

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,
Petitioner

v.

HALOZYME, INC.,
Patent Owner

Case PGR2025-00017
U.S. Patent No. 12,110,520

**DECLARATION OF GARY N. CHERR, PH.D. IN SUPPORT OF PATENT
OWNER'S RESPONSE**

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Halozyyme EX2072
Merck v. Halozyyme
PGR2025-00017

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I, Gary N. Cherr, 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 \$350 per hour.

3. I understand that this Declaration accompanies the Patent Owner’s Response filed in a PGR involving U.S. Patent No. 12,110,520. In preparing this Declaration, I reviewed each of the documents cited in this declaration in light of general knowledge in the art by December 28, 2012.

4. In formulating my opinions, I relied upon my experience, education, and knowledge in the relevant art. In formulating my opinions, at counsel’s request, I also considered the viewpoint of a person of ordinary skill in the art as defined below in Section V, by December 28, 2012, in light of general knowledge in the art.

II. MY BACKGROUND AND QUALIFICATIONS

5. I am a Professor Emeritus at the University of California Davis Departments of Environmental Toxicology and Nutrition and Professor VIII in the Departments of Environmental Toxicology and Nutrition at the Bodega Marine

Laboratory, where I was the Director for 13 years.

6. I have over 40 years of experience in the field of reproductive physiology, reproductive and developmental biology, toxicology, sperm cell physiology, fertility, infertility and contraception, and embryo defense mechanisms. My research has focused on invertebrate, fish and mammalian reproduction and development, and how environmental stressors impact these processes. These stressors include nanotechnology, endocrine disruptors, pharmaceuticals/personal care products, and petroleum compounds. My basic reproductive biology research includes studying the regulation of sperm motility, sperm surface molecules such as PH20 and beta defensins, mechanisms of fertilization biology, and comparative reproduction and development across phyla.

7. My *curriculum vitae* is submitted herewith as EX2073.

8. I graduated with a Bachelor's degree in Biology from Sonoma State University in 1979. I then received my Ph.D. in Zoology from University of California Davis in 1984. From 1983-1986, I was a National Institutes of Health Postdoctoral Fellow in the Department of Obstetrics and Gynecology in the School of Medicine at the University of California, Davis. My research focused on mammalian sperm-oocyte interactions, sperm capacitation, the acrosome reaction, and mechanisms of sperm motility and its role in sperm penetration of the oocyte-cumulus complex and the zona pellucida.

9. After my postdoctoral fellowship, I became an Assistant Research Biologist II (1986-1989), followed by an Assistant Research Biologist III (1989-1991), Assistant Research Biologist IV (1991-1993), and Associate Research Biologist I (1993-1995) at the Bodega Marine Laboratory at the University of California, Davis. Subsequently, in 1995-1997, I became an Associate Research Biologist II at the Bodega Marine Laboratory and the Department of Environmental Toxicology at the University of California, Davis, as well as a Lecturer in the Division of Biological Sciences at the University of California Davis. In 1997-1999, I was an Associate Research Biologist III at the Bodega Marine Laboratory and the Department of Environmental Toxicology at the University of California, Davis, followed by a Research Biologist I (1999) at the Bodega Marine Laboratory and the Department of Environmental Toxicology at the University of California, Davis.

10. I became Professor III (1999-2006) and, following promotion with tenure, became Professor IV (2006-2009) in the Departments of Environmental Toxicology and Nutrition at the Bodega Marine Laboratory. I was the Interim Director at the Bodega Marine Laboratory (2007-2008), Professor V and permanent Director (2009-2012), Professor VII and Director (2012-2015), and Professor VIII and Director (2019-2022) in the Departments of Environmental Toxicology and Nutrition at the Bodega Marine Laboratory. I became Professor

Emeritus in 2019 and Director Emeritus in 2022.

11. I have authored 155 peer-reviewed publications that discuss, for example, reproductive physiology, reproductive and developmental biology, toxicology, sperm cell physiology, sperm surface proteins involved in gamete interaction and sperm transport in the female tract as well as immunoprotection (e.g. PH20 and β -defensin 126), embryo defense mechanisms, biochemistry and cell biology of environmental stress, endocrine disruption, and environmental toxicology. Key among these are forty-two publications in mammalian reproduction including the biophysics of sperm penetration of the egg as well as PH20 function (eighteen of the forty-two publications) in sperm. I have also taught a number of undergraduate and graduate university courses, including *Mechanisms of Fertilization*, *Environmental Stress and Development*, *Environmental Factors Affecting Development* (Japan International Developmental Biology course), supervised eleven completed Ph.D. theses, and have had eight post-doctoral fellows in my lab.

III. SUMMARY OF OPINIONS

12. I have been asked to consider whether a person of ordinary skill in the art (“POSA,” defined in Section V below) would have expected any of the “modified PH20 polypeptides” to be useful as contraceptive vaccines in female mammals. I have read Dr. James J. Moon’s Declaration (EX2074), as presented by

counsel. In my Declaration here, like Dr. Moon, I use the phrase “modified PH20 polypeptides” to refer to polypeptides comprising an amino acid sequence that is at least 91% identical to the amino acid sequence of any one of SEQ ID NO: 3, 7, and 32-66¹, and includes a modification at position 324 selected from A, D, H, M, N, R and S. As I explain below in Section VII, by December 28, 2012, a POSA would have expected that polyclonal antibodies generated in female mammals (including humans) in response to any of the modified PH20 polypeptides, administered as vaccines, would cause contraception by binding to the sperm PH20 polypeptide in the female reproductive tract. Thus, a POSA would have expected that any of the modified PH20 polypeptides would be useful as contraceptive vaccines in female mammals (including humans).

13. I have been asked to consider whether the studies that Merck’s expert Dr. Hecht cites in his declaration (EX1003) suggest, as Dr. Hecht alleges, that “PH20 does not appear to induce formation of antibodies that affect fertility in many rodents or in humans.” EX1003, ¶¶110-112. For the reasons explained in Section VIII, I disagree with Dr. Hecht that any of his cited studies support his opinion. None of these studies would have undermined a POSA’s expectation to

¹ SEQ ID NOs: 3, 7, and 32-66 were provided by counsel and are included in Appendix A.

use any of the modified PH20 polypeptides as contraceptive vaccines in female mammals by December 28, 2012, as also explained in these publications. *See* Section VIII.

14. I have been asked to consider whether a POSA would have expected anti-PH20 monoclonal antibody(ies) against any of the modified PH20 polypeptides when administered into the vaginal cavity of human females to cause contraception. As I explain below in Section IX, by December 28, 2012, a POSA would have expected that anti-PH20 monoclonal antibodies when delivered into the vaginal cavity would cause contraception in human females irrespective of where on PH20 the antibodies bind.

IV. LIST OF DOCUMENTS CONSIDERED

In providing my testimony, I have considered the documents listed in the table below.

Exhibit No.	Description
1003	Declaration of Dr. Michael Hecht
1019	Hardy et al., "Assessment of contraceptive vaccines based on recombinant mouse sperm protein PH20," <i>Reprod.</i> , 127:325-334 (2004)
1020	Pomering et al., "Restricted Entry of IgG into Male and Female Rabbit Reproductive Ducts Following Immunization with Recombinant Rabbit PH-20," <i>Am. J. Reprod. Immunol.</i> , (3):174-82 (2002)

Exhibit No.	Description
1021	Baba et al., "Mouse Sperm Lacking Cell Surface Hyaluronidase PH-20 Can Pass through the Layer of Cumulus Cells and Fertilize the Egg," <i>J. Biol. Chem.</i> , 277(33):30310-4 (2002)
1022	Primakoff et al., "Reversible Contraceptive Effect of PH-20 Immunization in Male Guinea Pigs," <i>Biol. Reprod.</i> , 56(5):1142-6 (1997)
1023	Tung et al., "Mechanism of Infertility in Male Guinea Pigs Immunized with Sperm PH-20," <i>Biol. Reprod.</i> , 56(5):1133-41 (1997)
1024	Rosengren et al., "Recombinant Human PH20: Baseline Analysis of the Reactive Antibody Prevalence in the General Population Using Healthy Subjects," <i>BioDrugs</i> , 32(1):83-89 (2018)
1061	Rosengren et al., "Clinical Immunogenicity of rHuPH20, a Hyaluronidase Enabling Subcutaneous Drug Administration," <i>AAPS J.</i> , 17:1144-1156 (2015)
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)
2073	<i>Curriculum Vitae</i> of Gary N. Cherr, Ph.D.
2074	Declaration of James J. Moon, Ph.D. in Support of Patent Owner's Response
2100	Vines, C.V. et al., "Identification of a Hyaluronic Acid (HA) Binding Domain in the PH-20 Protein That May Function in Cell Signaling," <i>Molecular Reproduction and Development</i> , 60:542-552 (2001)
2101	Wassarman, P. et al., "Structure and Function of the Mammalian Egg Zona Pellucida," <i>Journal of Experimental Zoology (Mol Dev Evol)</i> , 285:251-258 (1999)

