UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,
Petitioner

v.

HALOZYME, INC.,
Patent Owner

Case PGR2025-00042
U.S. Patent No. 12,037,618

DECLARATION OF JAMES J. MOON, PH.D. IN SUPPORT OF PATENT OWNER'S RESPONSE

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Halozyme EX2074
Merck v. Halozyme
PGR2025-00042

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I, James J. Moon, 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 $800 per hour.

3. I understand that this Declaration accompanies a Patent Owner's Response filed in a PGR involving U.S. Patent No. 12,037,618. 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, I also considered the viewpoint of a person of ordinary skill in the art, as defined below in Section V, as of December 28, 2012, in light of general knowledge in the art.

II. MY BACKGROUND AND QUALIFICATIONS

5. I am the Interim Chair and the J. G. Searle Professor (with tenure) in the Department of Pharmaceutical Sciences in the College of Pharmacy and a Professor in the Department of Chemical Engineering and Biomedical Engineering, all at the University of Michigan. I am also a Member of the

Graduate Program in Immunology, a Member of the Comprehensive Cancer Center, and a Core Member at the Biointerfaces Institute, all at the University of Michigan. I am the Co-Founder and Chief Scientific Officer of Saros Therapeutics, LLC, and of EVOQ Therapeutics, LLC.

6. I have over 20 years of experience in developing novel therapeutics at the interface of immunology, engineering, and pharmaceutical sciences. My research has focused on advancing vaccines and immunotherapies through the application of cutting-edge engineering technologies. In particular, my laboratory develops precision drug delivery systems designed to target lymphoid organs and activate the immune system. These approaches are applied to vaccines and immunotherapies against cancer, infectious diseases, and autoimmune disorders. Within this broad area of research, our recent work focuses on the engineering of nanoparticles and biomaterials that can effectively deliver peptides, proteins, and nucleic acids to the immune system and their development as the platform technologies for the next-generation vaccines and immunotherapies. I am currently a principal investigator on seven grants sponsored by the National Institutes of Health.

7. My *curriculum vitae* is submitted herewith as EX2075.

8. I graduated with a Bachelor's degree in Bioengineering from the University of California at Berkeley in 2002. I then received my Ph.D. in

Bioengineering at Rice University in 2008. My Ph.D. thesis topic was "Synthesis of Biomimetic Hydrogels for Neovascularization *in vivo*."

9. From 2008-2012, I was a postdoctoral fellow in the Department of Materials Science & Engineering and Biological Engineering at Massachusetts Institute of Technology/Howard Hughes Medical Institute.

10. After my postdoctoral fellowship, I became a Member at the Michigan Nanotechnology Institute for Medicine and Biological Sciences (2012-2020), and I served as the John Gideon Searle Assistant Professor in the Department of Pharmaceutical Sciences, College of Pharmacy and as an Assistant Professor in the Department of Biomedical Engineering, College of Engineering, both at the University of Michigan (2012-2018). Subsequently, I served as an Associate Professor in the Department of Biomedical Engineering, College of Engineering and the John Gideon Searle Associate Professor in the Department of Pharmaceutical Sciences, College of Pharmacy, both at the University of Michigan (2018-2021).

11. I have authored more than 135 peer-reviewed publications, the majority of which discuss immunotherapies against cancer, infectious pathogens, and autoimmune disorders. My publications include papers on oral immunotherapies, strategies for controlling immune responses, and novel drug delivery systems.

12. In addition, I have presented over 325 invited lectures or conference presentations regarding development of vaccine technologies and immunotherapies against cancer, autoimmune disease, and infectious pathogens. I have also supervised eleven completed Ph.D. theses and have taught graduate-level courses at the University of Michigan, Ann Arbor, in the area of pharmaceutical biotechnology, drug delivery technology, nanotechnology for drug delivery, and pharmaceutical design. I am a named inventor on 30 issued or pending patent applications on topics including compositions and methods for improving immunotherapies and vaccines, and lipid nanoparticle and polymer-based drug delivery systems.

13. In 2025, I was named the Distinguished Graduate Mentor Award in the College of Pharmacy at the University of Michigan and the Innovation Champion at the University of Michigan.

