues that “the common disclosure identifies each of these substitutions [i.e., each of L317A, L317I, L317K, L317M, L317Q, or L317R] as causing PH20₁₋₄₄₇ to exhibit increased hyaluronidase activity.” EX1003, ¶¶126-128. However, a POSA interpreting claim 1 in view of the other dependent claims (together with the specification and prosecution history) would have found further support indicating that the term “modified PH20 polypeptide” still does not require hyaluronidase activity. Dependent claims 17-18, for example, specify further modifications to the modified PH20 polypeptide of claim 1, including glycosylation. EX1001, Claims 17-18. Claim 18 recites, “The modified PH20 polypeptide of claim 17, wherein the post-translational modification is *glycosylation*.” EX1001, Claim 18 (emphasis added). EX1001, Claim 18. Dr. Hecht states, “PH20 enzymes must be glycosylated to exhibit their catalytic activity.” EX1003, ¶197. And the common disclosure also states that glycosylation “is required for PH20 hyaluronidase activity.” EX1001, 70:60-71:4. Therefore, a POSA would have understood that claim 1 encompasses

both active and inactive mutants. Moreover, the term “active” is a functional term not found in the claims; the claimed modified PH20 polypeptides are *not* defined by any function. EX1001, Claims 1-2 and 6-30; EX1003, ¶107. And Dr. Hecht does not identify any claim term appearing in any of claims 1-2 and 6-30 that imposes a requirement for hyaluronidase activity.

87. Additionally, Dr. Hecht argues that the statement in the specification that modifications “can be in any PH20 polypeptide ... so long as the modified form exhibits hyaluronidase activity” suggests that the claimed modified PH20 polypeptides are limited to “active mutant[s]”; however, the specification only explains that modifications can be made to create active modified PH20 polypeptides, not that all claimed modified PH20 polypeptides must have hyaluronidase activity. EX1003, ¶¶128-129. Furthermore, the specification is not limited to two, mutually exclusive groups of mutants defined by either (i) above 40% or (ii) less than 20% activity. Table 9 of the specification, for example, provides 536 modified PH20 polypeptides that exhibit 120% or greater hyaluronidase activity of wild-type PH20, approximately 75 mutants that exhibited 300% or greater activity than wild-type, and 192 polypeptides that exhibit between 20-40% activity. EX1001, Table 9. Therefore, the claimed modified PH20 polypeptides are not limited to polypeptides falling into the two categories Dr. Hecht delineated in paragraph 98 of his declaration. EX1001, Table 9.

88. **Second**, as will be discussed further in Section IX below, the specification contemplates a credible (*i.e.*, valid) contraceptive utility for the modified PH20 polypeptides, and the specification does not distinguish between using active or inactive mutants for this contraceptive utility. Section IX. In particular, and as will be discussed further in Section IX below, the prior art cited by the specification, Primakoff 1988 and Tung 1997, reported that PH20 polypeptides are successful as contraceptives in guinea pigs. Section IX. The specification expressly states that “modified PH20 polypeptides provided herein can be used as vaccines in contraceptive applications,” without delineating between inactive or active mutants. EX1001, 187:40-42. In other words, a POSA would have understood that both inactive and active mutants could have been used for contraceptives.

89. Thus, altogether, a POSA would not have interpreted Claims 1-2 and 6-30 as being limited to active mutant PH20 polypeptides.

VIII. THE COMMON DISCLOSURE PROVIDES ADEQUATE WRITTEN DESCRIPTION SUPPORT FOR THE CLAIMED INVENTION

90. As explained in my analysis below, the claims are adequately described by the ample written description provided in the common disclosure. I provided a discussion of the legal principles relating to written description above in Section VI.B., and my analysis below follows those legal principles.

A. A POSA Would Have Recognized That the Claimed Modified PH20 Polypeptides All Include Common Structural Features, Which Are Defined by Amino Acid Sequence Identity

91. First, as discussed, claims 1-2 and 6-30 do not require hyaluronidase activity. Section VII. Rather, the scope of the claims is defined by specific *structural* features of the modified PH20 polypeptides. Section VII. Because Dr. Hecht assumes that the claims require hyaluronidase activity, he overlooks how the claims' structural features clearly define the scope of the claims in a manner that would have allowed a POSA to have visualized or recognized all members of the structurally defined genus of modified PH20 polypeptides.

92. Specifically, the scope of the claimed modified PH20 polypeptides is defined by the following common features: (i) that the modified PH20 polypeptide of claim 1 shares "at least 91%" of the *structure* of the disclosed sequences (SEQ ID NO: 3, 7 and 32-66), implicitly limiting any amino acid sequence variation to 9%, and (ii) that the modified PH20 polypeptide of claim 1 contains an amino acid modification (selected from A, I, K, M, Q, and R) at position 317 (with reference to amino acid positions set forth in SEQ ID NO: 3). EX1001, Claim 1.

93. Even Dr. Hecht and Dr. Park use these structural features to define the scope of the genus. EX1003, ¶¶115-120, 122; EX1004, ¶¶165-169, App'x F. Dr. Park, for example, determines the number of distinct polypeptides encompassed by the claims by using "91% sequence identity" to "human PH20 proteins having

varying lengths of C-terminal truncations” and “one substitution at a defined position to either one or one of six alternative amino acids.” EX1004, ¶165.

94. Moreover, the sequences for SEQ ID NO: 3, 7 and 32-66, which are provided in the sequence listing, are incorporated by reference (i.e., included) in their entirety in the '758 patent. EX1001, 4:4-12. Thus, the common disclosure fully describes the complete structure (*i.e.*, amino acid sequence) of SEQ ID NO: 3, 7 and 32-66 because a POSA could have readily visualized SEQ ID NO: 3, 7 and 32-66 by simply reviewing their corresponding amino acid sequences in the sequence listing. EX1001, 4:4-12.

95. SEQ ID NO: 3, 7 and 32-66 correspond to a series of C-terminal-truncations of unmodified PH20. EX1001, 12:63-13:1, 30:43-49. As such, these sequences are highly similar and only differ by single amino acid residue truncations with respect to the most similar length sequence(s). For example, SEQ ID No. 66 is the longest sequence, and SEQ ID. No. 65 is only one amino acid residue shorter than SEQ ID. No. 66. At the other end of the spectrum, SEQ ID No. 32 is the shortest sequence, and SEQ ID. No. 33 is only one amino acid residue longer than SEQ ID NO. 32 at its C-terminus, as illustrated in Figure A below:

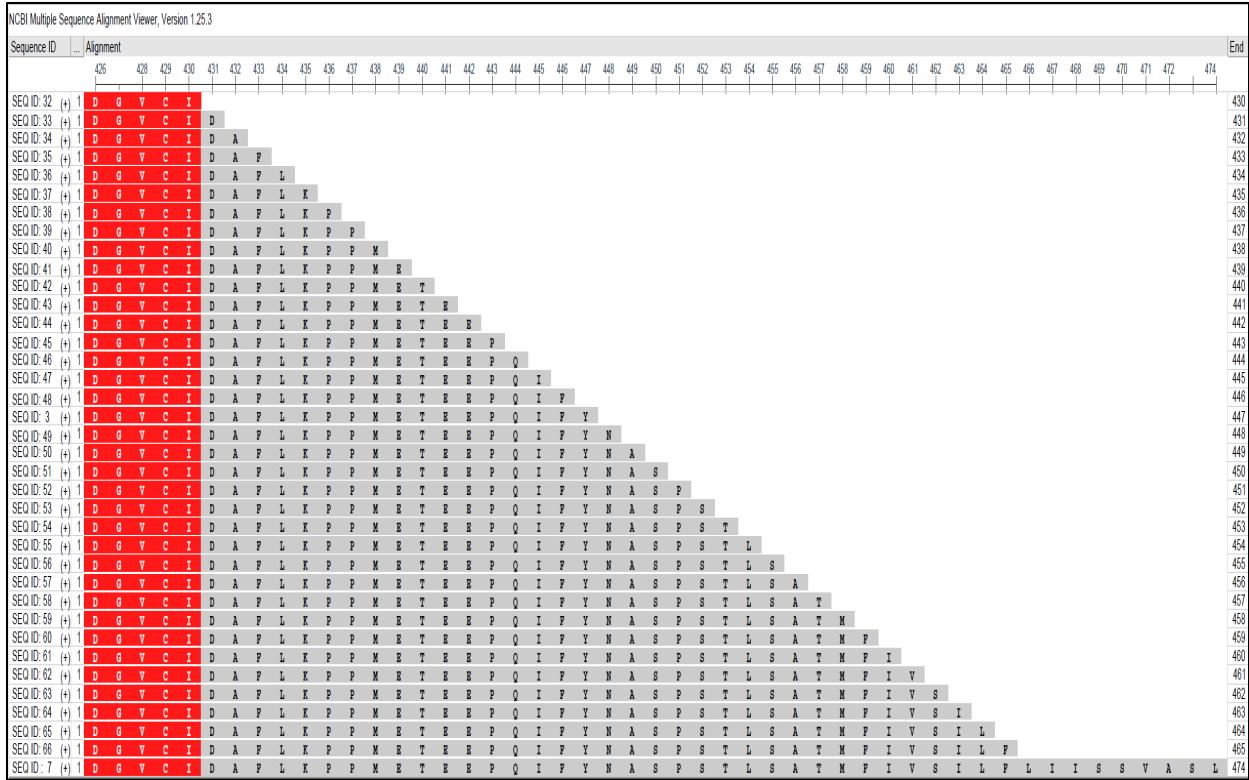


Figure A. Sequence alignment I prepared aligning the C-terminal portions of SEQ ID NO: 3, 7 and 32-66 and showing that each sequence differs by only a single amino acid residue at the C-terminus, with respect to the most similar length sequence(s). An enlarged copy of this Figure is provided as Appendix A.

96. Furthermore, a POSA could have readily visualized or recognized the claimed polypeptides that include sequences having at least 91% identity to SEQ ID NO: 3, 7 and 32-66, and including the claimed modification at position 317 (A, I, K, M, Q, or R), using the disclosure in the common disclosure and existing knowledge in the field. EX1001, 58:57-61:7. The '758 patent explains that sequence identity can be determined by aligning sequences to identify identical residues using either: a global alignment, where the full-length of two sequences is compared by aligning them from beginning to end, EX1001, 58:57-61:7; or by a

local alignment, where two sequences are aligned where they share amino acid similarity or identity, EX1001, 58:57-61:7. The '758 patent further explains that these alignments can be readily performed using “standard alignment algorithm programs,” EX1001, 58:57-61:7—although, for “such high levels of identity” (*i.e.*, of “above about 85-90%”), “the result ... can be assessed readily, often without relying on software,” EX1001, 61:1-5. Nonetheless, a POSA would have understood that such algorithms could be run on a computer to accelerate the process, and the '758 patent describes multiple exemplary algorithms that a POSA would have had knowledge of as of December 28, 2012, along with multiple exemplary publicly available programs for performing the alignments, such as BLAST.¹⁸ EX1001, 58:57-61:7; EX1004, ¶24.

97. Thus, a POSA as of December 28, 2012, equipped with the common disclosure, would have been able to readily visualize sequences having at least 91% identity to SEQ ID NO: 3, 7 and 32-66 because they could have considered every permutation of each of the recited sequences in an entirely predictable manner. Claim 1. Likewise, a POSA as of December 28, 2012 would have been able to align these at least 91% identity sequences with SEQ ID NO: 3 and then

¹⁸ Dr. Park acknowledges that a POSA also would have been able to perform a sequence alignment with CLUSTAL-Omega. EX1004, ¶24.

visualize replacing the amino acid corresponding to position 317 of SEQ ID No. 3 with A, I, K, M, Q, or R in an entirely predictable manner. EX1001, 58:57-61:7.

98. Moreover, the scientific and technical knowledge regarding performing sequence alignments was matured and well developed as of December 28, 2012. EX1001, 58:57-61:7. The art cited in the '758 patent regarding suitable algorithms for performing alignments includes art dating back to the 1970s, for example. EX1001, 58:57-61:7.¹⁹

99. In addition to the above, I further disagree with Dr. Hecht's opinion regarding the sufficiency of the description of the structural features common to all members of the claimed genus because his analysis is undergirded by his general misunderstanding that the claims require hyaluronidase activity. As I explained in Section VII above, the claims do not require any hyaluronidase activity. Dr. Hecht argues, however, that "[m]ore importantly, there are no 'double' or 'triple' (or more) mutants that combined sets of single mutations classified as causing both 'active['] mutants' and 'inactive' mutants or were *within particular regions of the PH20 sequence*"—and that the '758 patent "does not, for example, suggest that

¹⁹ "Exemplary algorithms for performing global alignment include the Needleman-Wunsch algorithm (Needleman et al. J. Mol. Biol. 48: 443 (1970))." EX1001, 58:57-61:7.

incorporating one of the specific single substitutions that caused that PH20₁₋₄₄₇ mutant to exhibit *increased activity* will cause a similar increase in the activity of any other PH20 polypeptide *that contains additional substitutions, regardless of their number, location or identity.*” EX1003, ¶¶131, 140 (emphasis added). But a POSA would have understood that the claims do not require hyaluronidase activity, so Dr. Hecht’s views are founded on an assumption that a POSA would not have made. Dr. Hecht also argues that “[t]here are no observations from the experimental results *on any specific secondary structures or structural motifs* within the PH20 protein *that were influenced (positively or negatively) by individual mutations*”—and that “[t]here also is no guidance regarding additional mutations that could be made to further enhance or alter the characteristics of these mutants.” EX1003, ¶139 (emphasis added). Again, the claims do not require hyaluronidase activity—therefore, none of Dr. Hecht’s above statements supports a conclusion that a POSA would not have been able to visualize or recognize all members of the claimed genus based on the common structural features (defined by amino acid sequence identity and a specific mutation at position 317) provided in the common disclosure.

100. Altogether, in view of the above, a POSA would have recognized that the claimed modified PH20 polypeptides all include common structural features, defined by amino acid sequence identity and a specific mutation at position 317,

such that a POSA would have been readily able to visualize or recognize all members of the claimed genus of modified PH20 polypeptides.

B. A POSA Would Have Recognized That the Claimed Modified PH20 Polypeptides Are Represented by a Representative Number of Species Falling within the Scope of the Structural Genus

101. As explained above, a POSA would have been readily able to visualize or recognize all members of the claimed genus of modified PH20 polypeptides based on the structural features common to all members of the structurally defined genus of modified PH20 polypeptides.

102. Nonetheless, the common disclosure also adequately describes the claimed genus of modified PH20 polypeptides because it provides an ample description of a representative number of species falling within the scope of the claimed genus of modified PH20 polypeptides.

103. Dr. Hecht argues that the species exemplified throughout the common disclosure are not sufficiently representative of the claimed modified PH20 polypeptides. EX1003, ¶¶103, 159. However, Dr. Hecht notes that the common disclosure provides a library of “6,753” PH20 mutants—which a POSA would have recognized as a significant number of exemplified species. EX1003, ¶¶103, 159. And the common disclosure explains that each modified PH20 polypeptide within this ~6,800 mutant library contains “a single amino acid mutation compared to ... residues 1-447 of SEQ ID NO: 3....” EX1001, 194:29-33. Additionally, of

the tested mutants, over 600 exhibited activity. EX1001, 227:23-28.