Exhibit No.	Description
2102	Yudin, A. et al., "Structure of the cumulus matrix and zona pellucida in the golden hamster: A new view of sperm interaction with oocyte-associated extracellular matrices," <i>Cell Tissue Res</i> 251:555-564 (1988)
2103	Tollner, T. et al., "Multifunctional glycoprotein DEFB126 – a curious story of defensing-clad spermatozoa," <i>Nature Reviews Urology</i> , Vol. 9, pp. 365-375 (July 2012)
2104	Visconti, P. et al., "The Molecular Basis of Sperm Capacitation," <i>Journal of Andrology</i> , 19(2):242-248 (March/April 1998)
2105	Wassarman, P. et al., "A profile of fertilization in mammals," <i>Nature Cell Biology</i> , Vol. 3, pp. E59-E64 (February 2001)
2106	Bailey, J., "Factors Regulating Sperm Capacitation," <i>Systems Biology in Reproductive Medicine</i> , 56:334-348 (2010)
2107	Sabeur, K. et al., "The PH-20 Protein in Human Spermatozoa," <i>Journal of Andrology</i> , 18(2):151-158 (March/April 1997)
2108	Hunnicutt, G. et al., "Sperm Surface Protein PH-20 Is Bifunctional: One Activity Is a Hyaluronidase and a Second, Distinct Activity is Required in Secondary Sperm-Zona Binding," <i>Biology of Reproduction</i> , 55:80-86 (1996)
2109	Tollner, T. et al., "Beta-Defensin 126 on the Surface of Macaque Sperm Mediates Attachment of Sperm to Oviductal Epithelia," <i>Biology of Reproduction</i> , 78:400-412 (2008)
2110	Tollner, T. et al., "Release of DEFB126 From Macaque Sperm and Completion of Capacitation Are Triggered by Conditions That Simulate Perioovulatory Oviductal Fluid," <i>Molecular Reproduction & Development</i> , 76:431-443 (2009)
2111	Yudin, A. et al., "Beta-Defensin 126 on the Cell Surface Protects Sperm from Immunorecognition and Binding of Anti-Sperm Antibodies," <i>Biology of Reproduction</i> , 73:1243-1252 (2005)

Exhibit No.	Description
2112	Yudin, A. et al., “The Carbohydrate Structure of DEFB126, the Major Component of the Cynomolgus Macaque Sperm Plasma Membrane Glycocalyx,” <i>Journal of Membrane Biology</i> , 207:119-129 (2005)
2113	Tollner, T. et al., “A Common Mutation in the Defensin DEFB126 Causes Impaired Sperm Function and Subfertility,” <i>Science Translational Medicine</i> , 3(92):1-9 (2011), with erratum
2114	Frayne, J. et al., “The potential use of sperm antigens as targets for immunocontraception; past, present and future,” <i>Journal of Reproductive Immunology</i> , 43:1-33 (1999)
2115	Yanagimachi, R., “Acceleration of the Acrosome Reaction and Activation of Guinea Pig Spermatozoa by Detergents and Other Reagents,” <i>Biology of Reproduction</i> , 13:519-526 (1975)
2116	Chamley, L. et al., “Antisperm antibodies and conception,” <i>Seminars in Immunopathology</i> , 29:169-184 (2007)
2117	Kremer, J. et al., “The significance of antisperm antibodies for sperm-cervical mucus interaction,” <i>Human Reproduction</i> , 7(6):781-784 (1992)
2118	Primakoff, P. et al., “A Map of the Guinea Pig Sperm Surface Constructed with Monoclonal Antibodies,” <i>Developmental Biology</i> , 98:417-428 (1983)
2119	Myles, D. et al., “Localized Surface Antigens of Guinea Pig Sperm Migrate to New Regions Prior to Fertilization,” <i>The Journal of Cell Biology</i> , 99:1634-1641 (1984)
2120	Chan, C. et al., “Identification of Linear Surface Epitopes on the Guinea Pig Sperm Membrane Protein PH-20,” <i>Life Sciences</i> , 64(22):1989-2000 (1999)
2121	Ganesan, R. et al., “Structural and mechanistic insight into how antibodies inhibit serine proteases,” <i>Biochemistry Journal</i> , 430:179-189 (2010)

Exhibit No.	Description
2122	Mestecky, J. et al., “Mucosal Immune System of the Human Genital Tract,” <i>The Journal of Infectious Diseases</i> , 179(Suppl 3):S470-S474 (1999)
2126	Suri, A., “Contraceptive vaccines targeting sperm,” <i>Expert Opinion on Biological Therapy</i> , 5(3):381-392 (2005)
2127	Morrow, R. et al., “Sustained release of proteins from a modified vaginal ring device,” <i>European Journal of Pharmaceutics and Biopharmaceutics</i> , 77:3-10 (2011)
2128	Hussain, A. et al., “The vagina as a route for systemic drug delivery,” <i>Journal of Controlled Release</i> , 103:301-313 (2005)
2129	Veazey, R. et al., “Prevention of virus transmission to macaque monkeys by a vaginally applied monoclonal antibody to HIV-1 gp120,” <i>Nature Medicine</i> , 9(3):343-346 (2003)
2130	Baloglu, E. et al., “Strategies to Prolong the Intravaginal Residence Time of Drug Delivery Systems,” <i>Journal of Pharmaceutical Science</i> , 12(3):312-336 (2009)
2131	Suarez, S. et al., “Sperm transport in the female reproductive tract,” <i>Human Reproduction Update</i> , 12(1):23-37 (2006)
2132	Cauci, S. et al., “Combination of vaginal pH with vaginal sialidase and prolidase activities for prediction of low birth weight and preterm birth,” <i>American Journal of Obstetrics and Gynecology</i> , 192:489-496 (2005)
2133	Flori, F. et al., “Menstrual cycle–related sialidase activity of the female cervical mucus is associated with exosome-like vesicles,” <i>Fertility and Sterility</i> , 88(Suppl 2):1212-1219 (October 2007)
2134	Mestecky, J. et al., “Antibody-mediated protection and the mucosal immune system of the genital tract: relevance to vaccine design,” <i>Journal of Reproductive Immunology</i> , 85:81-85 (2010)

Exhibit No.	Description
2135	Kim, S. et al., “Antibody Engineering for the Development of Therapeutic Antibodies,” <i>Molecules and Cells</i> , 20(1):17-29 (2005)
2136	Lardner, A., “The effects of extracellular pH on immune function,” <i>Journal of Leukocyte Biology</i> , 69:522-530 (April 2001)
2171	Tollner, T. et al., “Macaque Sperm Release ESP13.2 and PSP94 During Capacitation: The Absence of ESP13.2 Is Linked to Sperm-Zona Recognition and Binding,” <i>Molecular Reproduction and Development</i> , 69:325-337 (2004)
2172	Yudin, A. et al., “Characterization of the active site of monkey sperm hyaluronidase,” <i>Reproduction</i> , 121:735-743 (2001)
2173	Yudin, A. et al., “PH-20 but Not Acrosin Is Involved in Sperm Penetration of the Macaque Zona Pellucida,” <i>Molecular Reproduction and Development</i> , 53:350-362 (1999)

V. PERSON OF ORDINARY SKILL IN THE ART

15. I understand that patent law analyses are performed from the viewpoint of a person of ordinary skill in the art (POSA). 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.

16. I have been asked to apply the following definition of a POSA for purposes of my analysis provided here: 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 study of protein structure and function (e.g., chemistry, biochemistry, biology, biophysics). From 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 used to analyze protein structure (*i.e.*, sequence searching and alignments, protein modeling software, etc.). I understand that a POSA could also work as part of a multidisciplinary team.

17. I had at least the qualifications of a POSA by December 28, 2012. As an expert, I have been asked to provide opinions from the perspective of a POSA by December 28, 2012.