III. SUMMARY OF OPINIONS

14. I have been asked to consider whether a person of ordinary skill in the art ("POSA," defined in Section V) as of December 28, 2012, would have expected polyclonal antibodies generated in human females against any of the "modified PH20 polypeptides" to bind to the wild-type human PH20 polypeptide in vivo. Throughout, 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 32-66, and include a modification at position 309. I explain below in Section VII, that by December 28, 2012, a POSA would have expected that polyclonal antibodies generated in human females against any of the modified PH20 polypeptides would bind to the wild-type human PH20 polypeptide *in vivo*.

15. I have been asked to consider whether a POSA would have expected polyclonal antibodies generated in non-human female mammals against any of the modified PH20 polypeptides to bind to the wild-type PH20 polypeptide in vivo. As I explain below in Section VIII, by December 28, 2012, a POSA would have expected that polyclonal antibodies generated in female mammals against any of the modified PH20 polypeptides would bind to the wild-type PH20 polypeptide *in vivo*.

16. I have been asked to consider whether a POSA would have expected successful delivery of monoclonal antibodies to the vaginal cavity of human females. As I explain below in Section IX, by December 28, 2012, a POSA would have expected successful delivery of monoclonal antibodies to the vaginal cavity of human females to specifically target antigens in the female reproductive tract.

IV. LIST OF DOCUMENTS CONSIDERED

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

Exhibit No.	Description
2075	*Curriculum Vitae* of James J. Moon, Ph.D.
2122	Mestecky, J. et al., "Mucosal Immune System of the Human Genital Tract," *The Journal of Infectious Diseases*, 179(Suppl 3):S470-S474 (1999)
2135	Kim, S. et al., "Antibody Engineering for the Development of Therapeutic Antibodies," *Molecules and Cells*, 20(1):17-29 (2005)
2137	Lipman, N. et al., "Monoclonal Versus Polyclonal Antibodies: Distinguishing Characteristics, Applications, and Information Resources," *ILAR Journal*, 46(3):258-268 (2005)
2138	Rhee, J. et al., "Mucosal vaccine adjuvants update," *Clinical and Experimental Vaccine Research*, 1:50-63 (2012)
2139	Lycke, N., "Recent progress in mucosal vaccine development: potential and limitations," *Nature Review*, 12:592-605 (August 2012)
2140	Rudin, A. et al., "Differential Kinetics and Distribution of Antibodies in Serum and Nasal and Vaginal Secretions after Nasal and Oral Vaccination of Humans," *Infection and Immunity*, 66(7):3390-3396 (July 1998)
2141	Wu, H. et al., "Generation of Female Genital Tract Antibody Responses by Local or Central (Common) Mucosal Immunization," *Infection and Immunity*, 68(10):5539-5545 (October 2000)
2142	Russell, M., "Immunization for Protection of the Reproductive Tract: A Review," *American Journal of Reproductive Immunology*, 47:265-268 (2002)
2143	Uppada, S. et al., "Enhanced humoral and mucosal immune responses after intranasal immunization with chimeric multiple antigen peptide of LcrV antigen epitopes of Yersinia pestis coupled to palmitate in mice," *Vaccine*, 29:9352-9360 (2011)

Exhibit No.	Description
2145	Gallichan, W. et al., "Specific secretory immune responses in the female genital tract following intranasal immunization with a recombinant adenovirus expressing glycoprotein B of herpes simplex virus," *Vaccine*, 13(6):1589-1595 (1995)
2146	Johansson, E. et al., "Antibodies and Antibody-Secreting Cells in the Female Genital Tract after Vaginal or Intranasal Immunization with Cholera Toxin B Subunit or Conjugates," *Infection and Immunity*, 66(2):514-520 (February 1998)
2147	Bergquist, C. et al., "Intranasal Vaccination of Humans with Recombinant Cholera Toxin B Subunit Induces Systemic and Local Antibody Responses in the Upper Respiratory Tract and the Vagina," *Infection and Immunity*, 65(7):2676-2684 (July 1997)
2148	Neto, H. et al., "Efficacy and Safety of 1 and 2 Doses of Live Attenuated Influenza Vaccine in Vaccine-Naive Children," *The Pediatric Infectious Disease Journal*, 28(5):365-371 (May 2009)
2149	Rhorer, J. et al., "Efficacy of live attenuated influenza vaccine in children: A meta-analysis of nine randomized clinical trials," *Vaccine*, 27:1101-1110 (2009)
2150	Mielcarek, N., "Genital Antibody Responses in Mice after Intranasal Infection with an Attenuated Candidate Vector Strain of *Bordetella pertussis*," *Infection and Immunity*, 68(2):485-491 (February 2000)
2151	Houghton, A., "Immune recognition of self in immunity against cancer," *The Journal of Clinical Investigation*, 114(4):468-471 (August 2004)
2152	Wan, Y. et al., "Prepared and screened a modified TNF- α molecule as TNF-α autovaccine to treat LPS induced endotoxic shock and TNF-α induced cachexia in mouse," *Cellular Immunology*, 246:55-64 (2007)