104. Dr. Hecht further argues that the ~6,800 working examples are not representative of the “incredible diversity” of the claimed modified PH20 polypeptides. EX1003, ¶143. However, the diversity of the claims is significantly limited to at least 91% sequence identity; therefore, a POSA would have understood that the claims encompass a very homogeneous group of modified PH20 polypeptides. Indeed, Dr. Park—whom Dr. Hecht relies upon for his analysis—states that bee venom hyaluronidase and human PH20 are “highly homologous” despite only “sharing about 30% sequence identity.” EX1004, ¶¶40, 163. The claimed modified PH20 polypeptides require more than three times that sequence identity.

105. Dr. Hecht also states that the claims are not adequately described because “the sequence identity language in the claims captures the six modified PH20 polypeptides with two or three specific combinations of substitutions that the common disclosure says to not make.” EX1003, ¶163. I disagree with Dr. Hecht.

106. While the common disclosure discloses six select combinations that should not be made, as I will explain, these six select combinations fall *outside* the scope of the claimed modified PH20 polypeptides. EX1001, 77:55-57.

107. The common disclosure explains that P13A/L464W, N47A/N131A, N47A/N219A, N131A/N219A, and N333A/N358A should not be made if the

modified PH20 polypeptide contains *only* two amino acid replacements. EX1001, 77:55-57. The common disclosure subsequently states that, “[f]or purposes herein, reference to positions and amino acids for modification herein, including amino acid replacement or replacements, are with reference to the PH20 polypeptide set forth in SEQ ID NO:3.” EX1001, 77:63-66. Because none of P13A/L464W, N47A/N131A, N47A/N219A, N131A/N219A, and N333A/N358A include any modification at position 317, and the claims specifically require a modification at position 317, these combinations fall outside the scope of the claims.

108. Likewise, the common disclosure explains that N47A/N131A/N219A should not be made if the modified PH20 polypeptide contains *only* three amino acid replacements. EX1001, 77:55-57. Therefore, because this combination also does not include any modification at position 317 (as required by the claims), this combination also falls outside the scope of the claims.

109. Accordingly, a POSA would have recognized that these six select combinations were never encompassed by the claims. Dr. Hecht overlooks this fact.

110. Dr. Hecht also argues that PH20 with multiple substitutions are not adequately described in the common disclosure. EX1003, ¶141. However, Dr. Hecht (and Dr. Park) overlook descriptions of modified PH20 polypeptides containing multiple amino acid modifications that are encompassed by the claims

throughout the common disclosure.

111. For example, the common disclosure describes that “...any of such modified PH20 polypeptides contain a single amino acid modification, such as a replacement, and *combinations of modifications*...” EX1001, 18:43-49 (emphasis added); *e.g.*, EX1001, 48:46-50 (“Typically, a modified PH20 polypeptide contains, 1, 2, 3, 4, 5, 6, 7,...amino acid replacements.”); *and* EX1001, 75:63-67 (emphasis added) (“The modifications can be a single amino acid modification, such as single amino acid replacements (substitutions), insertions or deletions, or *multiple amino acid modifications, such as multiple amino acid replacements, insertions or deletions*. Exemplary modifications are amino acid replacements, including single or *multiple amino acid replacements*.”)

112. The common disclosure also describes multiply modified polypeptides containing at least one modification at the claimed position 317. *E.g.*, EX1001, 14:25-17:64 (emphasis added) (“[e]xemplary modifications include *at least one amino acid replacement* selected from among replacement with:... R at a position corresponding to *position 317*....*and/or* with Q at a position corresponding to position 447, with reference to amino acid positions set forth in SEQ ID NO: 3.”); *e.g.*, EX1001, 87:1-22 (emphasis added) (“In particular examples, provided herein is a modified PH20 polypeptide containing an amino acid replacement *or replacements* at a position or *positions* corresponding to....*317*...with reference to

amino acid positions set forth in SEQ ID NO: 3.”); and EX1001, 98:10-23 (emphasis added) (“For example, the modified PH20 polypeptides provided herein contain an amino acid replacement (substitution) at *one or more amino acid positions* corresponding to positions....317...with reference to amino acid positions set forth in SEQ ID NO: 3.”); and EX1001, 98:10-23 (emphasis added) (“In some examples, the modified PH20 polypeptides provided herein contain *one or more amino acid replacement(s) at a position(s) corresponding to position(s)*...317...and/or 326 with reference to positions set forth in SEQ ID NO: 3.”). Thus, a POSA would have understood that the common disclosure describes modified PH20 polypeptides containing multiple amino acid substitutions that are encompassed by the claims.

113. In addition to the above, I further disagree with Dr. Hecht’s opinion regarding the sufficiency of the number of representative species because his analysis is undergirded by his general misunderstanding that the claims require hyaluronidase activity. As I explained above, claims 2 and 6-30 do not require any hyaluronidase activity. Dr. Hecht argues that the ’758 patent contains “no mutants with a first mutation that led to its classification as an ‘active mutant’ and that then acquired a second mutation.” EX1003, ¶131. But the claims do not require hyaluronidase activity. He also argues that “[m]ore importantly, there are no ‘double’ or ‘triple’ (or more) mutants that combined sets of single mutations

classified as causing both ‘active[’] mutants’ and ‘inactive mutants’ mutants or were within particular regions of the PH20 sequence”—and “[a] significant number of the mutants (~12%) made were not characterized, and around 2.7% of the mutants had activity between 20% and 40%,” EX1003, ¶¶131, 138. But again, claims 2 and 6-30 do not require hyaluronidase activity—therefore, none of Dr. Hecht’s above statements support a conclusion that a POSA would not have been able to visualize or recognize all members of the claimed genus of modified PH20 polypeptides, especially in view of the ~6,800 working examples provided in the common disclosure.

114. Altogether, considering the significant homogeneity of the claimed modified PH20 polypeptides, the ample description of modified PH20 polypeptides containing multiple amino substitutions, and the ~6,800 working examples of single-replacement PH20 polypeptides, a POSA would have (i) been able to visualize or recognize all members of the claimed genus of modified PH20 polypeptides and (ii) found ample description of a representative number of species falling within the scope of the structural genus. As such, a POSA would have found that the common disclosure of the ’731 application (i.e., the “common disclosure”) provides sufficient written description for claims 1-2 and 6-30.

IX. THE COMMON DISCLOSURE WOULD HAVE ENABLED A POSA TO PRACTICE THE FULL SCOPE OF CLAIMS 1-2 AND 6-30 WITHOUT UNDUE EXPERIMENTATION

A. Practicing the Claimed Invention Would Not Have Required Undue Experimentation

115. In Section VI.C., I summarize the legal principles I applied in assessing whether the common disclosure would have enabled a POSA to practice the full scope of claims 1-2 and 6-30 without undue experimentation as of December 28, 2012, which is the filing date of the '731 application. As I explain below, a POSA on December 28, 2012, could have made and used the full scope of the claimed invention without undue experimentation. First, making the claimed modified PH20 polypeptides would not have required undue experimentation because making the claimed modified PH20 polypeptides would have been a matter of using routine molecular biology and protein biochemistry techniques for a POSA equipped with the guidance of the common disclosure on December 28, 2012, as discussed in Section IX.A.1 below. Second, using the claimed modified PH20 polypeptides also would not have required undue experimentation for a POSA equipped with the guidance of the common disclosure on December 28, 2012, because the modified PH20 polypeptides have multiple credible uses, including “therapeutic uses of modified PH20 polypeptides that have the ability to degrade hyaluronan,” as acknowledged by Dr. Hecht. EX1003, ¶108. As provided in the common disclosure, these therapeutic uses include: “treat[ing] diseases or

disorders associated with accumulation of HA²⁰” and “increas[ing] the dispersion and delivery of therapeutic agents” by “increas[ing] tissue permeability.” EX1001, 4:30-50. Furthermore, the modified PH20 polypeptides also have a credible use as contraceptives, *e.g.*, in experimental animals. These credible uses of the claimed modified PH20 polypeptides would have been evident to a POSA equipped with the common disclosure on December 28, 2012, as discussed in Section IX.A.2 below.

1. Making the Claimed Modified PH20 Polypeptides Would Not Have Required Undue Experimentation.

116. As discussed in Section VI.C., I understand that whether some experimentation is necessary does not necessarily make such experimentation *undue*, and that even a considerable amount of experimentation is not undue if it is merely routine. Also as discussed in Section VI.C., I understand that whether experimentation would have been undue is determined by considering and weighing the factors mentioned in Section VI.C, ¶56.²¹ Furthermore as discussed

²⁰ HA is an abbreviation for hyaluronan. EX1001, 4:23.

²¹ *i.e.*, (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the

in Section VI.C., I understand that enablement is assessed in view of the *knowledge provided by the patent specification itself.*²² As I will explain below in view of these considerations, on December 28, 2012, making the claimed modified PH20 polypeptides in light of the guidance provided in the common disclosure would have been routine.

117. First, regarding the nature of the invention, the nature of the invention is a modified PH20 polypeptide. Although, as discussed in Section X below, the prior art does not disclose or suggest making the particular modified PH20 polypeptides recited in the claims, a POSA would not have considered the nature of the invention to necessitate undue experimentation as of December 2012, because using recombinant protein expression to make modified polypeptides was commonplace as of December 2012 (as discussed below). In other words, the state of the prior art regarding making modified polypeptides generally was well established as of December 2012.

118. Nonetheless, Dr. Hecht argues that “[m]aking and identifying all of the

existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

²² I understand that enablement is also assessed in view of what was already known in the art as of December 28, 2012.

multiply-modified PH20 polypeptides that are within the immense set of polypeptides ... defined by the claims' sequence identity parameters is not only undue experimentation, it likely is impossible.” EX1003, ¶170. However, in view of the state of the prior art and the guidance provided in the common disclosure (e.g., molecular biology methods and sequence information), making the claimed modified PH20 polypeptides would have required nothing more than routine molecular biology and protein biochemistry techniques. EX1001, 135:28-39. The common disclosure explicitly states that “[t]he modifications provided herein can be made by standard recombinant DNA techniques such as are routine to one of skill in the art,” and states:

Polypeptides of a modified PH20 polypeptide set forth herein can be obtained by methods *well known in the art for protein purification and recombinant protein expression*. Polypeptides also can be synthesized *chemically*. Modified or variant, including truncated, forms can be engineered from a wildtype polypeptide *using standard recombinant DNA methods*. For example, modified PH20 polypeptides can be engineered from a wildtype polypeptide, such as by site-directed mutagenesis.

EX1001, 135:30-39, 137:35-37 (emphasis added). The inventors of the '758 patent further describe these routine molecular biology and protein biochemistry techniques in detail. EX1001, 135:40-137:32 (“Isolation or Preparation of Nucleic Acids Encoding PH20 Polypeptides”), 137:33-42 (“Generation of Mutant or

Modified Nucleic Acid and Encoding Polypeptides”), 137:43-140:63 (“Vectors and Cells”), 140:64-144:58 (“Expression” in various cell types and organisms, including: prokaryotic, yeast, insect, mammalian, and plant cells; and plants and insects themselves), 144:59-149:40 (“Purification”).

119. Thus, the common disclosure describes an overarching routine molecular biology and protein biochemistry method that can be used to produce the claimed modified PH20 polypeptides: recombinant protein expression (in various cells, insects, or plants). The first recombinant protein was produced in a bacterial cell in 1977²³, and biotech companies have been using recombinant protein expression to produce recombinant proteins commercially since 1982²⁴;

²³ EX2007, p. 1.

²⁴ EX2008, p. 1 (“In 1982 Food and Drug Administration approved Humulin, Eli Lilly’s recombinant insulin made from Genentech’s specially modified bacteria. It was the first drug produced through recombinant DNA technology and among the first genetically engineered products to be available to consumers.”). On February 27, 2025, I retrieved EX2008 online from a Smithsonian Institution (The National Museum of American History, Behring Center) and generated a PDF from the online webpage. EX2008 is true and accurate to the best of my knowledge. I consider EX2008 to be a reliable source of information containing the type of information

therefore, recombinant protein expression was well-established as of December 2012. Recombinant protein expression is a straightforward method involving, e.g.: isolating DNA from a source; inserting the DNA into an expression vector; and inserting the expression vector into a cell, insect, or plant. EX1001, 135:28-149:40. After the expression vector is inserted into the chosen cell, insect, or plant—the cell, insect, or plant will produce the protein of interest, which, as stated in the common disclosure, can then be purified according to standard protein purification methods: “Proteins, such as modified PH20 polypeptides, can be purified using standard protein purification techniques known in the art.” EX1001, 135:40-145:20. Given the guidance in the common disclosure, these techniques would have been routinely and predictably employed by—and well within the level of ordinary skill of—a POSA as of December 2012.

120. The common disclosure also provides all the sequences (i.e., SEQ ID NO: 3, 7 and 32-66) that a POSA would have needed to make the claimed modified PH20 polypeptides using these routine molecular biology and protein biochemistry techniques. EX1001, 4:8-12, 75:20-36; EX2006.

121. Furthermore, the inventors of the '758 patent provide additional

upon which an expert in the field would typically rely. Accordingly, I rely on EX2008 here.

detailed guidance on making the modified PH20 polypeptides by way of examples. In particular, Example 1 provides step-wise guidance regarding how to make recombinant human PH20 hyaluronidase, which a POSA would have been able to readily and predictably apply to make the claimed modified PH20 polypeptides, as of December 2012 in light of the guidance in the common disclosure. EX1011, 195:14-200:41. And Example 2 provides step-wise guidance regarding making a library of PH20 mutants, which a POSA also would have been able to readily and predictably apply to make the claimed modified PH20 polypeptides, as of December 2012, in light of the guidance in the common disclosure. EX1001, 193:34-224:50.

122. In particular, Example 2 explains that a PH20 mutant library can be made by: (i) cloning (*i.e.*, inserting) DNA encoding human PH20 into an expression vector, *i.e.*, creating a PH20 template; (ii) mutating the “DNA encoding human PH20” portion of the expression vector, *i.e.*, “mutagenesis” of the PH20 template; (iii) transfecting CHO-S cells with the mutated expression vector, *i.e.*, inserting the expression vector into cells; and (iv) incubating the cells overnight in cell culture media, *i.e.*, growing the cells overnight in a growth-supporting liquid. EX1001, 193:34-224:50. Example 2 explains that the modified PH20 polypeptides can be collected from the supernatant (*i.e.*, non-cell containing liquid), and Example 6 explains how these steps can be employed on a large scale.

EX1001, 193:34-224:50, 295:1-297:6.

123. This is a straightforward recombinant protein expression method for a POSA equipped with the guidance in the common disclosure. And as I explained in paragraph 119 above, recombinant protein expression is a routine molecular biology and protein biochemistry method and has been commonplace since at least the 1980's. Furthermore, Example 2 provides a detailed description of the expression vector (*i.e.*, PH20 template), including its complete sequence, which is included in the sequence listing for the common disclosure. And, Example 2 also states that the CHO-S cells are transfected according to the protocol from the manufacturer. Given the guidance in the common disclosure, a POSA would have been able to predictably apply these established recombinant expression methods exemplified in the common disclosure.