VI. TECHNICAL BACKGROUND/STATE OF THE ART

18. Below, I briefly discuss information that was part of the general knowledge in the art by December 28, 2012.

A. PH20

19. PH20 (also called, sperm adhesion molecule 1, testicular hyaluronidase, or in mouse SPAM1) is a sperm-associated protein involved in fertilization. EX1019, 325. “The PH20 protein is widely conserved among mammals,” such as guinea pig, rat, rabbit, mouse, fox, pig, monkey, chimpanzee, orangutans, and humans. *See* EX1019, 325. PH20 is localized in the plasma

membrane on the surface of sperm and in the sperm's acrosome² where it is bound to the inner acrosomal membrane. *See* EX1019, 325. PH20 is a multifunctional protein: it acts as a hyaluronidase (an enzyme that hydrolyzes, *i.e.*, digests, hyaluronic acid (hyaluronan, hyaluronate, or HA)); has hyaluronan-mediated sperm-signaling activity by way of an HA binding domain; and acts as a sperm receptor for oocyte's (egg's) zona pellucida³ on acrosome reacted (AR)⁴ sperm. EX1019, 325; EX2103, FIG. 3 legend.

B. Fertilization in mammals

20. A mammalian oocyte is surrounded by a thick, non-cellular layer composed of glycoproteins called the zona pellucida. EX2101, 251. The zona pellucida protects the oocyte during development and regulates interactions between the oocyte and sperm. EX2101, 251. Surrounding the oocyte and its zona pellucida is a layer of cumulus cells that nurture the developing oocyte. EX2102, Abstract, 555. During ovulation, the cumulus layer swells due to the production of

² The acrosome is a specialized organelle found in mammalian sperm. It is a cap-like structure that covers the anterior portion of the sperm head and contains enzymes, such as PH20, that are essential for penetrating the oocyte during fertilization.

³ The zona pellucida is a thick, non-cellular layer composed of glycoproteins that surrounds the oocyte (on the outside of the oocyte's plasma membrane). EX2102, 555.

⁴ When a sperm binds to an oocyte, it triggers the release of enzymes from sperm's acrosome in an event called an acrosome reaction. Sperm that have undergone this reaction are called acrosome reacted (AR) sperm.

a hyaluronic acid-rich extracellular matrix (ECM) that extends into the pores of the zona pellucida. *See* EX2102, 563. As a hyaluronidase, PH20 aids in sperm movement towards the oocyte for fertilization by digesting hyaluronic acid in the cumulus layer and in the zona pellucida, allowing sperm to penetrate through and reach the oocyte's plasma membrane where the sperm and oocyte fuse and fertilization occurs. *See, e.g.*, EX2173, Abstract, 360-361.

21. The female reproductive tract is highly immunocompetent near the time of ovulation with the peri-ovulatory cervical mucus containing IgA antibodies, and fluids in the vagina and uterus containing elevated levels of IgA and IgG antibodies. EX2103, 367. When moving through the female reproductive tract, sperm traverse mucosal fluid and extracellular matrices where they must evade the female immune system. EX2103, 365. To assist in this journey, mammalian sperm are “enclosed in an extensive glycocalyx—a dense scaffold of surface-associated oligosaccharides that serve as the primary interface between sperm and the multiple microenvironments of the female tract.” EX2103, 365. The glycocalyx coating contributes to protecting sperm by masking its otherwise highly immunogenic surface displaying a number of sperm-specific antigens (such as PH20). EX2103, 367.

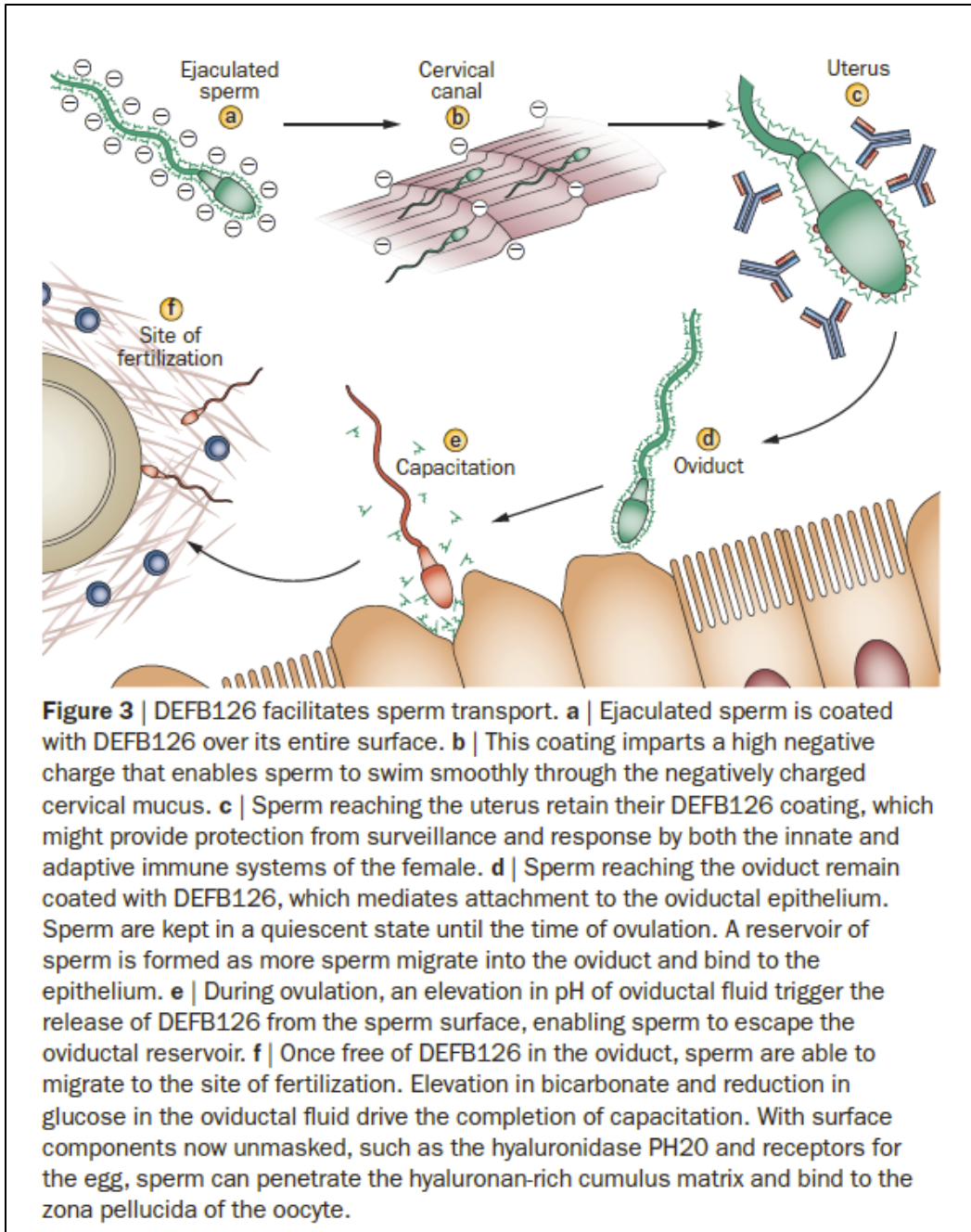
22. A glycoprotein called β -defensin DEFB126 is the major component of the sperm glycocalyx in primates (human and non-human). EX2103, 365.

β -defensin DEFB126 is linked to negatively charged oligosaccharides (*e.g.*, sialic acid) that facilitate sperm movement through the cervical mucus and cloak sperm from immune surveillance of the female reproductive tract. EX2103, 373, 368 (“DEFB126-containing glycocalyx effectively covers up other protein components on the sperm surface, making sperm essentially invisible to immune surveillance.”). In fact, it was known that where some men have a mutation in the DEFB126 gene that results in a reduction or loss of the sperm surface glycocalyx, the couples have reduced fertility because sperm exhibit decreased penetration of cervical mucus and impaired function in the upper reproductive tract. EX2113, 5, 6; EX2103, 371.

23. Upon reaching the oviduct (also called fallopian tube) in the upper reproductive tract, sperm attach to the oviductal epithelium via β -defensin DEFB126, waiting for ovulation to occur. EX2103, FIG. 3, 372. At ovulation, a rapid increase in bicarbonate secretion in the oviduct elevates the pH in the oviductal fluid from 7.2 to 7.8, while glucose levels decline. EX2103, 369, FIG. 3. These changes allow release of β -defensin DEFB126 from the sperm surface as the sperm complete capacitation and become capable of undergoing the acrosome reaction. EX2103, 373, FIG. 3. Capacitation involves molecular and physiological events that allow sperm to acquire the ability to fertilize the oocyte. EX2104. The release of β -defensin DEFB126 from the sperm surface at capacitation performs

two functions: (1) it frees the sperm from the oviductal epithelium, allowing sperm to migrate towards the oocyte, and (2) it unmask the proteins on the sperm surface, including PH20 that hydrolyzes hyaluronic acid in the cumulus layer to help sperm move towards the oocyte. EX2103, FIG. 3, 368 (disclosing that antibodies recognize PH20 when DEFB126 is removed). EX2106, EX2107, EX2108.