Exhibit No.	Description
2153	Dieudé, M. et al., "Autoantibodies to heat shock protein 60 promote thrombus formation in a murine model of arterial thrombosis," *Journal of Thrombosis and Haemostasis*, 7:710-719 (2009)
2154	Oliver, A. et al., "Rat and Human Myelin Oligodendrocyte Glycoproteins Induce Experimental Autoimmune Encephalomyelitis by Different Mechanisms in C57BL/6 Mice1," *The Journal of Immunology*, 171(1):462-468 (2003)
2155	Trentham, D. et al. "Autoimmunity to Type II Collagen: An Experimental Model of Arthritis," *The Journal of Experimental Medicine*, 146:857-868 (1977)
2156	Courtenay, J. et al., "Immunisation against heterologous type II collagen induces arthritis in mice," *Nature*, 283:666-668 (1980)
2157	Tomita, M. et al., "Hybridoma technologies for antibody production," *Immunotherapy*, 3(3):371-380 (2011)
2158	Excerpts from *Antibody Methods and Protocols*, Proetzel G. and Ebersbach H. eds., Humana Press (2012) (including Zhang, C., "Hybridoma Technology for the Generation of Monoclonal Antibodies," Chapter 7; and Lee, E. et al., "The Application of Transgenic Mice for Therapeutic Antibody Discovery," Chapter 8)
2159	Zeitlin, L. et al., "Topically Applied Human Recombinant Monoclonal IgG1 Antibody and Its Fab and $F(ab')_2$ Fragments Protect Mice from Vaginal Transmission of HSV-2," *Virology*, 225:213-215 (1996)
2160	Sherwood, J. et al., "Controlled release of antibodies for long-term topical passive immunoprotection of female mice against genital herpes," *Nature Biotechnology*, 14:468-471 (April 1996)
2161	Veselinovic, M. et al., "Topical gel formulation of broadly neutralizing anti-HIV-1 monoclonal antibody VRC01 confers protection against HIV-1 vaginal challenge in a humanized mouse model," *Virology*, 432:505-510 (2012)

Exhibit No.	Description
2162	Schweitzer, M. et al., "Microscopic, chemical and molecular methods for examining fossil preservation," *Comptes Rendus Palevol*, 7:159-184 (2008)
2167	Huang, C. et al., " Effect of sublingual administration with a native or denatured protein allergen and adjuvant CpG oligodeoxynucleotides or cholera toxin on systemic TH2 immune responses and mucosal immunity in mice," *Annals of Allergy, Asthma, and Immunology*, 99:443-452 (November 2007)

V. PERSON OF ORDINARY SKILL IN THE ART

17. 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.

18. 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.

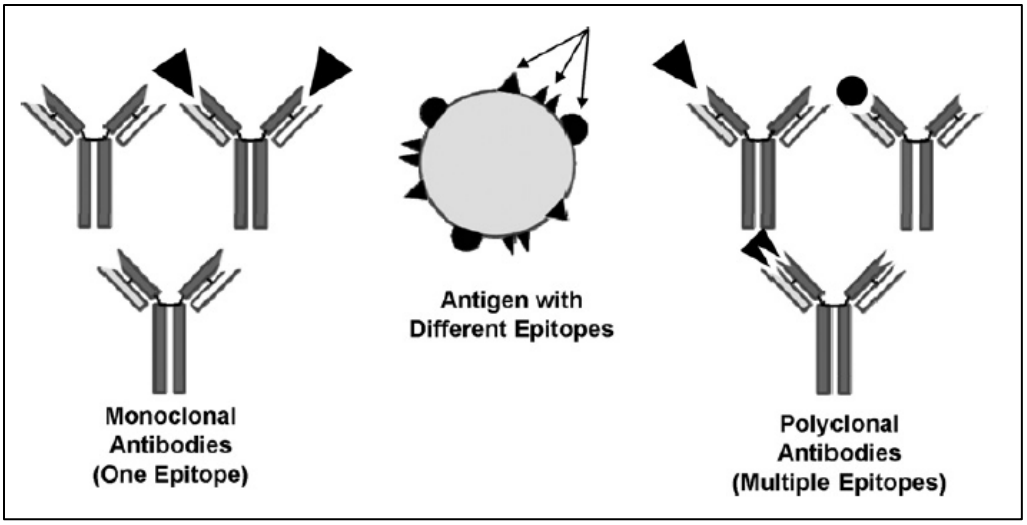
19. I had at least the qualifications of a POSA by December 28, 2012. As an expert, I have been asked to provide opinions from the perspective of a POSA as of December 28, 2012.