124. Thus, each of factors (2)-(7)²⁵ referenced in Section V.I., weighs in favor of concluding that a POSA would have been enabled to make the claimed

²⁵ *i.e.*, (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

modified PH20 polypeptides in light of the guidance provided in the common disclosure.

125. Indeed, Dr. Hecht states that such methodology was conventional. He stated: “The ’429 Patent also describes *conventional methods* of producing enzymatically active PH20₁₋₄₄₇ in CHO cells transfected with a bicistronic vector containing a DNA sequence encoding ... PH20.” EX1003, ¶198 (emphasis added).

126. And he further states:

I note that *conventional procedures* relating to production of the wild-type PH20₁₋₄₄₇ protein that are described in the ’429 Patent could be applied to produce forms of PH20₁₋₄₄₇ that incorporate a single amino acid substitution (e.g., the L317Q substitution I discuss below) *with little effort*. It involves using the *conventional techniques* of creating a modified nucleotide sequence encoding the PH20₁₋₄₄₇ sequence with the single amino acid change, inserting it into the vector described in the common disclosure, and then using the vector to transfect a CHO cell, again as is described in the common disclosure.

EX1003, ¶203 (emphasis added).

127. Furthermore, the breadth of the claims, which define the modified PH20 polypeptides by structure, would have weighed in favor of concluding that POSA would have been enabled to make the claimed modified PH20 polypeptides as of December 2012. The claims recite at least 91% identity to sequences that, as discussed in Section VIII above, are fully disclosed in the common disclosure.

Moreover, SEQ ID NO: 3, 7 and 32-66 merely represent a series of C-terminal *single* amino acid truncations, as demonstrated in Figure A in Section VIII.A above; therefore, SEQ ID NO: 3, 7 and 32-66 are highly similar. In view of this factor, therefore, a POSA would have been enabled to make the claimed modified PH20 polypeptides in light of the guidance provided in the common disclosure (which includes the sequence listing).

128. Regarding the quantity of experimentation, a POSA would not have needed to perform undue experimentation as of December 2012 because, as explained above, a POSA would have been able to make the claimed modified PH20 polypeptides in light of the guidance provided in the common disclosure and doing so would have required nothing more than repetition of routine molecular biology and protein biochemistry techniques, which could be further facilitated by the large-scale methods exemplified in the common disclosure common disclosure (as mentioned above). Thus, this factor also weighs in favor of concluding that a POSA would have been enabled to make the claimed modified PH20 polypeptides.

129. Dr. Hecht's analysis focuses on "identify[ing] all of the *enzymatically active* multiply-mutated PH20 polypeptides in the scope of the claims." EX1003, ¶189 (emphasis added). As such, Dr. Hecht presumes that a POSA would have been required to test the modified PH20 polypeptides for enzymatic activity. EX1003, ¶189. But, as I explained in Section VII above, the claims do not require

enzymatic activity. EX1003, ¶189. Therefore, a POSA would have understood that “identify[ing] all of the *enzymatically active* multiply-mutated PH20 polypeptides in the scope of the claims” would not be required to make and use the claimed modified PH20 polypeptides. EX1003, ¶189 (emphasis added).

130. Moreover, I further disagree with Dr. Hecht’s general opinion that making and using the claimed modified PH20 polypeptides would have required “undue” experimentation because Dr. Hecht fails to address the fact that the *nature* of any experimentation is merely routine; it is, therefore, not undue. EX1003, ¶¶134-135, 169, 185-193. And, as explained in paragraphs 117-123 above, the techniques required to make modified PH20 polypeptides would have been routine as of December 2012 for a POSA who was equipped with the guidance of the common disclosure.

131. In view of the above, and in accordance with the factors provided in Section VI.C, ¶56, a POSA would have been able to make the claimed modified PH20 polypeptides with routine molecular biology and protein biochemistry methods that were long-established and well within their skillset when provided with the guidance in the common disclosure, as of December 2012.

2. Using the Claimed Modified PH20 Polypeptides Would Not Have Required Undue Experimentation.

132. As discussed in Section VI.C, I understand that assessing whether using the claimed modified PH20 polypeptides would have been undue is also a matter

of considering and weighing the factors referenced in Section VI.C, ¶56.²⁶ And as also discussed in Section VI.C, I understand that evidence of a pharmaceutical property in any standard experimental animal is sufficient to establish that an invention is useful (i.e., has utility) in the context of assessing enablement.

133. As explained below, using the claimed modified PH20 polypeptides would not have required undue experimentation as of December 2012 because the modified PH20 polypeptides have multiple credible uses, including: “increase[ing] the dispersion and delivery of therapeutic agents” by “increase[ing] tissue permeability”; “treat[ing] diseases or disorders associated with accumulation of HA²⁷”; and “be[ing] used as vaccines in contraceptive applications.” EX1001, 4:21-50 and 187:41-42.

134. And Dr. Hecht does not dispute the “therapeutic uses of modified PH20

²⁶ *i.e.*, (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

²⁷ HA is an abbreviation for hyaluronan. EX1001, 4:23.

polypeptides that have the ability to degrade hyaluronan.²⁸ EX1003, ¶108.

Regarding the dispersion and delivery use, the common disclosure states:

[A]ny of the modified PH20 polypeptides provided herein that exhibit hyaluronidase activity based on its ability to degrade glycosaminoglycan(s) such as hyaluronan ... can be used as a spreading factor to increase the delivery and/or bioavailability of subcutaneously administered therapeutic agents.

EX1001, 174:7-13. Regarding the use relating to the treatment of diseases associated with accumulation of HA, the common disclosure states:

The modified PH20 polypeptides also can be used to treat a hyaluronan-disease or disorder that is characterized by an excess or accumulation of hyaluronan. For example, modified PH20 polypeptides provided herein can be used to for treating a tumor; for treating glycosaminoglycan accumulation in the brain; for treating a

²⁸ I note also that, although not required by the claims, the specification of the '758 patent details how to test modified PH20 polypeptides for their ability to degrade hyaluronan (*i.e.*, for their hyaluronidase activity) and cites multiple known assays for doing so. EX1001, 132:54-67, 170:45-172:55, 224:50-294:39, Examples 3-5, 298:6-305:54, Examples 8-11, 308:46-311:20, Examples 14-15. And the specification further explains that such hyaluronidase assays were known in the art as of 2012. EX1001, 52:13-15 (“Assays to assess hyaluronidase activity are known to one of skill in the art and described herein.”).

cardiovascular disorder; for treating an ophthalmic disorder; for treating pulmonary disease; for treating cellulite; and/or for treating a proliferative disorder.

EX1001, 174:23-31.

135. And the common disclosure explains that such uses have been approved as therapies in humans; the common disclosure states:

[V]arious forms of PH20 hyaluronidases have been prepared and approved for therapeutic use in humans. For example, animal-derived hyaluronidase preparations include Vitrase® hyaluronidase (ISTA Pharmaceuticals), a purified ovine testicular hyaluronidase, and Amphadase® hyaluronidase (Amphastar Pharmaceuticals), a bovine testicular hyaluronidase. Hylenex® hyaluronidase (Halozyme Therapeutics) is a human recombinant hyaluronidase produced by genetically engineered Chinese Hamster Ovary (CHO) cells containing nucleic acid encoding for soluble rHuPH20 (see e.g., U.S. Pat. No. 7,767,429).

EX1001, 174:34-44. Furthermore, the common disclosure explains that hyaluronidases can be used as cosmetic agents; the common disclosure states that “[H]yaluronidase also can promote akinesia in cosmetic surgery, such as blepharoplasties and face lifts.” EX1001, 174:58-60.

136. Moreover, the common disclosure cites multiple combination therapies using PH20, which a POSA would have understood could have been applied to the claimed modified PH20 polypeptides in view of the guidance in the common disclosure. EX1001, 175:57-67.

137. And the claimed modified PH20 polypeptides also have a credible contraceptive use, e.g., in experimental animals, as will be explained in further detail below.

138. Although Dr. Hecht questions the utility of the enzymatically inactive modified PH20 polypeptides, even the references he cites establish that PH20 was 100% effective as a contraceptive in guinea pigs.²⁹ EX1003, ¶109; EX1023, Abstract; EX2010, 1, Abstract.

139. Dr. Hecht does not dispute these findings in guinea pig studies. And, as I explained in Section V above, a POSA or at least a member of their team, would have had experience working with hyaluronidases. And I note again that Dr. Hecht, according to his *curriculum vitae* and Background and Qualifications, has no experience with hyaluronidases—nor with PH20 or contraceptives.³⁰ EX1003, ¶¶1-9 and Appendix B.

²⁹ “Here, we report that 100% effective contraception was obtained in male and female guinea pigs immunized with PH-20.” EX2010, p. 1, Abstract.

³⁰ I note also that Dr. Hecht’s declaration does not mention consulting with anyone having practical experience with hyaluronidases. EX1003.

a. The Common Disclosure, in Light of the Prior Art, Would Have Indicated That the Claimed Modified PH20 Polypeptides Are Useful as Contraceptives.

140. The common disclosure clearly states that the claimed modified PH20 polypeptides are useful as “antigens in contraception vaccines” and does not limit this utility to active or inactive modified PH20 polypeptides. EX1001, 75:60-62. The common disclosure explicitly states that the “[m]odified PH20 polypeptides provided herein can be used as vaccines in contraceptive applications” and that “[t]he polypeptides can be administered directly or can be administered as a recombinant virus to deliver the antigen.” EX1001, 187:41-51. Moreover, the prior art states that it would “clearly be advantageous to use a [modified PH20] polypeptide for immunization that is devoid of enzymatic activity.” EX1011, 814. Thus a POSA would not have presumed the modified PH20 polypeptides would have needed to have been enzymatically active to have a contraceptive effect. EX1001, 75:60-62; EX1011, 814. The common disclosure also explains the correlation between PH20 and contraceptives; the common disclosure states that “PH20 is present in the male reproductive tract, and is expressed in both the testis and epididymis and is present in sperm,” and was known to “play[] a role in fertilization by facilitating entry of the sperm through the cumulus layer surrounding the unfertilized egg.” EX1001, 188:9-13. And the common disclosure states: “PH20 plays a role in fertilization by facilitating entry of the sperm through

the cumulus layer surrounding the unfertilized egg. PH20 also is able to bind to hyaluronic acid (HA) on the zona pellucida during early phases of fertilization. This binding also initiates intracellular signaling that aids in the acrosome reaction. Immunization with PH20 has been shown to be an effective contraceptive in male guinea pigs.” EX1001, 188:15-18.

141. The common disclosure further explains this correlation between PH20 and contraception in detail. EX1001, 72:48-73:51. In particular, the common disclosure states that:

PH20 is normally expressed in sperm from a single testis-specific gene. *PH20 is a sperm-associated protein involved in fertilization.* PH20 is normally localized on the sperm surface, and in the lysosome-derived acrosome, where it is bound to the inner acrosomal membrane. PH20 is multifunctional and exhibits hyaluronidase activity, *hyaluronan (HA)-mediated cell-signaling activity*, and *acts as a sperm receptor* for the zona pellucida surrounding the oocyte when present on acrosome reacted (AR) sperm.

EX1001, 72:48-73:51 (emphasis added). The common disclosure also states that:

In addition to being a hyaluronidase, PH20 also appears to be a *receptor for HA-induced cell signaling*, and a *receptor for the zona pellucida* surrounding the oocyte. Due to the role of PH20 in fertilization, PH20 can be used as an *antigen for immuno-contraception*.

EX1001, 72:48-73:51 (emphasis added).

142. Furthermore, the common disclosure cites two credible, peer-reviewed scientific journal articles, neither of which Dr. Hecht substantively addresses or includes in his Exhibit List: Primakoff 1988 (EX2008) and Tung 1997 (EX1023), which teach that PH20 is an effective contraceptive in guinea pigs. EX1001, 187:52-56; EX1003, ¶109, pp. 146-147. Citing to Primakoff 1988 and Tung 1997, the common disclosure states that “[i]mmunization with PH20 has been shown to be an effective contraceptive in male guinea pigs” and that PH20 is “an effective contraceptive in female guinea pigs due to the generation of anti-PH20 antibodies that prevent sperm and egg binding.” EX1001, 187:52-56.

143. Primakoff 1988 specifically found “100% effective contraception was obtained in male and female guinea pigs immunized with PH-20”—and that the “contraceptive effect was long-lasting and reversible.” EX2010, Abstract (emphasis added). Notably, Primakoff 1988 was published in *Nature*—which is generally regarded as one of the world’s most prestigious, peer-reviewed, scientific journals; only ~8% of manuscripts submitted to *Nature* are deemed worthy of publication.³¹ And the studies in Primakoff 1988 were further validated nine years later by Primakoff 1997, which reported: “The results show that immunization of males with PH-20, even at low doses, results in a *reproducible, completely*

³¹ EX2012, p. 2.

effective contraceptive action.” EX1022, 1142 (emphasis added). Tung 1997

reported similar results to Primakoff 1997, reporting:

Most males that became infertile after PH-20 immunization (and all that received a total dose $\geq 5 \mu\text{g}$) showed either a complete loss of sperm from the caudae epididymides or the presence of only abnormal sperm in the caudae.

EX1023, 1138 (emphasis added).

144. Dr. Hecht acknowledges that the common disclosure describes the contraceptive utility of PH20 and cites to both Primakoff 1988 (EX2010) and Tung 1997 (EX1023) as demonstrating that PH20 is an effective contraceptive in guinea pig. Yet, he states that the claimed modified PH20 polypeptides have no utility as contraceptive vaccines because of subsequent studies conducted in other—*non-guinea pig*—animals. Specifically, he points to subsequent publications reporting efforts to immunize *rats or mice* with PH20. EX1003, ¶¶110-113. However, those studies relating to rats and mice are not determinative of their effects in guinea pigs and do not undermine the use of PH20 as a contraceptive in guinea pigs. EX1019-EX1021.

145. Dr. Hecht also points to “publications reporting on the *human* testing of Hylenex® (wild-type PH20₁₋₄₄₇).” EX1003, ¶¶109-112 (emphasis added). But the references Dr. Hecht cites regarding the studies in humans were published after December 2012—specifically, in 2015 and 2018, as he acknowledges—and thus

would not have informed a POSA's knowledge as of December 28, 2012. EX1003, ¶¶111-112.

146. For these reasons, Dr. Hecht simply fails to account for the reproduced data from the guinea pig experiments. Moreover, as I noted above, Dr. Hecht, according to his *curriculum vitae* and Background and Qualifications, has no practical experience with hyaluronidases, PH20, or contraceptives, whereas a POSA or a member of the POSA's multidisciplinary team would have had practical experience with hyaluronidases. EX1019-EX1021; Section V; EX1003, ¶¶1-9, Appendix B. A POSA as of December 2012 would have known that the data indicated a "strong rationale" for using PH20 for the development of anti-sperm contraceptive vaccines because, at the time, the data indicated that PH20 was an "exciting proposition" and a "viable alternative to other modalities of contraception." EX2009, 5. Therefore, Dr. Hecht seems to have excluded art that would have been known to a POSA in his analysis.