24. After traversing through the cumulus layer, sperm reach the oocyte's zona pellucida and bind to it. EX2103, FIG. 3. Once bound, sperm complete the acrosome reaction, which triggers the release of soluble enzymes (*e.g.*, PH20) from inside the sperm's acrosome, such that PH20 hydrolyzes the extracellular matrix in the cumulus layer immediately surrounding the bound sperm and in the zona pellucida pores. EX2105, E59. This helps sperm penetrate the cumulus layer and zona pellucida to reach the oocyte's plasma membrane where fertilization (sperm-oocyte fusion) occurs. EX2105, E59. I have reproduced below Figure 3 from Toller 2012 showing these various stages along a sperm's passage through female reproductive tract in primates.



EX2103, FIG. 3.

25. By December 28, 2012, several agents that disable β -defensin DEFB126 protection on primate sperm were known in the art. These agents either remove β -defensin DEFB126 from the sperm surface similar to capacitation events

(*e.g.*, caffeine and dibutyryl cAMP; bicarbonate and glucose), or they remove sialic acid linked to β -defensin DEFB126 (*e.g.*, sialidase)—in both instances, exposing the sperm surface proteins (including PH20). EX2112, 126 (discussing caffeine and cAMP); EX2110, 433-434, 437-438 (discussing cAMP and caffeine, or bicarbonate and glucose); EX2111, 1249 (discussing sialidase); EX2103, 368 (discussing treating sperm with neuraminidase), 369 (discussing bicarbonate and glucose).

26. For example, elevated bicarbonate and lowered glucose was known to mimic capacitation events and facilitate removal of β -defensin DEFB126 to expose sperm surface proteins including PH20. EX2110, 433-434, 438 (“[A]t the time of ovulation, conditions of pH, HCO₃⁻, and glucose in the oviductal lumen are sufficient to trigger the release of sperm from [binding to the] epithelium in a fully capacitated state.”); EX2103, 369 (“The bicarbonate and glucose composition of primate oviductal fluid at the time of ovulation is sufficient to trigger the release of DEFB126 from macaque sperm.”).

27. Sialidase was known to digest sialic acid linked to β -defensin DEFB126 to expose sperm surface proteins, including PH20, without removing β -defensin DEFB126 from the sperm surface. EX2111, Abstract (“Sperm treated with neuraminidase to remove sialic acid on DEFB126 . . . were shown to still possess DEFB126, but lacked the sialic acid component of the glycoprotein.”),

1249 (“[W]hen DEFB126 was exposed to a sialidase it lost its cloaking ability.”); EX2109, 410 (“Removal of terminal sialic acid residues with NMase [*i.e.*, sialidase] also removes immunoprotection of sperm surface proteins, presumably exposing receptors that enable sperm to recognize and attach to the zona pellucida.”); EX2112, 122.

28. Once sperm surface proteins, such as PH20, are unmasked upon removal of β -defensin DEFB126 immunoprotection, antibodies against these proteins can bind to them on the sperm surface. EX2111, 1248 (“Sperm that were fully capacitated before exposure to the antibodies showed evidence of strong antibody recognition of all sperm, indicating that epitopes were exposed for antibody recognition following DEFB126 release.”); EX2171, 336. Sialidase treatment of sperm, which exposes proteins like PH20, also prevents sperm from penetrating cervical mucus because of the removal of the negative charge on the sperm surface. EX2109, 407; EX2103, 367 (“Treatment of sperm with neuraminidase, which removes terminal sialic acid groups, eliminates most of the negative charge from DEFB126 and therefore reduces the surface charge of sperm. Neuraminidase treatment dramatically inhibits sperm mucus penetration *in vitro*, comparable in magnitude to removal of DEFB126 or treatment of sperm with anti-DEFB126 antibodies.”).

VII. A POSA WOULD HAVE EXPECTED THAT MODIFIED PH20 POLYPEPTIDES WOULD BE USEFUL AS CONTRACEPTIVE VACCINES IN FEMALE MAMMALS

29. By December 28, 2012, due to its role in mammalian fertilization, PH20 was a known target for contraception, and POSAs considered PH20 polypeptide vaccines for contraception in mammals for the reasons explained below. *See, e.g.*, EX2114, Abstract, 8.

30. In light of Dr. Moon's declaration (EX2074), I have been asked to opine on whether, by December 28, 2012, POSAs would have expected any of the modified PH20 polypeptides (defined in ¶12) to be useful as contraceptive vaccines in female mammals, such as human, chimpanzee, Cynomolgus monkey, Rhesus monkey, marmoset, orangutan, gibbon, cow, mouse, rat, rabbit, guinea pig, and red fox.

31. PH20 polypeptides with any of SEQ ID NOs: 3, 7, and 32-66 are at least 430 amino acids long. *See* Appendix A; *see also* EX2074, ¶¶42, 50. Thus, POSAs would have expected that the modified PH20 polypeptides would display multiple epitopes to the host immune system and stimulate anti-PH20 polyclonal antibodies (*i.e.*, a collection of different antibodies) against these different epitopes⁵. EX2100; EX2172; *see also* EX2074, ¶¶20-23, 42-43, 50-55, 64. As Dr.

⁵ An epitope on an antigen (*e.g.*, a polypeptide) is a portion of an antigen that physically interacts with an antibody.

Moon explains, POSAs would have expected the polyclonal antibodies generated against any of the modified PH20 polypeptides to bind to the PH20 polypeptide of sperm in the reproductive tract of the female mammal. EX2074, ¶¶14-15, 32-59.

32. POSAs would have known that antibodies that bind to sperm (anti-sperm antibodies) caused infertility. *See, e.g.*, EX2116, Abstract (“[B]ecause these antibodies [that bind to sperm antigens] can induce infertility they have the potential to be developed for contraceptive purposes in humans and also for the control of feral animal populations.”); EX2114, 3 (“The rationale and feasibility of using sperm-specific proteins as immunocontraceptive targets derives from the well documented antifertility effect of naturally occurring anti-sperm antibodies in infertile couples.”). Thus, POSAs would have known that the binding of antibodies to sperm PH20 polypeptide in the female reproductive tract would cause contraception irrespective of where the antibodies bind on the PH20 polypeptides.

33. POSAs would have known that the binding of anti-PH20 antibodies to epitopes of PH20 polypeptide on the sperm surface would prevent sperm from fertilizing the oocyte by, *e.g.*, inhibiting sperm motility, inducing sperm agglutination, reducing penetration of cervical mucus by sperm, interfering with sperm capacitation or the acrosome reaction, or stimulating sperm lysis via the complement pathway. EX2114, 3, 18-19; EX2117, Abstract; EX2116, 172, 173. For example, Frayne 1999 discloses that “the detrimental effect of [anti-sperm]

antibodies on fertility is primarily caused by their ability to trap, or agglutinate, sperm in semen and cervical mucus.” EX2114, 3; *see also* 17 (stating that “an alternative approach [to targeting gamete interaction] may be to generate antibodies against abundant sperm-specific antigens. This may then lead to sperm agglutination, thereby preventing their progression through the female tract”). Similarly, Chamley 2007 discloses that the “[h]igh levels of ASA [(anti-sperm antibodies)] have been shown to block penetration of cervical mucus by highly motile sperm and also to significantly reduce fertilization of human oocytes.” EX2116, 172; *see also* EX2116, 173 (“The ability of ASA to disrupt normal interactions of sperm with the cervical mucus and inhibit sperm penetration into cervical mucus has been described in many studies.”), 174 (discussing that anti-sperm antibodies can adversely alter capacitation and the acrosome reaction), 174-175 (discussing that anti-sperm antibodies bound to a sperm surface can stimulate the complement pathway that causes sperm lysis). Kremer 1992 discloses that “[a]ntisperm IgA on spermatozoa or in cervical mucus can severely inhibit sperm penetration of cervical mucus and migration through it” and that the “[d]isturbance of the sperm-cervical mucus interaction” “leads to reduced fertility.” EX2117, Abstract; *see also* EX2117, 784 (“Sperm penetration into cervical mucus and subsequent migration can be severely inhibited by antisperm IgA on the spermatozoa or, in rare cases, in cervical mucus.”).

34. POSAs would have further known that the binding of anti-PH20 antibodies to epitopes of sperm PH20 polypeptide in the female reproductive tract would prevent PH20's hyaluronidase activity by allosteric effects irrespective of where the antibodies bound on PH20 polypeptides. For example, antibodies were known to inhibit protease activity through mechanisms such as conformational changes in enzymes or by prevention of substrate access to the active site, without necessarily binding to the catalytic site. EX2120, 1996, 1998; EX2121, 182. Thus, POSAs would have known that the binding of anti-PH20 antibodies generated in response to any of the modified PH20 polypeptides to sperm PH20 polypeptide in the female reproductive tract would prevent fertilization irrespective of where the antibodies bind on PH20 polypeptides.

35. In fact, by December 28, 2012, PH20 polypeptide vaccines had been successfully used for contraception in female guinea pigs. *See, e.g.*, EX2119; EX1022; EX2010; EX1023. In *in vitro* studies, anti-PH20 antibodies inhibited sperm-oocyte binding, reduced PH20's hyaluronidase activity, and inhibited fertilization. EX2172, 742; EX2173, 359. In *in vivo* studies, female guinea pigs were less fertile when immunized with guinea pig PH20 polypeptide. *See, e.g.*, EX2010. For example, Primakoff 1988 (which published in the prestigious, peer-reviewed journal *Nature*) reports a study showing that “100% effective contraception was obtained in male and female guinea pigs immunized with PH-

20” polypeptide via subcutaneous or intramuscular injection and that the “contraceptive effect was long-lasting and reversible.” EX2010, Abstract (emphasis added). Chan 1999 uses the anti-PH20 serum generated in female guinea pigs that were rendered infertile in response to guinea pig PH20 polypeptide vaccine and shows that the antibodies bind to live guinea pig sperm (unlike the serum in control guinea pigs who remained fertile). EX2120, 1997-1998, FIG. 3.

36. Moreover, by December 28, 2012, POSAs would have known that “[s]uccessful immunocontraception using sperm antigens is dependent on achieving sufficient sperm-specific antibody in the reproductive ducts to prevent fertilization.” EX1020, Abstract; EX2114, 14 (disclosing that “although systemic immunoglobulins may contribute to antibody levels in the female reproductive tract, effective immunocontraception directed against sperm-specific antigens [] necessitate that regimes induce efficient local immune responses in the reproductive tract, rather than simply generating high levels of circulating antibodies”). Thus, to improve PH20 vaccine’s contraceptive effect in mammals, POSAs would have selected a route known to elicit a strong antibody response in the female reproductive tract.

37. By December 28, 2012, POSAs would have selected a mucosal route for PH20 polypeptide vaccines, particularly the intranasal route that was known to

elicit a stronger antibody response in the female reproductive tract compared to the other routes. *See, e.g.*, EX1020, Abstract, 181; EX2114, 16; EX2122, Abstract; *see also* EX2074, ¶¶24-28. POSAs would have known that “a number of studies [had] revealed that . . . *intranasal immunisation yields by far the best antibody response in reproductive fluids*[,] significantly *better* than those achieved by oral, vaginal, rectal or indeed systemic immunization.”⁶ EX2114, 16 (emphasis added).

Mestecky 1999 supports this understanding, stating that “intranasal immunization of various species, including humans, was efficient at inducing antigen-specific antibody responses in the female genital tract.” EX2122, Abstract. Similarly, Frayne 1999 discloses that “nasal immunisation may warrant particular consideration as an effective and acceptable approach to human immunecontraception.” EX2114, 16, 22. And Pomeroy 2002 after observing failed contraception in rabbits using a subcutaneous route—which triggered in the female reproductive tract “less than 0.2% of [the antibody] levels induced in plasma”—recommends “mucosal immunization strategies” for PH20 vaccines. EX1020, Abstract, 181; *see also* EX2114, 17 (disclosing that in macaque monkeys and mice, only “up to 27%” of the antibodies in the oviductal fluids were found to be derived

⁶ Systemic immunization is the immunization that triggers an immune response throughout the body and not just at the administration site. This is achieved through, *e.g.*, intramuscular, intravenous, or subcutaneous injection.

from serum after systemic immunization). Thus, POSAs would have selected a mucosal route, particularly an intranasal route, for administration of PH20 polypeptides for contraception. *See also* EX2074, ¶¶24-28, 46, 58.

38. To further boost anti-PH20 antibodies in the female reproductive tract in response to PH20 polypeptide vaccines, POSAs would have selected known, routine techniques, such as a potent mucosal adjuvant or one or more booster doses after the initial vaccine dose. EX2114, 18-19; *see also* EX2074, ¶¶29-31, 46, 58. For example, subunit B of cholera toxin (lacking toxicity) was a known “effective adjuvant when used for intranasal immunisation.” EX2114, 18. Similarly, POSAs often selected booster doses for administration after the initial vaccine dose for further improving an antibody response against the administered antigen. EX2146, Abstract; *See also* EX2074, ¶¶30-31, 46, 58.

39. Optionally, by December 28, 2012, to further improve the contraceptive effect of the PH20 polypeptide vaccine, POSAs would have selected known systems to deliver just before sex in women vaccinated with any of the modified PH20 polypeptides an agent that removes β -defensin DEFB126 protection from the sperm surface and exposes the surface PH20 polypeptide on sperm to the anti-PH20 antibodies generated in response to the PH20 vaccine. One such agent is sialidase (neuraminidase), an enzyme that removes sialic acid linked to β -defensin DEFB126 to expose PH20 polypeptide (and other polypeptides) on

the sperm surface. EX2111, 1250; *see also* Section VI.B. POSAs, for example, would have selected intranasal route to vaccinate human females with any of the modified PH20 polypeptides to stimulate anti-PH20 polyclonal antibodies in the reproductive tract and would have selected well-known, routine systems, such as gel, film, or ring, to deliver into the vaginal cavity sialidase before sex. EX2127, Abstract, 4; EX2128, Abstract, 308, 309; EX2129, 344.

40. By December 28, 2012, systems such as “solutions, suppositories, gels, foams ... [had] been used as vaginal formulations,” as well as “vaginal ring” and “bioadhesive drug delivery systems” had been used for “vaginal delivery of different therapeutic agents,” such as relaxin, estradiol, and insulin. EX2128, 304-305; *see also* EX2074, ¶61. For example, “[v]aginal rings [were] used for contraceptive and hormone replacement therapy,” such as commercially available NuvaRing[®] and Femring[®]. EX2128, 308. And, a “bioadhesive [] gel, Replens[®], [was] available in the market, which is used to retain moisture and lubricate vagina.” EX2128, 309. Thus, POSAs would have selected well-known, routine systems to successfully deliver sialidase into the vaginal cavity of female humans by December 28, 2012.

41. POSAs would have expected sialidase delivered into the human vaginal cavity to be active in the reproductive tract. POSAs would have known that the pH of the human vagina is typically 3.8-4.2 (EX2130, 313) and that the pH is

elevated to 7.2 during intercourse when semen is present to buffer the pH to protect sperm from the vagina's acidic conditions (EX2131, 24). POSAs would have known that the optimum pH for sialidase is typically around pH 5 and would have expected sialidase to retain activity at the vagina's 3.8 to 7.2. EX2133, Abstract (stating that the "cervical mucus from pregnant and nonpregnant women had significant sialidase activity" at pH 4.2 (typical pH of the vagina and cervix) and this endogenous "[s]ialidase activity in cervical mucus of healthy women reaches a maximum in the ovulatory phase"), 1214 (stating that "[a]n active [sialidase] enzyme with an optimum pH around 4.2" was found in vaginal and cervical mucus of women, "with a peak of activity in ovulatory phase"); EX2132, 495 ("[S]ialidase in vaginal fluid has a maximal hydrolytic activity at pH 5."); EX2112, 121 (showing that sialidase removed β -defensin DEFB126 from macaque (a primate, similar to humans) sperm in PBS (phosphate-buffered saline) known to have pH \sim 7.2).

42. Thus, POSAs would have expected that sialidase delivered into the human female's vaginal cavity prior to intercourse would unmask surface PH20 polypeptide on the sperm passing through the vaginal cavity (at the elevated pH following semen deposition) and that the anti-PH20 antibodies generated in response to the modified PH20 polypeptide vaccines would bind to the exposed PH20 on the sperm surface in the female reproductive tract. As I explain above in

¶¶32-35, this binding of polyclonal antibodies to the various epitopes of the sperm PH20 polypeptide in the female reproductive tract would agglutinate sperm, impede mucus penetration, and/or induce a complement response to kill sperm. Furthermore, antibody binding to PH20 would prevent PH20's hyaluronidase activity by allosteric inhibition, or if bound to the enzymatically active site, directly inhibiting hyaluronidase activity—thus preventing sperm from moving forward and reaching the upper reproductive tract for fertilization. And if sperm reached the upper reproductive tract, they would be unable to penetrate the oocyte's cumulus layer or the extracellular matrix in the zona pellucida to fertilize the oocyte because the polyclonal antibodies present in the upper tract would bind to the various epitopes on sperm's PH20 polypeptide and prevent PH20's signaling function and hyaluronidase activity by allosteric inhibition or by binding to the enzymatically active site.