147. Notably, none of the publications Dr. Hecht cites (*i.e.*, Hardy 2004, Pomeroy 2002, Baba 2002, Rosengren 2018, and Rosengren 2015) contradicts any finding in Primakoff 1988, Tung 1997, or Primakoff 1997 regarding the contraceptive utility of PH20 in guinea pigs. EX1003, ¶¶110-112; EX1019-EX1021; EX1024; and EX1061. Specifically:

- Hardy 2004 reported studies in *mice* and acknowledged the "strong

immunocontraceptive effect in guinea pigs.” EX1019, 333 (emphasis added);

- Pomeroy 2002 reported studies in *rabbits* and acknowledged that “[i]mmunization of both male and female guinea-pigs with the sperm antigen rPH-20 has been shown to elicit infertility.” EX1020, 175 (emphasis added);
- Baba 2002 reported studies in *mice* and—importantly, identified that PH20 is *not essential* for fertilization *in mice*, stating: “PH-20 is not essential for fertilization, *at least in the mouse....*” EX1021, Abstract (emphasis added); and
- Rosengren 2018 and Rosengren 2015 both reported studies in *humans*, and Rosengren 2015 noted that guinea pigs “experienced infertility following PH20 immunization,” citing Primakoff 1997. EX1061, 1154.

148. And both Pomeroy 2002 and Baba 2002 only assessed whether PH20 was essential to fertilization *in mice*. EX1020, 175; EX1021, Abstract. Chao (also cited by Dr. Hecht) is also consistent with the findings of Primakoff 1988, Primakoff 1997, and Tung 1997. Chao reports that the C-terminal domain of mammalian PH-20 “is responsible for the secondary binding of the acrosome-reacted sperm to the zona pellucida (a glycoprotein membrane) of oocyte *during fertilization.*” EX1006, 6916 (emphasis added).

149. Altogether, none of the references cited by Dr. Hecht dispute or undermine the effectiveness of the claimed modified PH20 polypeptides as a contraceptive in guinea pigs. EX1006, 6916; EX1019, 333; EX1020, 175; EX1021,

Abstract; EX1061, 1154. Moreover, guinea pigs are a standard experimental animal, hence the term “guinea pig” is often colloquially used to refer to the subjects of an experiment.³²

150. In view of the above, a POSA would have found it credible (i.e., valid) that the claimed modified PH20 polypeptides could be effective contraceptives, particularly considering that (i) Lin 1993 reports that the “deduced amino acid sequence of human PH-20 ... is 59% *identical* with guinea pig PH-20, suggesting they may have *a conserved function and immunogenicity*” and (ii) as Dr. Park acknowledged, bee venom hyaluronidase and human PH20 are “highly homologous” despite only “sharing about 30% sequence identity.” EX1004, ¶40;

³² EX2011, p. 1 (“a subject of research, experimentation, or testing”)]. On February 27, 2025, I retrieved EX2011 from Merriam-Webster Online Dictionary using the Wayback Machine (URL: [https://web.archive.org/web/20100221175034/http://www.merriam-webster.com/dictionary/guinea pig](https://web.archive.org/web/20100221175034/http://www.merriam-webster.com/dictionary/guinea%20pig)) and generated a PDF from the online webpage. The Wayback Machine retrieval was made on February 21, 2010. EX2011 is true and accurate to the best of my knowledge. I consider EX2011 to be a reliable source of information containing the type of information upon which an expert in the field would typically rely. Accordingly, I rely on EX2011 here.

EX2013, 10075 (emphasis added).

151. In view of the above, a POSA would have understood that the common disclosure discloses that claimed modified PH20 polypeptides could be used as contraceptives in guinea pigs.

B. Merck's Own Patented Claims Have Similarities to Claims 1-2 and 6-30

152. I have been asked to assess whether Merck's own patented claims have similarities to Claims 1-2 and 6-30.³³ In U.S. Patent No. 7,872,107 (filed December 29, 2006, and claiming the benefit of the filing date of U.S. Application No. 60/755,382, filed December 30, 2005), Merck claimed the following:

1. A variant of an IL-12p40 protein, the variant being at least *90% identical to SEQ ID NO:2* and comprising an *amino acid alteration at one or more positions corresponding to residues 258-266*, wherein the amino acid alteration comprises an amino acid substitution selected from the group consisting of Lys260Asn, Lys260Gln, and Lys260Gly.

EX2015³⁴, 516-524 (emphasis added).

³³ I assessed only U.S. Patent No. 7,872,107 in this analysis.

³⁴ EX2015 is the file history of U.S. Patent No. 7,872,107. I retrieved the file history of U.S. Patent No. 7,872,107 from the United States Patent and Trademark Office Patent Center (at <https://patentcenter.uspto.gov/>) and generated a PDF from

153. Like the claimed modified PH20 polypeptide of the common disclosure, Merck's claimed modified polypeptide (a variant of an IL-12p40 protein) was defined only by its structure—i.e., by a percent identity to a given amino acid sequence with a single amino acid substitution. EX2015, 516-524.

154. Similarly, Merck's claimed sequence, SEQ ID NO: 2, contained 306 amino acids; the claimed sequences of the common disclosure (SEQ ID NO: 3, 7 and 32-66) contain 430 to 465 amino acids. EX2015, 516-524; EX1001, Claims 1-2 and 6-30; EX2006. I note also that Merck's claimed "at least 90%" sequence identity is in fact *lower* than the "at least 91%" sequence identity requirement of the claimed modified PH20 polypeptides here. EX2015, 516-524.

155. Thus Merck has previously patented structurally defined modified polypeptides requiring only "at least 90%" identity to a sequence that is 306 amino acids in length and contains one of three mutations at a single location (Lys260Asn, Lys260Gln, or Lys260Gly). EX2015, 516-524. In other words, Merck has previously patented structurally defined modified polypeptides similar to those claimed here—despite the large genus claimed by Merck. EX2015, 516-524. And the USPTO determined that Merck's claims were enabled. EX2015, 516-

the online webpage. I separated the resultant PDF into three parts (three total PDFs). EX2015 is true and accurate to the best of my knowledge.

524.

156. Claims 1-2 and 6-30 are similarly enabled. As discussed above, on December 28, 2012, a POSA given the guidance in the common disclosure would have been able to readily make and use the full range of modified PH20 polypeptides identified in the claims without undue experimentation. Rather, any experimentation would have been routine given the guidance in the common disclosure (i.e., the common disclosure).

X. CLAIMS 1-2 AND 6-30 WOULD NOT HAVE BEEN OBVIOUS IN VIEW OF CHAO AND THE '429 PATENT

157. In Section VI.D, I summarize the legal principles I applied in assessing obviousness in view of the asserted prior art and the general knowledge in the background art from the viewpoint of a POSA at the time of the invention. I apply those principles in my analysis here. In considering obviousness, I address the timeframe of “before December 29, 2011,” in order to respond to Dr. Hecht’s and Dr. Park’s analysis regarding that same timeframe—a timeframe that is before the December 30, 2011 filing date of Halozyme’s ’313 provisional application to which the ’758 patent is related. EX1003, ¶11; EX1004, ¶10.

158. Dr. Hecht’s declaration states that Dr. Hecht reviewed Dr. Park’s declaration, and Dr. Hecht repeatedly agrees with Dr. Park and/or bases his analysis (at least in part) on Dr. Park’s analysis. EX1003, ¶¶20-22, 85, 122-125, 158, 215-220, and 224-237. For convenience, however, I refer to Dr. Park’s and

Dr. Hecht's arguments collectively as Dr. Hecht's arguments.

159. Briefly, Dr. Hecht argues: (1) that the '429 patent would have motivated a POSA to make single amino acid substitutions in “non-essential regions”; and (2) that the multiple sequence alignment of five different hyaluronidases and the structural information regarding Hyal-1 (“Hyal-1”) in Chao would have indicated where such “non-essential regions” would have been located in PH20. EX1003, ¶¶209-216.

160. Dr. Hecht concludes that the combination of the '429 patent and Chao would have motivated a POSA to specifically mutate position 317 of PH20. EX1003, ¶221. Specifically, he concludes that a POSA “would have expected the L317Q substitution in PH20₁₋₄₄₇ to be tolerated.”³⁵ EX1003, ¶222. He also concludes that a POSA would have had reasonably expected that mutating L317 to glutamine (Q) “would exhibit comparable activity to the unmodified PH20₁₋₄₄₇ enzyme.” EX1003, ¶222. And Dr. Hecht further concludes that a “skilled artisan also would have expected that the PH20₁₋₄₄₇ protein incorporating a single amino acid substitution in a non-essential region would generally have the same therapeutic uses and utilities as described with respect to the PH20₁₋₄₄₇ protein.”

³⁵ L is an abbreviation for the amino acid leucine; and Q is an abbreviation for glutamine. EX1003, ¶115.

EX1003, ¶207.

A. Even in Combination, Chao and the '429 Patent Fail to Disclose or Suggest a L317 Mutation of PH20, Much Less a L317 Mutation to Glutamine (Q), as Required by Claims 1-2 and 6-30.

161. As I summarized in Section VI.C. above, I understand that, in determining the scope and content of the prior art and ascertaining the differences between it and the claimed invention, a patent challenger may (1) specify where each element of the claim is found in the prior art or (2) explain why a POSA exercising common sense or ordinary creativity would have bridged any gaps (*i.e.*, missing elements) between the prior art and the claimed invention to produce the claimed invention.

162. First, I assess whether all elements of claims 1-2 and 6-30 can be found in Chao and the '429 patent. Second, I assess whether a POSA would have nonetheless supplied the missing elements from Chao and the '429 patent using common sense or ordinary creativity.

1. Chao and the '429 Patent Do Not Disclose Any Mutation of L317, Nor Do Chao and the '429 Patent Disclose Any Mutation of L317 to Glutamine (Q), as Required by Claims 1-2 and 6-30.

163. Claim 1 recites:

A^[36] *modified PH20 polypeptide*, comprising one or more amino acid modifications in an unmodified PH20 polypeptide, wherein: the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of *SEQ ID NOs: 3, 7 and 32-66*; amino acid modifications are selected from the group consisting of amino acid replacements(s), deletion(s), and/or insertion(s); the modified PH20 polypeptide comprises an amino acid replacement at a position corresponding to residue 317, with reference to amino acid positions set forth in SEQ ID NO:3; the replacement at the position corresponding to *residue 317* is selected from the group consisting of *A, I, K, M, Q, and R*; corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the amino acid sequence of SEQ ID NO:3; and the modified PH20 polypeptide has *at least 91% sequence identity* to a polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7 and 32-66.

EX1001, Claim 1 (emphasis added).

164. Neither Chao nor the '429 patent disclose “an amino acid modification at a position corresponding to position 317” as required by claims 1-2 and 6-30.

EX1001, Claim 1; EX1005; EX1006. And neither Chao nor the '429 patent disclose replacing L317 with an amino acid “selected from the group consisting of A, I, K, M, Q, and R.” EX1001, Claim 1; EX1005; EX1006. Instead, Chao focuses

³⁶ I understand the term “a” to mean one or more.

on the three-dimensional structure of human hyaluronidase-1 (“hHyal-1”) by describing its resolved crystal structure, and the ’429 patent focuses on soluble neutral hyaluronidase glycoproteins (“sHASEGPs”). EX1005; EX1006. Neither a mutation at L317, much less a mutation of L317 to glutamine (Q), is mentioned whatsoever in Chao or the ’429 patent. EX1005; EX1006. Accordingly, these claim elements are missing from the prior art Dr. Hecht cites.

165. Moreover, Dr. Hecht does not provide a reasonable explanation as to how or *why* a POSA would have nonetheless supplied these missing elements, as I explain below. EX1003; EX1005; EX1006.

2. Dr. Hecht Does Not Adequately Explain Why a POSA Would Have Supplied the Missing L317 Mutation or Modified the Missing Mutation of L317 to Glutamine (Q) based on Chao and the ’429 Patent Using Common Sense or Ordinary Creativity.

166. Dr. Hecht does not explicitly argue that either common sense or ordinary creativity supplies the missing L317 mutation, much less the mutation of L317 to glutamine (Q). EX1003. Rather, he summarized Dr. Park’s methodology as follows:

[Dr. Park’s] methodology included (i) using a multiple-sequence alignment to identify non-essential regions of PH20 (including position 317), (ii) *identifying the amino acids that occur at those non-essential regions* in the proteins in the set used for the alignment, and (iii) *assessing whether amino acid substitutions appearing in nature at position 317 would be tolerated by PH20.*

EX1003, ¶215 (emphasis added). This summary of Dr. Park’s methodology jumps from identifying amino acid residues within “non-essential regions” to assessing whether substitutions at position 317 would be “tolerated by PH20.” EX1003, ¶215. Dr. Hecht does not explain why a POSA would have arrived at the specific L317 locus. Nor does he explain why a POSA would have jumped to mutating L317 to glutamine (Q). EX1003, ¶215.

167. Dr. Hecht states: “Position 317 is within a non-essential region of the PH20 sequence, based on my review of Dr. Park's analysis.” EX1003, ¶217.³⁷ Notwithstanding whether position 317 is in a “non-essential region,” which I will discuss in Section X.B below, Dr. Hecht does not explain *why* a POSA would have selected position 317 from any other residue within the purported “non-essential region” surrounding L317 or any other “non-essential” region purportedly

³⁷ Dr. Park alleges that, based on his 88-sequence alignment, “a skilled artisan would have deemed ‘essential residues’” to be located where “non-identical amino acids appear[] in less than ~5% of the proteins in the data set.” EX1004, ¶30. But this statement is unsupported by any reference, and Dr. Park cites only to his own declaration and appendices for support. EX1004, ¶¶30-32. And Dr. Hecht relies on this determination by Dr. Park without any additional further support. EX1003, ¶215; EX1004, ¶¶30-32.

identified by Dr. Park. EX1003, ¶215.

168. Instead of providing a reason to focus on position 317 that is based on common sense or ordinary creativity of a POSA or any teaching or suggestion in the art, as will be discussed further below, Dr. Park states that he was “asked by counsel to report [his] conclusions with respect to position 317.” EX1004, ¶103. Dr. Hecht then relied on Dr. Park’s declaration without providing any further reason based on the common sense or ordinary creativity of a POSA or any teaching or suggestion in the art. EX1004, ¶103; EX1003, ¶¶20-22, 85, 122-125, 158, 215-221, and 225-235. But a POSA reading the ’429 patent in combination with Chao would not have had a reason to mutate position 317.

B. Even in Combination, Chao and the ’429 Patent Would Not Have Provided Any Motivation to Make a L317 Mutation of PH20, Much Less a L317 Mutation to Glutamine (Q), as Required by Claims 1-2 and 6-30.

169. As I summarized in Section VI.D, I understand that one way of showing obviousness is by establishing that a POSA would have had both (i) a reason to modify or combine the teachings of the prior art to achieve the claimed invention and (ii) a reasonable expectation of success in doing so. I address both of these inquiries in turn.

1. Chao and the '429 Patent Would Not Have Motivated a POSA to Make the Claimed L317 Mutation.

a. The '429 Patent Would Not Have Provided Any Reason to Make Single Amino Acid Mutations in “Non-Essential” Regions.

170. Dr. Hecht argues that the '429 patent describes “that making a single amino acid substitution within a non-essential region of PH20 would be tolerated by the enzymatically active forms of PH20 being described in the '429 Patent”— and states that “in general, single amino acid substitutions in non-essential regions of polypeptides’ ... ‘do not substantially alter biological activity.’” EX1003, ¶206.

171. However, as explained below, the '429 patent does not identify any regions of PH20 as being non-essential. EX1005. And contrary to Dr. Hecht’s testimony, the '429 patent does not provide any *reason* to make a single amino acid substitution in “non-essential” regions. Instead, the '429 patent merely states that “[s]uitable conservative substitutions of amino acids are known to those of skill in this art and *can be* made generally without altering the biological activity” and states that making modifications at non-essential positions generally will not “alter[] the biological activity.” EX1005, 16:14-22 (emphasis added). These statements in the '429 patent would not have provided a POSA with any *reason* to make an L317Q mutation of PH20. Indeed, a POSA would have been disinclined to expend resources (e.g., time or materials) to make a mutation that was expected not to “alter[] the biological activity,” and Drs. Hecht and Park have not identified

any reasons to make such a mutation.

172. And, as explained below, Chao does not fill in any of these shortcomings of the '429 patent's teachings.

b. Chao Would Not Have Identified “Non-Essential” Regions.

173. Dr. Hecht states that “Chao provided an annotated alignment of the five human hyaluronidase enzymes which identified *conserved residues* among the set of five related proteins.” EX1003, ¶83 (emphasis added). He argues that the conserved residues identified by Chao are “essential” and argues that a POSA would have combined Chao and the '429 patent because “the '429 Patent would have encouraged a skilled artisan to make modified PH20 proteins having single amino acid substitutions in non-essential regions.” EX1003, ¶212.

174. However, Chao never identified any residues as “essential” in its annotated alignment, and the word “essential” is not even mentioned in Chao. EX1006, 6916, FIG. 3. Accordingly, a POSA would not have interpreted Chao as identifying essential or non-essential residues in its annotated alignment. EX1006, 6916, FIG. 3. And as explained in Section X.B.c below, a POSA would not have interpreted Chao as identifying non-conserved residues as “non-essential.”

c. A POSA Would Not Have Been Motivated to Prepare nor Rely on the 88-Sequence Alignment Prepared by Dr. Hecht Because Dr. Park's Alignment Includes Mostly Non-PH20 Sequences.

175. Dr. Park argued that the non-conserved regions he purportedly identified “align with what [he] considers to be the ‘non-essential regions’ referred to by the ’429 patent.” EX1004, ¶32. He identified non-conserved regions by: (1) identifying “largely invariant residues that a skilled artisan would have deemed ‘essential’ in PH20₁₋₄₄₇” from a multiple sequence alignment of 88 hyaluronidases and (2) “identif[ying] important residues in hyaluronidase proteins or which reported experimental results showing that modifying single residues impaired or eliminated activity of the enzymes.” EX1004, ¶¶26, 30.

176. Of the 88 sequences that Dr. Park aligned, only 18 are PH20 sequences. EX1004, ¶27; EX1056. The remaining 70 sequences are for other hyaluronidases, including, *e.g.*, Hyal-1, Hyal-2, Hyal-3, Hyal-4, Hyal-5, and Hyal-6. EX1004, ¶27; EX1056.³⁸ Dr. Park contends that his 88-sequence alignment is more informative

³⁸ Hyal is an abbreviation for hyaluronidase. I note that the proper nomenclature for these proteins is HYAL1, HYAL2, HYAL3, HYAL4, HYAL5, and HYAL6; however, because Hyal-1 is not capitalized in Chao, I use the above nomenclature throughout (i.e., Hyal-1, Hyal-2, Hyal-3, Hyal-4, Hyal-5, and Hyal-6) for consistency.

than Chao's alignment because he included "homologous proteins from human and non-human species." EX1004, ¶93.

177. However, a POSA would not have been motivated to prepare the 88-sequence alignment prepared by Dr. Park because he includes so many disparate, evolutionarily distant sequences—many of which are not even from humans, such as a tunicate (a marine invertebrate animal). EX1056. And furthermore, a POSA would not have been motivated to rely on such an 88-sequence alignment because different hyaluronidases were known to have different enzymatic functions and substrates before December 29, 2011. EX1056; EX2018, 33495, 33507; EX2019, 653, 658; EX2020, 286; EX2021, 296; EX1008, 825; EX2022, 6-7. EX1001, 72:48-51 and 160:1-6; EX1006, 6911, 6915-6916.

i. Different Hyaluronidases Were Known to Have Different Functions and Substrates before December 29, 2011³⁹.

178. For example, before December 29, 2011, it was known that Hyal-3

³⁹ In assessing written description and enablement, I refer to December 28, 2012—the filing date of the '731 application that is related to the '758 patent.⁴⁰ Dr. Park merely states: "*I believe* the positions I identified in Appendix D-2 [non-conserved positions in Park's alignment], including position 317, align with what I consider to be the 'non-essential regions' referred to by the '429 Patent."

does not exhibit *any* enzymatic activity and that Hyal-2 is only weakly enzymatically active or in many cases, *inactive*. EX2018, 33495, 33507; EX2019, 653, 658; EX2020, 286. Hyal-2 was known to be a receptor for a retrovirus in sheep before December 29, 2011. EX2021, 296. And Hyal-4 was known to catalyze different substrates than PH20. EX1008, 825; EX2022, 6-7. EX1001, 72:44-47, 166:62-67. Hyal-4 was identified specifically as a chondroitinase, meaning it catabolizes (*i.e.*, breaks down) chondroitin sulfate of proteoglycans. EX1008, 825; EX2022, 6-7.

179. By contrast, PH20 is a sperm-associated protein involved in fertilization, and its natural substrate is hyaluronan. EX1001, 72:44-47, 166:62-67. And Chao explained that Hyal-1 does not “contain glycosylphosphatidylinositol-signal sequences” and is not “membrane-bound upon maturation”—unlike PH20, which *does* contain a glycosylphosphatidylinositol-signal sequence and *is* membrane bound. EX1006, 6911; EX1004, ¶36.

180. Chao also acknowledged “different catalytic properties” and “differ[ences] in their catalytic efficiencies and pH profiles” between different human hyaluronidases. EX1006, 6914, 6916. Chao notes that for Hyal-1, the “activity optimum is at pH 3.8.” EX1006, 6915. I note that, by contrast, the activity

EX1004, ¶32.

of PH20 was measured at a pH of 7.4 in the specification. EX1001, 226:6-9.

181. A POSA, therefore, would have known that different hyaluronidases were known to have different functions and substrates. Thus, a POSA would not have been motivated to prepare the 88-sequence alignment prepared by Dr. Park nor rely on such an alignment considering the wide variety of hyaluronidases included, at least some of which were specifically known to have had different functions and substrates before December 29, 2011.

ii. Chao Suggested that Non-Conserved Residues May Be Responsible for Different Catalytic Properties between Different Hyaluronidases.

182. Additionally, rather than suggesting that non-conserved residues were non-essential, as proposed by Dr. Park, Chao stated that the non-conserved residues “may be responsible for the *different catalytic properties* of the human hyaluronidases” and that sequence variations “may contribute to the apparent different substrate specificity” between different hyaluronidases. EX1006, 6915-6916 (emphasis added).

183. A POSA, therefore, would not have considered the non-conserved regions to be “non-essential” in PH20—particularly considering the differences in function, catalytic properties, and pH profiles of different hyaluronidases, as I described above. EX1006, 6911, 6914. Instead, a POSA would have understood that PH20 has different attributes than other hyaluronidases. EX1006, 6911-6916;

EX1056; EX2018, 33495, 33507; EX2019, 653, 658; EX2020, 286; EX2021, 296; EX1008, 825; EX2022, 6-7; EX1001, 72:44-47, 166:62-67. And a POSA would have understood from Chao that the non-conserved residues may have been responsible for these different attributes. EX1006, 6911-6916; EX1056; EX2018, 33495, 33507; EX2019, 653, 658; EX2020, 286; EX2021, 296; EX1008, 825; EX2022, 6-7; EX1001, 72:44-47, 166:62-67.

iii. Dr. Park Mischaracterizes the Non-Conserved Residues in Chao.

184. Figure 3 of Chao depicted a multiple sequence alignment identifying *invariant conserved residues* between five different hyaluronidases: Hyal-1, Hyal-2, Hyal-3, Hyal-4, and PH-20 (below). EX1006, FIG. 3, 6916.

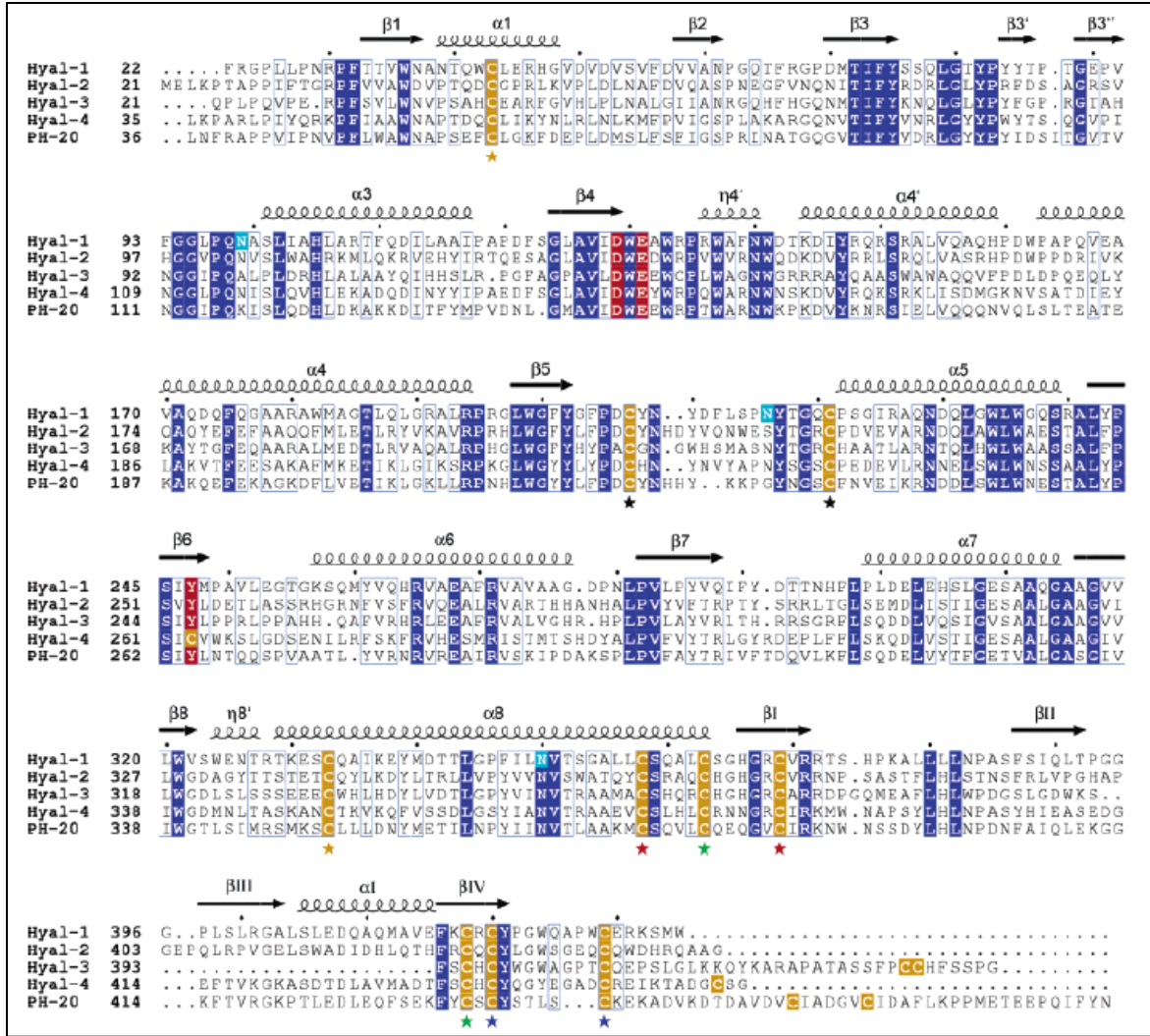


Figure A. Original Figure 3 of Chao. Invariant residues are depicted in royal blue; catalytic residues are depicted in red; cysteine residues are depicted in orange; and Hyal-1 N-glycosylated asparagine residues are depicted in turquoise. EX1006, FIG. 3, 6916.

185. As seen in Dr. Park’s annotation of Figure 3 of Chao below, he identifies all non-conserved regions as “non-essential” as follows:

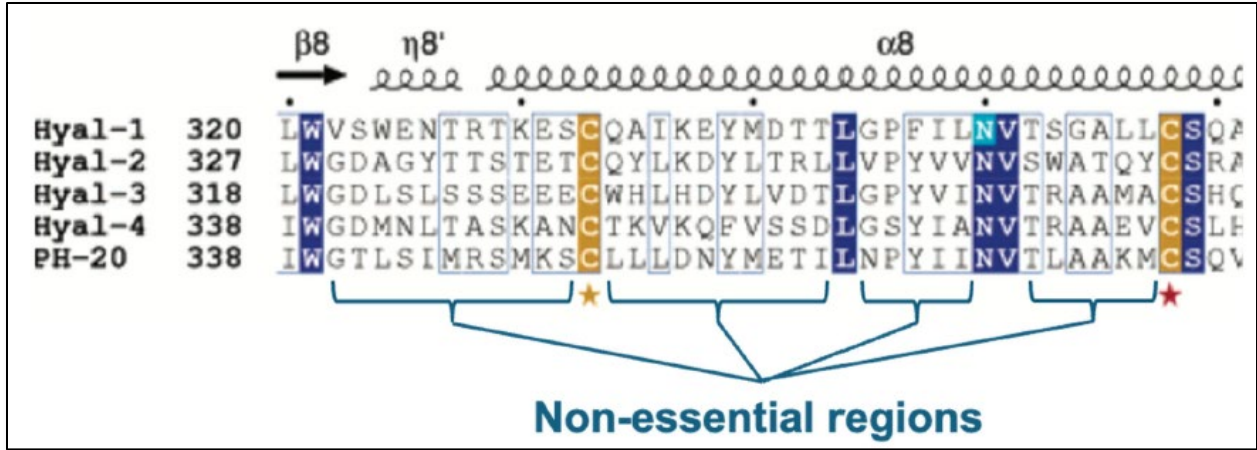


Figure B. Annotation of Figure 3 of Chao by Dr. Park. Dr. Park identifies variant regions as “non-essential.” EX1001, ¶32.

186. I disagree with Dr. Park’s annotation of Figure 3 of Chao because he wrongly deems non-conserved regions to be “non-essential” without providing support for this assertion.⁴⁰ EX1001, ¶32.