43. In sum, by December 28, 2012, POSAs would have expected the polyclonal antibodies generated in female mammals (including humans) in response to any of the modified PH20 polypeptides, as defined in ¶12, (appropriately administered as vaccines) would cause contraception by binding to sperm PH20 polypeptide in the female reproductive tract. Thus, a POSA would have expected that any of the modified PH20 polypeptides with optimized administration to be useful as contraceptive vaccines in female mammals by

December 28, 2012.

VIII. DR. HECHT'S CITED PUBLICATIONS WOULD NOT HAVE UNDERMINED A POSA'S EXPECTATION THAT THE MODIFIED PH20 POLYPEPTIDES WOULD BE USEFUL AS CONTRACEPTIVE VACCINES IN MAMMALS

44. I have been asked to opine on whether the following publications that Dr. Hecht discusses in his declaration (EX1003) would have altered a POSA's expectation regarding the contraceptive effect of any of the modified PH20 polypeptides (as defined in ¶12) as vaccines in mammals: Rosengren 2015 (EX1061); Rosengren 2018 (EX1024); Hardy 2004 (EX1019); Pomeroy 2002 (EX1020); and Baba 2002 (EX1021). EX1003, ¶¶110-112. Dr. Hecht asserts that these studies "suggest that PH20 does not appear to induce formation of antibodies that affect fertility in many rodents or in humans." EX1003, ¶112. I disagree with Dr. Hecht. As I explain below, by December 28, 2012, none of these studies would have undermined a POSA's expectation of successfully using any of the modified PH20 polypeptides as contraceptive vaccines in female mammals, as also discussed in these publications.

45. *Initially*, both Rosengren 2015 (EX1061) and Rosengren 2018 (EX1024) published after 2012, and thus POSAs would not have considered them when contemplating using PH20 polypeptides as contraceptive vaccines in humans (or other mammals) by December 28, 2012. *Moreover*, neither of these studies investigates PH20 polypeptide's role as a contraceptive vaccine, and for this

additional reason, POSAs would not have considered them for PH20 polypeptide contraceptive vaccines in humans (or other mammals). For example, Rosengren 2015 “summarizes rHuPH20 [(i.e., recombinant human PH20)] immunogenicity findings from clinical trials where rHuPH20 was co-administered with SC human immunoglobulin, trastuzumab, rituximab, or insulin” “to facilitate *dispersion* of subcutaneously delivered fluids and drugs.” EX1061, Abstract (emphasis added). Thus, Rosengren 2015 discusses immunogenicity of PH20 polypeptides administered as a *spreading or dispersion agents*, and not as a vaccine that would have included an adjuvant to stimulate the host immune response against PH20 polypeptides.

46. Rosengren 2018 similarly does not discuss PH20 polypeptide contraceptive vaccines (which would have included PH20 polypeptides with an adjuvant) to stimulate the host immune response against PH20 polypeptides. Instead, Rosengren 2018 reports on the “prevalence of rHuPH20-reactive antibodies in the general [human] population and the potential associations with fertility and autoimmunity diseases” by assessing “blood sample[s] collect[ed]” from “healthy subjects . . . without prior exposure to rHuPH20.” EX1024, Abstract, 84. Rosengren 2018’s conclusion that “no evidence of negative effects on fertility could be determined in rHuPH20-reactive antibody-positive subjects of either sex” simply confirms prior-art knowledge that anti-PH20 antibodies in

“blood sample[s]” do not have a strong correlation with infertility or contraceptive effect. EX1024, 84, 87; EX2114, 14 (stating that “effective immunocontraception directed against sperm-specific antigens [] necessitate that regimes induce efficient local immune responses in the reproductive tract, rather than simply generating high levels of circulating antibodies”); EX2134. In fact, even in blood samples, Rosengren 2018 reports weak anti-PH20 antibody titers in the subjects, with no assessment of anti-PH20 antibody titers in the reproductive tract. EX1024, 85, 87. Thus, neither Rosengren 2015 nor Rosengren 2018 would have undermined POSAs’ expectation that any of the modified PH20 polypeptides would be useful as contraceptive vaccines in female mammals, including humans.

47. None of Hardy 2004 (EX1019), Pomeroy 2002 (EX1020), and Baba 2002 (EX1021) would have also undermined a POSA’s expectation to use any of the PH20 polypeptides as contraceptive vaccines in female mammals. Rather, these references re-emphasize the contraceptive success with the PH20 polypeptide vaccines in guinea pigs. For example, Hardy 2004 acknowledges that guinea pig PH20 (“gpPH20”) was “the most promising” sperm protein for a contraceptive vaccine “when tested in a guinea pig model,” with a “strong contraceptive effect reported for gpPH20 in guinea pigs.” EX1019, Abstract, 332. Pomeroy 2002 similarly acknowledges that “[i]mmunization of both male and female guinea-pigs with the sperm antigen rPH-20 has been shown to elicit infertility.” EX1020,

Abstract, 175. Thus, after reviewing these references, POSAs would have known that PH20 polypeptides would be useful as contraceptive vaccines in guinea pigs.

48. These studies also acknowledge the limitations of their experimental design and recommend modifications for successful contraception with PH20 polypeptide vaccines. For example, both Pomeroy 2002 and Hardy 2004⁷ acknowledge that their immunization strategies failed to generate high enough antibody titers in the reproductive tract sufficient to mediate contraception. EX1019; EX1020.

49. Pomeroy 2002 reports that although rabbits receiving PH20 polypeptides via the subcutaneous route “induced high levels of specific [anti-PH20] IgG [antibodies] in plasma,” the “plasma-IgG entry into the FRT [(female reproductive tract)] is [] restricted,” with the “luminal fluid from the vagina, uterus and oviduct contain[ing] only 0.016, 0.078 and 0.072%, respectively, of plasma IgG levels.” EX1020, 178, 180 (“Entry of anti-rPH-20 IgG into the female reproductive ducts was also restricted with levels of rPH-20-specific IgG in free-flow fluid from the vagina, uterus and oviduct containing between 0.016 and 0.072% of plasma IgG levels.”) (“In the studies presented here we have clearly shown that entry of plasma IgG into rabbit reproductive ducts, both male and

⁷ Baba 2002 (EX1021) discloses a study that does not administer PH20 polypeptides to an animal.

female, is restricted to less than 0.2% of plasma levels.”), Abstract (“The IgG antibody entry into the reproductive ducts of both male and female rabbits is restricted to less than 0.2% of levels induced in plasma following subcutaneous immunization.”). Accordingly, Pomeroy 2002 concludes that “[t]his finding raises doubts about the suitability of rPH-20 to induce immunocontraception in rabbits using strategies optimized for induction of a serum antibody response” and recommends “mucosal administration strategies.” EX1020, Abstract, 181 (“Our data suggest that, in the rabbit at least, immunization with reproductive antigens expressed only in the reproductive tract using routes which induce predominantly plasma IgG are unlikely to result in reduced fertility because antibody cannot access the reproductive ducts.”).

50. Hardy 2004 similarly details that “there may have been insufficient mPH20 antibodies generated in the reproductive tracts to cause infertility in mice using the [intraperitoneal] immunization regimes of the present study,” similar to Pomeroy 2002 where “the inability to cause sterility was directly attributed to insufficient PH20 antibodies in the male and female reproductive tracts” of rabbits. EX1019, 332.