187. As I explained above, a POSA would have understood from Chao that the non-conserved residues may have been responsible for the differences between PH20 and the other hyaluronidases Chao aligned. EX1006, 6911-6916; EX1056; EX2018, 33495, 33507; EX2019, 653, 658; EX2020, 286; EX2021, 296; EX1008, 825; EX2022, 6-7; EX1001, 72:44-47, 166:62-67.

⁴⁰ Dr. Park merely states: “*I believe* the positions I identified in Appendix D-2 [non-conserved positions in Park’s alignment], including position 317, align with what I consider to be the ‘non-essential regions’ referred to by the ’429 Patent.” EX1004, ¶32.

188. Chao exemplifies the loop region between $\beta 5$ and $\alpha 5$ as an example of a non-conserved region that may be responsible for catalytic differences between PH20 and the other homologous proteins in its alignment. EX1006, 6915-6916. I outline (in red) this loop region between $\beta 5$ and $\alpha 5$ here:

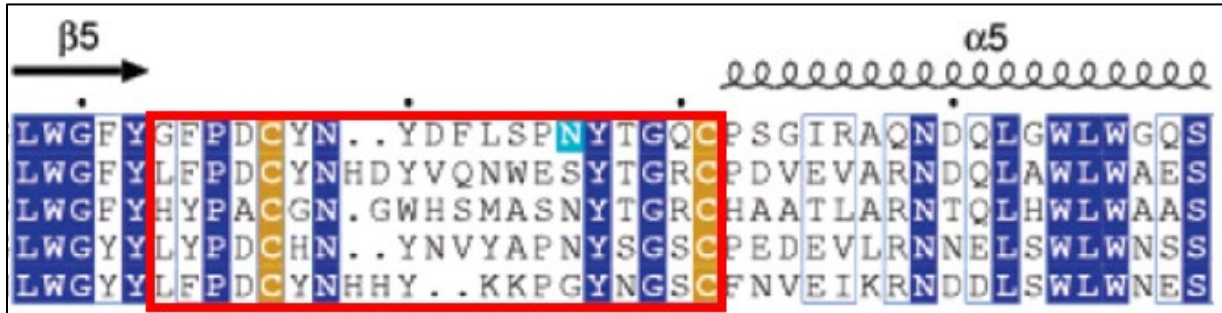


Figure C. Annotation of Figure 3 of Chao by Dr. Triggs-Raine. The non-conserved region is outlined in red, and the non-conserved residues are uncolored. EX1006, FIG. 3. The invariant conserved residues are depicted in royal blue.

189. Chao explains that “the loop connecting $\beta 5$ and $\alpha 5$... varies in length, composition, and potential glycosylation” between the five aligned hyaluronidases. EX1006, 6915-6916. Chao then explicitly states: “Such variations may be responsible for the different catalytic properties of the human hyaluronidases.” EX1006, 6916.

190. Other prior art references support Chao’s observation that non-conserved residues may impact the activity and function of proteins. EX2016, 2; EX1014, 21, 55. In Pils 2005, for example, the authors reported that “functional sites can vary in subfamilies and homologous protein sequences can perform different functions using *a different set of functional residues.*” EX2016, 2

(emphasis added).

191. And Brandon and Tooze 1991 explains that “[w]hen homologous amino acid sequences from different species are compared, it is found that insertions and deletions of a few residues occur almost exclusively *in the loop regions*” since “cores are much more stable than loops” during evolution. EX1014, 21. Brandon and Tooze 1991 further explains that “substrate specificity and catalytic function *reside in loop regions* which are separated from the residues of the α helices and β strands that contribute to the structural stability of these domain structures” and that “loop regions” (like the loop region in Figure 3 of Chao above) “frequently participate in forming binding sites and enzyme sites.” EX1014, 21, 55. In other words, Brandon and Tooze 1991 explains that, in homologous proteins (such as Hyal-1 and PH20), non-conserved loop regions are often responsible for catalytic differences between the homologous proteins. EX1014, 21, 55. Dr. Hecht, citing Green⁴¹, argues that non-conserved residues are where “variation ... thus is tolerated in proteins.” EX1003, ¶49. However, Green does not equate non-conserved with non-essential residues.⁴² EX1017.

⁴¹ EX1017.

⁴² Green merely notes that the degree of conservation at amino acid positions can give insight “applicable to protein engineering.” EX1017, p. 224. Dr. Park also

192. The observations of the authors of Brandon and Tooze 1991 are consistent with Chao's observations regarding the loop connecting $\beta 5$ and $\alpha 5$. As seen in Figure 3 of Chao, the loop regions (*i.e.*, the regions between the α -helical or β -sheet regions) contain many varied—*i.e.*, non-conserved—residues. EX1006, FIG. 3, 6916. Therefore, a POSA would have understood from Pils 2005, Brandon and Tooze 1991, and Chao that the regions containing many non-conserved residues “may be responsible for the *different catalytic properties* of the human hyaluronidases.” EX1006, 6915-6916 (emphasis added); EX1014, 21, 55; EX2016. Thus, a POSA would not have presumed that such non-conserved regions would have been “non-essential.”

193. In conclusion, a POSA would not have had any motivation to make a mutation at L317 in view of Chao and the '429 patent.

cites Steipe as explaining that “sequence identity information [can] identify single amino acid substitutions that would be tolerated.” EX1004, ¶23. But Steipe does not suggest that non-conserved residues are non-essential either; Steipe merely notes that some “functional residues” can be replaced without losing structural stability. EX1016, p. 186.

d. Chao Did Not Provide “New, Highly Relevant Structural Features for Evaluating Structural Features of PH20.”

194. Dr. Hecht argues that Chao provided “new, highly relevant structural features for evaluating structural features of PH20.” EX1003, ¶86. I disagree because, as mentioned above, the primary focus of Chao was discussing the three-dimensional structure of Hyal-1—not PH20. EX1005, Abstract. I also disagree because Chao did not identify any new PH20 sequences or new PH20 structural information. EX1006.

195. And Dr. Hecht does not explain why Chao’s three-dimensional Hyal-1 structural information would have motivated a POSA to make a mutation at L317. EX1003. Dr. Hecht states: “A notable finding in Chao was its identification of the ‘Hyal-EGF’⁴³ domain in the C-terminal region of human hyaluronidases.” EX1003, ¶84. But Chao only identified an EGF-like domain in Hyal-1. EX1006, 6911. Also, this domain was many amino acids away from position 317, and Dr. Hecht does not explain why it would have directed a POSA to consider position 317 for a modification.

⁴³ Chao refers to the “EGF-like” domain of Hyal-1, not “Hyal-EGF,” as referenced in Dr. Hecht’s declaration. EX1003, ¶84; EX1006, p. 6913 (emphasis added).

196. Dr. Hecht argues that the Hyal-1 EGF-like domain identified in Chao (corresponding to residues 337-409 in PH20) “had been experimentally shown to be necessary or important to the catalytic activity of hyaluronidases.” EX1003, ¶88. Chao states, however, that “the EGF-like domain is located remotely from the active site (over 30 Å away), and thus is not likely to be involved in substrate recognition (Figure 4B)” —and Chao accordingly questions: “What then is the role of this domain?” EX1006, 6916.

197. Furthermore, Chao explains that the EGF-like domain contains a β -hairpin unit, and Chao states: “Because the sequence of the β -hairpin region *varies significantly* within the *hyaluronidase family* (Figure 3), the *partner identity* or *affinity may vary* for each enzyme.” EX1006, 6917 (emphasis added). In other words, Chao explains that, if present, this EGF-like domain likely varies between hyaluronidases. EX1006, 6917. And moreover, Chao states: “Now that the 3D structure of hHyal-1 has revealed the presence of a novel HyalEGF-like domain, *a search for partners and characterization of their interactions are timely.*” EX1006, 6917 (emphasis added). In other words, Chao explains that any interactions between possible EGF-like domains in other hyaluronidases and their substrates need to be first sought—and if found, further characterized (*i.e.*, studied). EX1006, 6917.

198. In sum, a POSA would not have interpreted the EGF-like domain

identified in Hyal-1 as providing new information, nor would a POSA have interpreted the EGF-like domain identified in Hyal-1 as being “experimentally shown to be necessary or important to the catalytic activity of hyaluronidases.” EX1003, ¶88.

199. Paramount to the above, however, none of Dr. Hecht’s remarks regarding the EGF-like domain identified in Hyal-1 explains *why* it would have motivated a POSA to specifically mutate L317.

e. Drs. Hecht and Parks’ Stated Reason for Focusing on Position 317 is Not Based on the Prior Art.

200. While Drs. Hecht and Park recognized there were ~370 non-conserved residues in Chao’s alignment, they offered no reason based on the prior art (Chao or the ’429 patent) to focus on L317. Instead, Dr. Park stated that he was “asked by counsel to report my conclusions with respect to position 317.” EX1003, ¶83; EX1004, ¶¶92-93, 102-103. Dr. Hecht merely states that “[p]osition 317 is within a non-essential region ... between C316 and L327” (EX1003, ¶217), which he

illustrates with a cropped and annotated portion of Figure 3 of Chao follows:

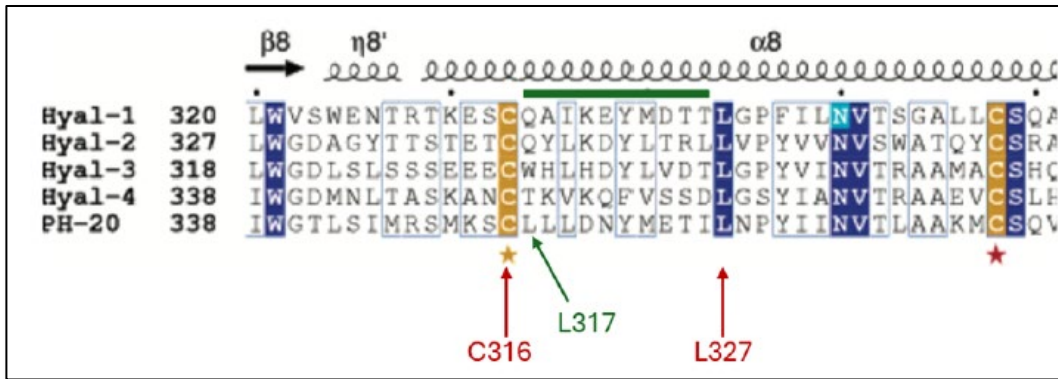


Figure D. Dr. Hecht's cropped and annotated portion of Figure 3 of Chao. EX1003, ¶217.

201. But there are 90 bounding essential residues in Chao's Figure 3 (highlighted in yellow, blue, and red), and ~370 non-conserved residues that fall within these 90 bounding residues. I illustrate Chao's ~370 non-conserved residues (outlined in red) below. EX1006, 6916, FIG 3.

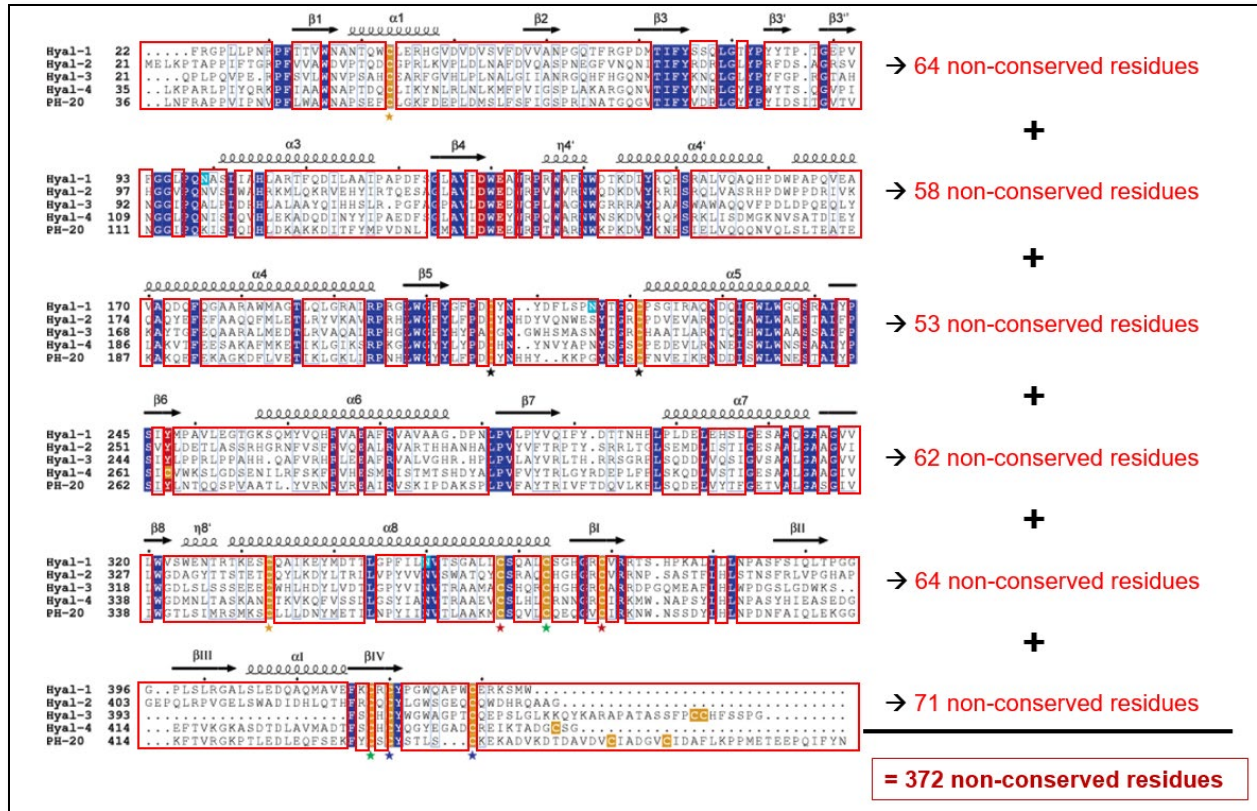


Figure E. My annotation of Figure 3 of Chao. The non-conserved regions are outlined in red, and the non-conserved residues are uncolored, identifying a total of 372 non-conserved residues. EX1006, FIG. 3.

202. Drs. Hecht and Park do not establish why a POSA would have mutated L317 rather than any of the other 371 non-conserved amino acids. EX1004; EX1005. And, similarly, Dr. Park’s alignment, which is not a prior art reference, identifies “379 positions in PH20₁₋₄₄₇” that he considers “non-essential.” EX1004, ¶¶26-29, 31-32, Appendix D-1. And Dr. Park does not explain why a POSA would have selected position 317 from among the other 378 options in his alignment. EX1004, ¶¶26-29, 31-32, Appendix D-1.

203. In total, in view of my discussions in Sections X.A and X.B.1a-e, a

POSA would not have been motivated to mutate L317 in view of Chao and the '429 patent. Notwithstanding all of the above, I also explain here why a POSA would not have been motivated to mutate L317 to glutamine (Q).

f. Drs. Hecht and Park Do Not Establish That a POSA Would Have Been Motivated to Mutate L317 to Glutamine (Q).

i. Dr. Park's Assessment of the Prevalence of Glutamine (Q) at L317 among Hyaluronidases Does Not Inform the Prevalence of Q at L317 in PH20.

204. Dr. Hecht argues that Dr. Park's report identifies glutamine (Q) as the most prevalent amino acid at position L317 of his 88-sequence alignment.

EX1003, ¶218. As discussed in Section X.B.1c above, a POSA would not have found Dr. Park's 88-sequence alignment to be informative, especially because it contains mostly hyaluronidases that are not PH20s. Indeed, only 18 of the 88 sequences are from PH20 enzymes. EX1004, ¶27; EX1056.

205. Drs. Hecht and Parks' analyses and opinions are further undermined by the fact that even if a POSA would have aligned only the PH20 sequences that Dr. Park obtained, they would have found that glutamine (Q) is *not* present at position 317 *in any* of the 18 PH20 sequences, as depicted below.

ii. Glutamine (Q) Is Not a Conservative Substitution for Leucine (L).

208. Dr. Hecht argues that Chao and a multiple-sequence alignment of proteins homologous to PH20 would have suggested glutamine (Q) as a single substitution at position 317. EX1003, ¶¶212-216. But glutamine (Q) is not a conservative substitution for leucine (L).⁴⁵ EX1005, 16:27-36; EX2017, 3. And the '429 patent does not indicate that glutamine (Q) is a conservative substitution for leucine (L). EX1005, 16:27-36. The '429 patent states: "Other substitutions are also permissible and can be determined empirically or in accord with known conservative substitutions," Drs. Hecht and Park do not propose that glutamine (Q) is otherwise a permissible conservative substitution for leucine (L). EX1003; EX1004. Additionally, I further confirmed that glutamine (Q) is not a conservative substitution by referencing a patent application claiming a peptide. EX2017⁴⁶, 3. Table 1 of European Patent Application No. EP0953574A1 (below) does not list

⁴⁵ Other claimed substitutions at position 317 (e.g., H, K, R, and S) are also not conservative substitutions for leucine (L). EX1005, 16:27-36; EX2017, 3.

⁴⁶ EX2017 is European Patent Application Publication No. 0953574 A1. I retrieved European Patent Application Publication No. 0953574 A1 from Google Patents (at <https://patents.google.com/>) and generated a PDF from the online webpage. EX2017 is true and accurate to the best of my knowledge.

glutamine (Q) as a conservative substitution for leucine (L). The fact that glutamine (Q) is not a conservative substitution for leucine (L) is understandable considering that glutamine (Q) is a polar, hydrophilic amino acid; and leucine (L) is a nonpolar, hydrophobic amino acid. EX1014, 6 and 69-70.

Amino acid	Conservative substitution by
Ser (S)	Thr, Gly, Asn
Arg (R)	His, Lys, Glu, Gln
Leu (L)	Ile, Met, Phe, Val, Tyr
Pro (P)	Ala, Thr, Gly
Thr (T)	Pro, Ser, Ala, Gly, His, Gln
Ala (A)	Pro, Gly, Thr
Val (V)	Met, Ile, Tyr, Phe, Leu
Gly (G)	Ala, Thr, Pro, Ser
Ile (I)	Met, Leu, Phe, Val, Tyr
Phe (F)	Met, Tyr, Ile, Leu, Trp, Val
Tyr (Y)	Phe, Trp, Met, Ile, Val, Leu
Cys (C)	Ser, Thr, Met
His (H)	Gln, Arg, Lys, Glu, Thr
Gln (Q)	Glu, His, Lys, Asn, Thr, Arg
Asn (N)	Asp, Ser, Gln
Lys (K)	Arg, Glu, Gln, His
Asp (D)	Asn, Glu, Gln
Glu (E)	Gln, Asp, Lys, Asn, His, Arg
Met (M)	Ile, Leu, Phe, Val

Figure G. Table 1 of European Patent Application No. EP0953574A1. Q (Gln) is not listed as a conservative substitution for L (Leu). EX2015, 3.

iii. The Helix Propensity of Glutamine (Q) Would Not Have Motivated a POSA to Mutate L317 to Q.

209. Dr. Hecht states that “Chao reports that position 317 is within an α – helix secondary structure designated $\alpha 8$.” EX1003, ¶220. Thus Dr. Hecht argues mutating L317 to glutamine (Q) “would be a favorable change” because

“glutamine has a high helix propensity.” EX1003, ¶220. However, Pace, the reference that Dr. Hecht cites as supporting the α -helical propensity of glutamine, explains that five *other* amino acids, including leucine,⁴⁷ have a *higher* helix propensity than glutamine. EX1050, Abstract, Table 2. Drs. Hecht and Park do not explain why a POSA would have selected glutamine for its helix propensity when five *other* amino acids, including the wild-type leucine at position 317, have a higher helix propensity than glutamine.

210. Thus, considering the above, a POSA would not have found Dr. Park’s 88-sequence alignment to be informative in choosing glutamine (Q) as a single substitution at L317 for PH20 in the way Dr. Park did.

211. Therefore, even when viewed in combination, Chao and the ’429 patent do not suggest mutating L317 to glutamine (Q).⁴⁸ EX1005; EX1006.

⁴⁷ Alanine, lysine, arginine, and methionine also have higher helix propensities than glutamine. EX1050, Abstract, Table 2.

⁴⁸ My reasoning with respect to mutating L317 to glutamine (Q) also applies to alanine (A), histidine (H), methionine (M), or serine (S). Section X.B.1f. Thus, even in combination, Chao and the ’429 patent do not suggest mutating L317 to A, H, M, or S. EX1004, ¶¶124-141.

iv. Drs. Hecht and Park Do Not Explain Why a POSA Would Have Been Motivated to Undertake Nearly 30 Discrete Steps to Make the L317 Mutation to glutamine (Q).

212. Unable to identify any disclosure in the '429 patent or Chao that suggests making an L317 substitution to glutamine (Q), Drs. Hecht and Park argue that a POSA would have found it obvious to engage in a lengthy series of steps set forth in Drs. Hecht and Parks' declarations. EX1003, ¶¶83, 195, 217-222; EX1004, ¶¶20-145, Appendix C, Appendix D-1.

213. Indeed, Drs. Hecht and Park argue that a POSA would have engaged in nearly 30 discrete steps to arrive at an L317Q mutation as follows:

- 1) Review Halozyme's Hylenex biological product. EX1003, ¶195.
- 2) Superimpose the HYAL1 and bee venom hyaluronidase structures.
EX1004, ¶¶89-91.
- 3) Align five human hyaluronidases of Chao. EX1003, ¶83.
- 4) Identify a characteristic pattern for the Hyal-EGF domain of PH20.
EX1004, ¶¶97-98.
- 5) Identify invariant residues by analyzing a multiple sequence alignment of a set of published hyaluronidase sequences that was available in December of 2011. EX1004, ¶26.
- 6) Review scientific literature that identified important residues in hyaluronidase proteins or which reported experimental results showing

- that modifying single residues impaired or eliminated activity of the enzymes. EX1004, ¶¶26, 88.
- 7) Generate a dataset of sequences that were homologous to PH20 and that were publicly available by 2011 by performing a BLAST search using the human PH20 sequence in FASTA format (Uniprot P38567). EX1004, ¶¶28, 141-142.
 - 8) Perform a search against the “reference proteins” database. EX1004, ¶¶141-142.
 - 9) Download the search results as a text file. EX1004, ¶¶141-142.
 - 10) Copy the header section of the text file into a separate file to decrease the amount of text so the data would have been easier to manipulate. EX1004, ¶142.
 - 11) Extract the accession numbers of the retrieved sequences from the last column and save them as a list of alphanumeric codes in a temporary file. EX1004, ¶142.
 - 12) Write and run another perl script to identify any duplicates. EX1004, ¶142.
 - 13) For any duplicates, keep only the longest isoform of each unique enzyme from each organism to yield a final set of 88 unique sequences which were homologous to human PH20 and available by December

2012. EX1004, ¶142.
- 14) Save this list as a text file. EX1004, ¶142.
 - 15) Write and run a third perl script to retrieve the FASTA format for each sequence from the file with the original BLASTP results and save the results as a new file. EX1004, ¶143.
 - 16) Use Clustal Omega to generate a multiple sequence alignment. EX1004, ¶144.
 - 17) Upload 88 sequences in FASTA format. EX1004, ¶144.
 - 18) Save the MSA generated to a local file. EX1004, ¶145.
 - 19) Use Clustal Omega to determine whether a residue is “conserved” or “semi-conserved,” which takes into account how similar a residue is across all of the sequences. EX1004, ¶29.
 - 20) Use alignment to identify 68 largely invariant residues that a skilled artisan would have deemed “essential residues” in PH20₁₋₄₄₇. EX1004, ¶¶30-32, 41-43, Appendix D-1.
 - 21) Identify the 379⁴⁹ positions other than the 68 essential residues deemed

⁴⁹ Dr. Park purports to have identified 379 non-essential amino acid positions in PH20₁₋₄₄₇ based on his alignment of 88 sequences. EX1004, ¶31, Appendix D-2.

- “non-essential” residues. EX1004, ¶31.
- 22) Determine whether position 317 is within a non-essential region of PH20₁₋₄₄₇. EX1004, ¶¶32, 31, Appendix D-2; EX1003, ¶217.
- 23) Identify the frequencies of amino acids that occur in sequences homologous to PH20. EX1003, ¶¶214-216; EX1004, ¶21.
- 24) Determine the variability in the amino acids at non-conserved positions. EX1004, ¶¶21, 31, 41-42; EX1003, ¶218.
- 25) Determine that the residue at position 317 in PH20 is leucine (L). EX1004, ¶¶30-21, 41-43, 105, Appendix D-1; EX1003, ¶218.
- 26) Determine the most prevalent amino acid at position 317 of the 88 sequence alignment is glutamine (Q), which appears at position 317 in ~30% of the 88 proteins. EX1003, ¶218.
- 27) Determine the second most-frequently occurring amino acid at position 317 of the 88-sequence alignment is threonine (T), which appears at position 317 in ~21.59% of the 88 proteins. EX1004, ¶43; EX1003, ¶218.
- 28) Determine that glutamine is an obvious choice for substituting the leucine at position 317. EX1003, ¶¶221-222.

214. But Drs. Hecht and Park do not explain why a POSA would have been motivated to undertake all of these steps. In particular, Drs. Hecht and Park do not explain why a POSA would have been motivated to undertake these steps to

prepare an L317Q-containing PH20 polypeptide with “at least comparable hyaluronidase activity as unmodified PH20₁₋₄₄₇.” EX1003, ¶234. And furthermore Drs. Hecht and Park do not sufficiently explain all of these steps.

215. Dr. Park also does not adequately explain the perl scripts he wrote, how he used them, or how he assessed their reliability. EX1004, ¶¶142-143. For example, Dr. Park states: “To generate a file with these 88 sequences in FASTA format, I wrote and ran another perl script.” EX1004, ¶143. But he does not cite or describe what perl script he used, nor explain how he determined whether his further custom perl script produced the intended results. EX1004, ¶¶142-143.

216. Therefore Dr. Park did not sufficiently explain all of the steps he undertook, and Dr. Hecht did not supply sufficient additional explanation.

v. The Hydrophilicity of Glutamine (Q) Would Not Have Motivated a POSA to Mutate L317 to Q.

217. Dr. Hecht argues that because “the side chain of the leucine at position 317 is solvent exposed,” glutamine (Q) would have been an obvious choice for substituting L317 because glutamine (Q) is a hydrophilic residue. EX1003, ¶231. First, Dr. Hecht does not provide a reason regarding why a POSA would have been motivated to modify a solvent-exposed residue. Second, Dr. Hecht does not explain why a POSA would have modified L317 rather than any other solvent-exposed residue in PH20. Third, a POSA would have understood that lysine (Lys)

and arginine (Arg) are *more hydrophilic* than glutamine, as depicted in Table 12.1 from Brandon & Tooze 1991 (duplicated in Figure H below). EX1014, 245.

Amino acid	Phe	Met	Ile	Leu	Val	Cys	Trp	Ala	Thr	Gly	Ser	Pro	Tyr	His	Gln	Asn	Glu	Lys	Asp	Arg
A	2.8	1.9	4.5	3.8	4.2	2.5	-0.9	1.8	-0.7	-0.4	-0.8	-1.6	-1.3	-3.2	-3.5	-3.5	-3.5	-3.9	-3.5	-4.5
B	3.7	3.4	3.1	2.8	2.6	2.0	1.9	1.6	1.2	1.0	0.6	-0.2	-0.7	-3.0	-4.1	-4.8	-8.2	-8.8	-9.2	-12.3

Row A is from J. Kyte and R.F. Doolittle; row B, from D.A. Engelman, T.A. Steitz, and A. Goldman.

Figure H. Table 12.2 from Brandon & Tooze 1991. Lysine (Lys) and arginine (R), labeled in red, are more hydrophilic than glutamine (Gln) labeled in blue. EX1014, 24.

218. Thus, in view of Sections X.A-X.B, a POSA would have had no motivation to make the claimed L317 mutation to glutamine (Q) before December 29, 2011. What is clear, however, is that Dr. Hecht relied upon Dr. Park’s analysis for identifying substitutions, and Dr. Park’s analysis focused on L317 because he was “asked by counsel to report [his] conclusions with respect to position 317.” EX1004, ¶103; EX1003, ¶20.

C. Drs. Hecht and Park Have Not Established That, in the Absence of the Guidance Provided in the Specification, Chao and the ’429 Patent Would Have Provided a POSA with a Reasonable Expectation That an L317 Mutation of PH20 to glutamine (Q) Would Have Produced a Polypeptide with “at Least Comparable Hyaluronidase Activity as Unmodified PH20₁₋₄₄₇”

219. As I summarized in Section VI.D, I understand that one way of showing obviousness is by establishing that a POSA would have had both (i) a reason to modify or combine the teachings of the prior art to achieve the claimed invention and (ii) a reasonable expectation of success in doing so. As I explained

above, a POSA would not have had a motivation to leap from the teachings of Chao and the '429 patent to make an L317 mutation of PH20 to glutamine (Q) as required by claims 1-2 and 6-30.

220. In view of the legal principles summarized in Section VI.D., and as explained by my analysis below, Drs. Hecht and Park also have not shown that Chao and the '429 patent would have provided a POSA with a reasonable expectation of successfully producing a protein exhibiting “at least comparable hyaluronidase activity as unmodified PH20₁₋₄₄₇,” without the guidance in the common disclosure. EX1003, ¶234. I note again that the claims *do not require enzymatic activity*, but Dr. Hecht argues that a POSA “would reasonably expect that the L317Q substitution in PH20 would be tolerated, yielding a protein that exhibits at least comparable hyaluronidase activity as unmodified as unmodified PH20₁₋₄₄₇.” EX1003, ¶234.

221. In fact, Dr. Hecht goes as far as saying that “based on modeling techniques available in 2011, the L317Q substitution would be expected to be a neutral change with the potential to have a slightly favorable impact to the protein structure.” EX1003, ¶230.