51. POSAs would have known, as Hardy 2004 and Pomeroy 2002 also acknowledge, that the poor contraception seen after administering PH20 polypeptides via non-mucosal routes in Hardy 2004 (intraperitoneal route in mice)

and Pomeroy 2002 (subcutaneous route in rabbits) reflect the reproductive biology of mice and rabbits. For example, Hardy 2004 discloses that unlike other “species including guinea pig [], man [] and rabbit []” where “PH20 appears to be expressed in the male reproductive tract only,” in mice “mPH20 (SPAM-1) expression is more widespread” and this “more widespread expression of mPH20 in mice could also affect the ability to break tolerance to PH20 by active immunization in this species.” EX1019, 333. In other words, Hardy 2004 explains that because, unlike in guinea pigs, PH20 expression in mice is not limited to the male reproductive tract, female mice have a high tolerance to PH20 self-antigen and the non-mucosal administration route used (intraperitoneal) did not trigger a strong immune response to PH20 polypeptide vaccines to induce sufficient anti-PH20 antibodies in the female reproductive tract. Further, Hardy 2002 acknowledges that, unlike the “outbred” guinea pigs used in Primakoff 1988 (EX2010) and Tung 1997 (EX1023), its study uses “inbred” mice, which “did not produce [the appropriate PH20-specific immune] responses” required for contraceptive effect. EX1019, 332.

52. Pomeroy 2002 similarly explains that “[i]n the guinea-pig[,] PH20 is found predominantly on the post-acrosomal head region whilst in the rabbit it is found mainly in the acrosomal contents and the subacrosomal/perinuclear material,” and as a result, the low levels of anti-PH20 antibodies in the female reproductive tract (“less than 0.2% of plasma IgG levels”) after its non-mucosal

PH20 vaccination (subcutaneous) is “unlikely to be sufficient to prevent fertilization, particularly as sperm spend only a few minutes in the vagina after mating” in rabbits. EX1020, 181.

53. Moreover, POSAs would have known that sperm capacitation in guinea pigs may occur lower in the female reproductive tract compared to other mammals and thus antigens on sperm surface, including PH20, would be exposed for a longer duration in a female guinea pig’s reproductive tract than in other mammals. EX2115, Abstract (showing that “guinea pig spermatozoa are potentially capable of an immediate acrosome reaction and activation upon leaving the epididymis”).

54. Finally, although Baba 2002 reports that male “mice carrying a null mutation in the *PH-20* gene” “were still fertile,” with sperm “possess[ing] a reduced ability to disperse cumulus cells from the cumulus mass, resulting in delayed fertilization,” Baba 2002 would not have undermined POSAs’ expectation that any of the modified PH20 polypeptides would be useful as contraceptive vaccines. EX1021, Abstract. POSAs would have known that Baba 2002 does not address the effect of anti-PH20 antibodies against sperm of normal mice that retain a wild-type PH20 gene. POSAs would have known that in normal mice PH20 would be expressed on the sperm surface. POSAs, therefore, would have expected that the polyclonal antibodies generated in female mice in response to any of the

modified PH20 polypeptides would bind to PH20 polypeptide present on the surface of sperm from normal mice. *See also* EX2074, ¶¶48-59. As explained above in ¶¶32-35, POSAs would have known that this binding would prevent sperm from moving forward in the female reproductive tract by mechanisms discussed above (*e.g.*, by agglutinating sperm, impeding mucus penetration, and/or inducing a complement response to kill sperm). *See* Section VII. Thus, even though Baba 2002 concludes that “PH-20 is not essential for fertilization, at least in the mouse,” POSAs would have known that any of the modified PH20 polypeptides would generate polyclonal antibodies in the female mice that would bind to sperm PH20 polypeptide in the reproductive tract of these females and cause contraception. EX1021, Abstract.

55. By December 28, 2012, Hardy 2004 (EX1019), Pomeroy 2002 (EX1020), and Baba 2002 (EX1021) would have not undermined POSAs’ expectation of contraception using any of the modified PH20 polypeptides as a vaccine in female mammals, because POSAs would have optimized such vaccines by applying one or more of the following well-known, routine approaches to generate a strong antibody response in the female reproductive tract: mucosal (*e.g.*, intranasal) administration of the modified PH20 polypeptides; potent mucosal adjuvants; booster doses; and vaginally administering agents that remove β -defensin DEFB126 protection from sperm (*e.g.*, sialidase) in women vaccinated

with the modified PH20 polypeptide. *See* Section VII.

56. In sum, for the reasons I explain above and in Section VII, I disagree with Dr. Hecht that any of these studies “suggest[s] that PH20 does not appear to induce formation of antibodies that affect fertility in many rodents or in humans.” EX1003, ¶112. Instead, in my opinion, POSAs would have expected any of the modified PH20 polypeptides with optimized administration to be useful as contraceptive vaccines in female mammals, including humans, by December 28, 2012.

IX. A POSA WOULD HAVE EXPECTED ANTI-PH20 ANTIBODIES ADMINISTERED INTO THE FEMALE VAGINAL CAVITY TO CAUSE CONTRACEPTION

57. POSAs would have selected systems to deliver monoclonal antibodies generated against the modified PH20 polypeptides into the vaginal cavity of human females. By December 28, 2012, antibodies were considered as a therapeutic with at least 19 monoclonal antibodies in clinical use. EX2135, Abstract. By December 2012, antibodies had been successfully delivered through vaginal route, *e.g.*, via gels, films, and rings. EX2127, Abstract, 4; EX2128, Abstract, 308, 309; EX2129, 344. “[S]olutions, suppositories, gels, foams ... [had] been used as vaginal formulations” along with “vaginal ring” and “bioadhesive drug delivery system” for “vaginal delivery of different therapeutic agents,” such as monoclonal antibodies. EX2128, 304-305, 309; EX2127, Abstract, 4. For example, Morrow

2011 discloses using vaginal rings to deliver “monoclonal antibody” against HIV.

EX2127, Abstract. Thus, POSAs would have selected well-known, routine systems for successful delivery of anti-PH20 monoclonal antibodies into human female’s vaginal cavity. *See also* EX2074, ¶¶16, 61-63, 65.

58. POSAs would have additionally expected the anti-PH20 antibodies delivered in the vaginal cavity to be active, because antibodies were known to be stable and active at a broad pH range, including the pH of about 4-7 found in the human vagina. EX2130, 313 (stating that the typical pH of human vagina is 3.8-4.2); EX2131, 24 (stating that the pH of human vagina is elevated to 7.2 during intercourse when semen is present); EX2136, 526 (disclosing that the optimum pH for complement recognition of antibodies on cells, causing cell lysis is pH 6.4 and that IgG can exhibit the highest affinity binding between pH 6-6.5). POSAs would have known that anti-PH20 monoclonal antibodies when delivered into the vaginal cavity would bind to sperm PH20 polypeptide when sperm glycocalyx was removed or modified (*e.g.*, by sialidase treatment), and for the reasons explained above in Section VII, the antibodies upon binding to sperm would prevent sperm from moving forward in the reproductive tract.

59. POSAs would have used routine techniques, such as hybridoma technology, to obtain monoclonal antibodies. EX2118, 418; *see also* EX2074, ¶60. To improve the contraceptive effect of the delivered antibodies, POSAs would

have selected well-known, routine systems to deliver a combination of different monoclonal antibodies that bind to PH20 polypeptide of sperm, each binding to different epitopes on the sperm PH20 polypeptide, similar to the polyclonal antibodies generated in response to modified PH20 polypeptide vaccines. *See also* EX2074, ¶62.

60. Optionally, to further improve the contraceptive effect of the delivered monoclonal antibodies, for the reasons explained in Section VII above, POSAs would have used well-known agents that remove β -defensin DEFB126 protection and expose PH20 polypeptide sperm (*e.g.*, sialidase). For example, POSAs would have selected well-known, routine systems for co-delivery of PH20 antibodies and sialidase in the vaginal cavity using known delivery systems, such as vaginal ring. EX2126, 388 (stating that “[p]reformed monospecific antibodies to sperm antigens may also be combined in intravaginal sperm-specific spermicides for immunocontraceptive purposes”); *see* Section VII. As explained above in Section VII, POSAs would have expected sialidase delivered in the human vaginal cavity to be active at the vagina’s typical pH of 3.8-4.2 and at its elevated pH of 7.2 during intercourse. Thus, as explained in Section VII, POSAs would have expected sialidase delivered in the vaginal cavity would unmask PH20 polypeptides on the surface of the sperm passing through the vaginal cavity and the anti-PH20 antibodies would bind to the exposed PH20 and prevent sperm from moving

forward in the female reproductive tract towards the oocyte.

61. In sum, POSAs would have expected contraceptive effects when using anti-PH20 antibodies generated in response to any of the modified PH20 polypeptides when administered into the vaginal cavity of human females using known formulations and techniques.

X. CONCLUSION

62. As I explain in Section VII, by December 28, 2012, POSAs would have expected that any of the modified PH20 polypeptides (as defined in ¶12) would be useful as contraceptive vaccines in female mammals (including humans). POSAs would have expected that polyclonal antibodies generated in female mammals (including humans) in response to any of the modified PH20 polypeptides would bind to the sperm PH20 polypeptide in the female reproductive tract, leading to contraception.