222. To support this assertion, Drs. Hecht and Park propose that a POSA would have engaged in over fifty steps that are not outlined in Chao and/or the '429 patent, as follows:

- 1) Prepare PH20 structural model to visualize amino acid substitutions in PH20.
EX1004, ¶¶33-36, 147-150.
- 2) Use SWISS-MODEL to generate a model of the PH20 structure using the
HYAL1 structure. EX1004, ¶¶39-40.
- 3) Determine that the PH20 model was reliable by assessing the QMEAN value
for the model. EX1004, ¶148.
- 4) Analyze the C-terminus region's local QMEAN reliability using B-factor
scores in the modeled PH20 structure. EX1004, ¶150.
- 5) Use HYAL1 as the template structure for PH20 in SWISS-MODEL.
EX1004, ¶152.
- 6) Devise a consistent, objective methodology for assessing substitutions using
the PH20 model. EX1004, ¶¶102-103.
- 7) Assess possible interactions between the wild-type residue and its
neighboring amino acids. EX1004, ¶¶44-47, 53-60, 65-85.
- 8) Assess possible interactions between an amino acid at a particular position
with solvent. EX1004, ¶45.
- 9) Determine hydrophobicity and sterics of each neighboring amino acid.
EX1004, ¶46.
- 10) Consider the varying characteristics of side chains of each amino acid and
their interactions, including hydrophobic residues with other hydrophobic

residues, van der Waals attractions between residues, hydrogen bonding among polar residues. EX1004, ¶¶48-52.

- 11) Consider factors within the context of the specific location of the substitution, including whether the residue being substituted is on the surface of the protein's structure or buried within protein's structure. EX1004, ¶¶53-54.
- 12) Define a classification system for assessing single amino acid substitutions in PH20. EX1004, ¶55.
 - a. Changes that were likely to stabilize the protein.
 - b. Changes that were either neutral or mildly positive or negative for the local protein structure.
 - c. Changes that were likely to be significantly destabilizing.
- 13) Inspect the PH20 structure produced using the PyMol viewer to identify the neighbors of the residues to assess in the wild-type PH20 sequence. EX1004, ¶56.
- 14) Note "neighbors" that were within ~ 5 Å of the side chain of the amino acid being evaluated, with greater number of neighbors indicative of the residue being buried and fewer neighbors indicative of a solvent accessible surface residue. EX1004, ¶¶56-57.
- 15) Determine the fractional solvent accessible surface area ("SASA") to

quantitatively measure whether a residue is solvent accessible. EX1004, ¶58.

- 16) Inspect the distance between neighbors and a particular residue to determine whether there was likely a van der Waals interaction. EX1004, ¶59.
- 17) Periodically use a custom script, which runs within the PyMol environment to show all of the neighboring amino acids encompassed in a shell, allowing one to visualize the chemical moieties surrounding an amino acid at a given position EX1004, ¶60.
- 18) Use the “mutagenesis” feature of PyMol, which replaces an amino acid at a defined position with another amino acid, to evaluate whether a mutation would have been likely be tolerated. EX1004, ¶61.
- 19) Consider the chemical similarity of the substitution to the wild-type amino acid at the position being evaluated. EX1004, ¶62.
- 20) Assess interactions with neighboring residues to determine impact of substitution, including: EX1004, ¶¶63, 85.
- 21) For each substitution, consider whether the change introduces a hydrophobic residue into a hydrophilic environment EX1004, ¶¶64-68.
- 22) For each substitution, evaluate its compatibility with the predicted secondary structures at that position. EX1004, ¶¶69-73.
- 23) For each substitution, consider how the substitution would have altered

steric interactions compared to the wild-type residue. EX1004, ¶¶74-79.

24) For each substitution, consider tertiary interactions that might be influenced by a substitution. EX1004, ¶¶80-83.

25) Consult the structure of human HYAL1 and/or bee venom hyaluronidase to consider how a particular substitution might influence the structure of PH20 (reflects the evolutionary influences of the protein's structure). EX1004, ¶84.

26) Balance the type of impact of the substitutions based on the magnitude of each interaction may have on the protein's structure. EX1004, ¶85.

27) Assign a score for each substitution reflecting the aggregate effect.
EX1004, ¶¶86-87.

- a. A score of 1 (reduce protein stability), 2 (no effect or slightly positive or negative effect), or 3 (improve overall stability).

28) Consider the biochemical and structural data reported in the scientific literature, including Chao, Zhang, Stern, and Arming. EX1004, ¶¶88-101.

29) Evaluate and assign scores to many different substitutions to develop a consistent and unbiased methodology to evaluate potential substitutions.
EX1004, ¶¶102-103.

Analysis of Position 317:

30) Assess the local environment near position 317317 in PH20, which is

leucine (L) in the wild-type form of human PH20. EX1004, ¶105.

- 31) Visualize L317 within the PH20 model using PyMol. EX1004, ¶107.
- 32) Confirm that L317 was not near the active site. EX1004, ¶107.
- 33) Note that L317 has seven neighbors. EX1004, ¶107.
- 34) Inspect placement of neighboring amino acids and their interactions with L317. EX1004, ¶107.
- 35) Confirm more distant, non-neighboring amino acids do not interact with L317. EX1004, ¶107.
- 36) Determine that residue L317 is located at a solvent-exposed position on helix 8 ($\alpha 8$). EX1004, ¶108.
- 37) Determine that L317 has an fSASA of 0.42, which is significantly higher than the median fSASA value for leucine, which is 0.05. EX1004, ¶108.
- 38) Determine that the solvent exposure of L317 and the hydrophilicity of its closest neighbors suggest that inter-residue contacts may not be a critical factor for single amino acid substitutions at position 317. EX1004, ¶109.
- 39) Determine that the lack of consistent biochemical properties among neighbors suggests that many different types of amino acids may be tolerated as single amino acid substitutions at position 317 without causing a significant change in stability or activity. EX1004, ¶109.
- 40) Determine that some neighbors around position 317 may provide

hydrophobic and van der Waals contacts through their aliphatic side chains.

EX1004, ¶110.

- 41) Conclude that L317 may interact weakly with these neighbors because they are separated by a distance greater than 5 Å from L317; therefore, L317 could be substituted with several other amino acids, so long as the single substitution does not present any problematic interactions. EX1004, ¶110.
- 42) Create custom scripts that run within the PyMol environment. EX1004, ¶¶60, 162.
 - a. Inspect positions.
 - b. Identify each residue, its neighbors, the distance between the residue and each neighbor, as well as the surface environment.
 - c. Display the pockets of a particular location in the structure using a script that invokes display options built into PyMol.
- 43) Use a built-in function in PyMol that replaces the amino acid in the structure at a position with a different amino acid ("mutagenesis"). EX1004, ¶¶61, 107, 118, 163.
- 44) Assess numerous substitutions representing diverse interactions, including L317Q, L317R, L317M, and L3147I. EX1004, ¶¶112-138.
- 45) Evaluate the L317Q substitution in PH20₁₋₄₄₇. EX1004, ¶¶112-119.
- 46) For L317Q, determine that glutamine (Q) is found at position 317317 in

about 30% of the 88 proteins reviewed. EX1004, ¶112.

- 47) Determine that glutamine can tolerate a solvent-accessible environment because it is a hydrophilic amino acid. EX1004, ¶113.
- 48) Use the PyMol protein mutagenesis feature, which suggested rotamer 14 as the best fit for glutamine at position 317. EX1004, ¶114.
- 49) Determine that, when glutamine was substituted in position 317:
- a) It has an fSASA of 0.34, which is similar to the mean fSASA value of 0.38 for glutamine;
 - b) It may form hydrogen bonds with nearby residues, including E31 and N321, that may enhance the stability around position 317 and offset the loss of hydrophobic contacts between M313, K314, and L318—and leucine. EX1004, ¶¶115-118.
- 50) Conclude that the hydrogen bonds formed with nearby residues, including E31 and N321, should offset the loss of hydrophobic contacts between M313, K314, and L318—and leucine, such that the L317Q mutation will have a neutral, or even slightly positive, effect on the stability of the protein. EX1004, ¶117.
- 51) Confirm that the modeled structure with L317Q, which incorporates energy minimization, supported the evaluation based on PyMol's protein mutagenesis feature. EX1004, ¶118.

- 52) Assign the L317Q mutation a score of 2 in view of the expected effects of the L317Q mutation. EX1004, ¶119.
- 53) Assess whether arginine (R) would have been tolerated at position 317. EX1004, ¶¶120-126.
- 54) Conclude that L317R would be tolerated. EX1004, ¶126.
- 55) Assess whether methionine (M) would have been tolerated at position 317. EX1004, ¶¶127-133.
- 56) Conclude that L317M would be tolerated. EX1004, ¶133.
- 57) Assess whether isoleucine (I) would have been tolerated at position 317. EX1004, ¶¶134-138.
- 58) Conclude that L317I would be tolerated.⁵⁰ EX1004, ¶138.

223. Drs. Hecht and Park provide no explanation demonstrating that a POSA would have been motivated to carry out these more than fifty steps to form a reasonable expectation that making the L317Q mutation of PH20 would have yielded a PH20 polypeptide with “at least comparable hyaluronidase activity as

⁵⁰ I note that Dr. Park provides no assessment regarding whether alanine (A) or lysine (K) would have been tolerated at position 317, nor does he conclude that a POSA would have determined that alanine or lysine would have been tolerated at position 317.

unmodified PH20₁₋₄₄₇,” absent the guidance in the specification. EX1003, ¶234.

224. Additionally, similarly to the nearly 30 steps previously described above, Dr. Park also does not fully explain the above more than fifty steps here although they, too, include creating and using custom scripts. EX1004, ¶¶60, 162, 164, App’x E, F.

225. Dr. Park also states that he “periodically used a custom script that [he] wrote which runs within the PyMol environment” that “shows all of the neighboring amino acids encompassed in a shell, allowing one to visualize the chemical moieties surrounding an amino acid at a given position.” EX1004, ¶60..

226. But he does not explain what he means by “periodically,” nor does he explain how these scripts work to “visualize the chemical moieties surrounding an amino acid at a given position.” EX1004, ¶60.

227. In sum, the combination of Chao and the ’429 patent do not provide any guidance suggesting that mutating L317 to glutamine (Q) would have yielded a PH20 polypeptide with “at least comparable hyaluronidase activity as unmodified PH20₁₋₄₄₇.” EX1003, ¶234; EX1005; EX1006.

228. Thus Drs. Hecht and Park have failed to show that a POSA would have had a reasonable expectation that making the L317 mutation to glutamine (Q) would have yielded a PH20 polypeptide with “at least comparable hyaluronidase activity as unmodified PH20₁₋₄₄₇” before December 29, 2011 and absent the

guidance in the specification. EX1003, ¶234.

D. Dr. Hecht's Declarations in Related Proceedings Further Reveal that the '429 Patent and Chao Would Not Have Provided Any Reason to Make a D320K Mutation.

229. Dr. Hecht has submitted declarations in thirteen other related proceedings. As explained in my first declaration, Dr. Hecht applies essentially the same references and reasoning in each case in which he challenges the claims based on obviousness, but to different claimed modifications.⁵¹ EX2001, ¶¶133-135. In my first declaration, I illustrated this point with exemplary excerpts of Dr. Hecht's declarations in twelve of the related proceedings. EX2001, ¶134.

230. I further illustrate this point with exemplary excerpts from Dr. Hecht's additional declaration related to U.S. Patent No. 12,264,345. EX2067. Dr. Hecht's declaration related to U.S. Patent No. 12,264,345 was filed after I signed my first declaration. EX2067.

231. The text that is deleted relative to Dr. Hecht's '600 patent declaration is depicted in red strike through, and the text that is new relative to Dr. Hecht's '600 patent declaration is depicted in blue underline text:

⁵¹ EX1003; EX2029-2034, EX2036, EX2038, EX2057, EX2061, and EX2063-EX2064. Obviousness was not challenged in the proceeding related to U.S. Patent No. 12,077,791. EX2063.

Exemplary Excerpt 1	
Comparative Patent	Deleted Text Is Depicted in Red; New Text Is Depicted in Blue
US Patent No. 12,264,345 PGR2025-00052 EX2067, ¶239; EX2030, ¶200	I note that these conventional procedures relating to production of the wild-type PH20 ₁₋₄₄₇ protein <u>that are described in the '429 patent</u> could be applied to produce forms of PH20 ₁₋₄₄₇ that incorporate a single amino acid substitution (e.g., the D320K <u>M313K</u> substitution I discuss below, <u>§ VI.D</u>) with little effort.

Exemplary Excerpt 2	
Comparative Patent	Deleted Text Is Depicted in Red; New Text Is Depicted in Blue
US Patent No. 12,264,345 PGR2025-00052 EX2067, ¶240; EX2030, ¶201	The '429 Patent reports that expressing the D320K PH20₁₋₄₄₇-mutant <u>PH20₁₋₄₄₇ mutants</u> in a CHO cell yields a glycosylated form of the protein that is enzymatically active.

Exemplary Excerpt 3	
Comparative Patent	Deleted Text Is Depicted in Red; New Text Is Depicted in Blue
US Patent No. 12,264,345 PGR2025-00052 EX2067, ¶252; EX2030, ¶213	Position 320 <u>313</u> is within a non-essential region of the PH20 sequence, based on my review of Dr. Park's analysis[] and the sequence alignment in Chao.

Exemplary Excerpt 4	
Comparative Patent	Deleted Text Is Depicted in Red; New Text Is Depicted in Blue
US Patent No. 12,264,345 PGR2025-00052 EX2067, ¶256; EX2030, ¶216	Given the explanations above, a A skilled artisan, in 2011, would have readily identified position 320 313 as being in one of the non-essential regions of PH20 ₁₋₄₄₇ contemplated by the '429 Patent.

232. As can be seen from the above excerpts, Dr. Hecht’s analysis is also substantially the same in his declaration submitted in support of the PGR Petition filed against U.S. Patent No. 12,264,345. EX2067.

233. In closing, Drs. Hecht and Park appear to have relied on hindsight, based on the direction of counsel, rather than any teachings or suggestions stemming from the prior art that would have motivated a POSA to make an L317Q mutation. Drs. Hecht and Park fail to identify any disclosure of a mutation of L317 (or an L317 mutation to glutamine (Q)) in Chao and the '429 patent, whether explicitly or as would have been supplied by the common sense or ordinary creativity of a POSA. And absent the guidance of the specification, Drs. Hecht and Park further fail to establish that a POSA would have had a motivation to combine Chao and the '429 patent to make a L317 mutation of PH20 or establish that a POSA would have reasonably expected that mutating L317 to glutamine (Q) would have resulted in a modified PH20 polypeptide with at least comparable

hyaluronidase activity as unmodified PH20₁₋₄₄₇. As depicted above, Drs. Hecht and Parks' analysis is, in essence, based on cherry-picking using hindsight rather than reflecting the view of a POSA reading the '429 patent in combination with Chao.

XI. CONCLUSION

234. In view of the facts above, and in accordance with the legal principles described in Section VI, a POSA would have found that the common disclosure shared by the '758 patent and the '731 application (filed December 28, 2012) adequately described and enabled the subject matter of claims 1-2 and 6-30. Additionally, in view of the facts above, and in accordance with the legal principles described in Section VI, a POSA would have found that claims 1-2 and 6-30 would not have been obvious to a POSA before December 29, 2011 (the date Dr. Hecht used in his analysis).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Executed on this 17th day of July 2025.


Barbara Triggs-Raine, Ph.D.