63. As I explain in Section VIII, none of the publications that Merck's expert Dr. Hecht cites in ¶¶110-112 of his declaration would have undermined POSAs' expectation to use any of the modified PH20 polypeptides (as defined in ¶12) as contraceptive vaccines in female mammals by December 28, 2012.

64. As I explain in Section IX, POSAs would have expected that a monoclonal antibody(ies) against any of the modified PH20 polypeptides when delivered into the vaginal cavity would cause contraception in women.

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 26th day of December, 2025.



Gary N. Cherr, Ph.D.

Cherr Declaration Appendix A

I. PH20 polypeptide sequences

SEQ ID NO: 3 (mature human PH20 36-482)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHL D KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEF EKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDL SWLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTL SIM RSMKSCLLLD NYMETILNPY IINVT LA AKM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADV KDTDAV 420

DVCIADGVCI DAFLKPPMET EEPQIFY 447

SEQ ID NO: 7 (mature, full-length human PH20)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHL D KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEF EKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDL SWLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

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IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAKM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI DAFLKPPMET EEPQIFYNAS PSTLSATMFI VSILFLIIS VASL 474

SEQ ID NO: 32 (mature human PH20 36-465)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHL D KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDL SWLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAKM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI 430

SEQ ID NO: 33 (mature human PH20 36-466)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHL D KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

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WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSQLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAKM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI D 431

SEQ ID NO: 34 (mature human PH20 36-467)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLK KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSQLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAKM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI DA 432

SEQ ID NO: 35 (mature human PH20 36-468)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

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LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSQLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTLSIM RSMKSCLLD NYMETILNPY IINVTLAAKM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI DAF 433

SEQ ID NO: 36 (mature human PH20 36-469)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSQLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTLSIM RSMKSCLLD NYMETILNPY IINVTLAAKM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI DAFL 434

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SEQ ID NO: 37 (mature human PH20 36-470)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHL D KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDL SWLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTL SIM RSMKSCLLLD NYMETILNPY IINVT LA AKM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADV KDTDAV 420

DVCIADGVCI DAFLK 435

SEQ ID NO: 38 (mature human PH20 36-471)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHL D KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDL SWLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTL SIM RSMKSCLLLD NYMETILNPY IINVT LA AKM CSQVLCQEQG
VCIRKNWNSS 360

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DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI DAFLKP 436

SEQ ID NO: 39 (mature human 36-472)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLWLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAMK CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI DAFLKPP 437

SEQ ID NO: 40 (mature human 36-473)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLWLWNE STALYPSIYL
NTQQSPVAAT 240

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LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAKM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI DAFLKPPM 438

SEQ ID NO: 41 (mature human PH20 36-474)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKPGYN GSCFNVEIKR NDDLSQLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAKM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI DAFLKPPME 439

SEQ ID NO: 42 (mature human PH20 36-475)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

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RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSQLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAKM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI DAFLKPPMET 440

SEQ ID NO: 43 (mature human PH20 36-476)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLK KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSQLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAKM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI DAFLKPPMET E 441

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SEQ ID NO: 44 (mature human PH20 36-477)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHL D KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDL SWLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTL SIM RSMKSCLLD NYMETILNPY IINVT LA AKM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKD TDAV 420

DVCIADGVCI DAFLKPPMET EE 442

SEQ ID NO: 45 (mature human PH20 36-478)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHL D KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDL SWLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTL SIM RSMKSCLLD NYMETILNPY IINVT LA AKM CSQVLCQEQG
VCIRKNWNSS 360

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DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI DAFLKPPMET EEP 443

SEQ ID NO: 46 (mature human PH20 36-479)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLWLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAKM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI DAFLKPPMET EEPQ 444

SEQ ID NO: 47 (mature human PH20 36-480)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLWLWNE STALYPSIYL
NTQQSPVAAT 240

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LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAKM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI DAFLKPPMET EEPQI 445

SEQ ID NO: 48 (mature human PH20 36-481)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKPGYN GSCFNVEIKR NDDLSQLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAKM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI DAFLKPPMET EEPQIF 446

SEQ ID NO: 49 (mature human PH20 36-483)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

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RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSQLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI DAFLKPPMET EEPQIFYN 448

SEQ ID NO: 50 (mature human PH20 36-484)

LNFRAAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLK KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSQLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI DAFLKPPMET EEPQIFYNA 449

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SEQ ID NO: 51 (mature human PH20 36-485)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHL D KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKPGYN GSCFNVEIKR NDDL SWLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTL SIM RSMKSCLLD NYMETILNPY IINVT LA AKM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKD TDAV 420

DVCIADG VCI DAFLKPPMET EEPQIFYNAS 450

SEQ ID NO: 52 (mature human PH20 36-486)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHL D KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKPGYN GSCFNVEIKR NDDL SWLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTL SIM RSMKSCLLD NYMETILNPY IINVT LA AKM CSQVLCQEQG
VCIRKNWNSS 360

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DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKDTDAV 420

DVCIADGVCI DAFLKPPMET EEPQIFYNAS P 451

SEQ ID NO: 53 (mature human PH20 36-487)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSQLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAKM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKDTDAV 420

DVCIADGVCI DAFLKPPMET EEPQIFYNAS PS 452

SEQ ID NO: 54 (mature human PH20 36-488)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSQLWNE STALYPSIYL
NTQQSPVAAT 240

Cherr Declaration Appendix A

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAKM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI DAFLKPPMET EEPQIFYNAS PST 453

SEQ ID NO: 55 (mature human PH20 36-489)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKPGYN GSCFNVEIKR NDDLSQLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAKM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI DAFLKPPMET EEPQIFYNAS PSTL 454

SEQ ID NO: 56 (mature human PH20 36-490)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

Cherr Declaration Appendix A

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSQLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAKM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI DAFLKPPMET EEPQIFYNAS PSTLS 455

SEQ ID NO: 57 (mature human PH20 36-491)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLK KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSQLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAKM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI DAFLKPPMET EEPQIFYNAS PSTLSA 456

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SEQ ID NO: 58 (mature human PH20 36-492)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHL D KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEF EKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDL SWLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTL SIM RSMKSCLLLD NYMETILNPY IINVT LA AKM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADV KDTDAV 420

DVCIADGVCI DAFLKPPMET EEPQIFYNAS PSTLSAT 457

SEQ ID NO: 59 (mature human PH20 36-493)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHL D KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEF EKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDL SWLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTL SIM RSMKSCLLLD NYMETILNPY IINVT LA AKM CSQVLCQEQG
VCIRKNWNSS 360

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DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI DAFLKPPMET EEPQIFYNAS PSTLSATM 458

SEQ ID NO: 60 (mature human PH20 36-494)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSQLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAKM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI DAFLKPPMET EEPQIFYNAS PSTLSATMF 459

SEQ ID NO: 61 (mature human PH20 36-495)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSQLWNE STALYPSIYL
NTQQSPVAAT 240

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LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAKM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI DAFLKPPMET EEPQIFYNAS PSTLSATMFI 460

SEQ ID NO: 62 (mature human PH20 36-496)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKPGYN GSCFNVEIKR NDDLSQLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAKM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI DAFLKPPMET EEPQIFYNAS PSTLSATMFI V 461

SEQ ID NO: 63 (mature human PH20 36-497)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

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RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSQLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAMK CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI DAFLKPPMET EEPQIFYNAS PSTLSATMFI VS 462

SEQ ID NO: 64 (mature human PH20 36-498)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLK KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSQLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAMK CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI DAFLKPPMET EEPQIFYNAS PSTLSATMFI VSI 463

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SEQ ID NO: 65 (mature human PH20 36-499)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHL D KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKPGYN GSCFNVEIKR NDDL SWLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTL SIM RSMKSCLLD NYMETILNPY IINVT LA AKM CSQVLCQEQG
VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADV KDTDAV 420

DVCIADGVCI DAFLKPPMET EEPQIFYNAS PSTLSATMFI VSIL 464

SEQ ID NO: 66 (mature human PH20 36-500)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTFIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHL D KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKPGYN GSCFNVEIKR NDDL SWLWNE STALYPSIYL
NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF
GETVALGASG 300

IVIWGTL SIM RSMKSCLLD NYMETILNPY IINVT LA AKM CSQVLCQEQG
VCIRKNWNSS 360

Cherr Declaration Appendix A

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE
KADVKTDAV 420

DVCIADGVCI DAFLKPPMET EEPQIFYNAS PSTLSATMFI VSILF 465

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