VI. TECHNICAL BACKGROUND

20. Vaccines introduce into the vaccinated subject's (host's) body one or more molecules known as antigens (*e.g.*, polypeptides or attenuated organisms) that stimulate the vaccinated subject's immune system to generate polyclonal antibodies that bind to the antigen(s). EX2137. "Antibodies are host proteins found in plasma and extracellular fluids that serve as the first response and comprise one of the principal effectors of the adaptive immune system." EX2137, 258; *see also id.*, 266 (stating that antibodies bind to "*e.g.*, proteins, carbohydrates, and nucleic acids"). Antibodies, also referred to as "immunoglobulins (Ig)," are "produced in response to molecules and organisms" called antigens, which contain regions called epitopes that the immune system recognizes. "Antibodies bind to an epitope on an antigen," "which they ultimately neutralize and/or eliminate." EX2137, 258, 259.

21. Antibodies are glycoproteins produced by specialized cells: a type of B cell (B lymphocytes) called plasma cells. EX2137, 258. When the vaccinated

subject's immune system encounters an antigen, the B cells recognize and bind to an epitope of the antigen and differentiate into antibody secreting plasma cells, with "each [cell] producing antibodies that recognize the identical antigenic epitope as was recognized" by the B cell. EX2137, 259. "Because most antigens are highly complex, they present numerous epitopes that are recognized by a large number lymphocytes." EX2137, 259. "Each lymphocyte is activated to proliferate and differentiate into plasma cells, and the resulting antibody response is **polyclonal**." EX2137, 259 (emphasis in original). Thus, the antibodies generated in a host in response to an antigen are polyclonal antibodies, i.e., a collection of different antibodies, generated by different B lymphocytes recognizing different epitopes on an antigen, and that bind to different epitopes on the same antigen. EX2137, 259, 261 ("[P]olyclonal sera are a composite of antibodies with unique specificities."). In contrast, "**monoclonal** antibodies (MAbs) are antibodies produced by a single B lymphocyte" and they bind to a single epitope on the antigen. EX2137, 259 (emphasis in original). I have included below a figure depicting monoclonal and polyclonal antibodies and their binding to an antigen.



EX2162, FIG. 6.

22. In the above figure, the central image depicts "an antigen (possibly a protein or virus) exposing multiple epitopes on the surface to which antibodies may bind." EX2162, FIG. 6 legend. The figure also depicts that "[m]onoclonals will bind only one type of epitope (black triangle), while polyclonal antibodies will bind multiple epitopes (black triangle, circle, or double triangle)" on the antigen. EX2162, FIG. 6 legend.

23. Although structural (i.e., conformational) changes in an antigen (such as those resulting from intentional denaturation of a protein antigen) can affect the "strength of the interaction" between an antigen and antibody, the "impact of [a] conformational change [in an antigen] is of less concern" for polyclonal antibodies because polyclonal antibodies "recognize multiple epitopes, some of which are likely to be linear" and because "conformational changes [in an antigen] may not influence all epitopes to the same degree." EX2137, 260; *see also id*., 261

("[B]ecause PAbs [(polyclonal antibodies)] are heterogeneous and recognize a host of antigenic epitopes, the effect of change on a single or small number of epitopes is less likely to be significant."). Denatured proteins were known to trigger an antibody response in the host. *See*, *e.g.*, EX2167, 448 (showing that in mice "vaccination with CM-OVA [urea-denatured ovalbumin)] with or without adjuvant induces higher systemic and mucosal antibody responses, characterized by strong serum IgG and saliva SIgA antibody levels" than native OVA (ovalbumin)), Abstract ("Sublingual vaccination with OVA or CM-OVA plus adjuvant CT [(cholera toxin)] or CpG [(CpG oligodeoxynucleotides)] all can induce systemic and mucosal immunity.").

24. Mammalian immune systems have two distinct compartments: (1) a systemic compartment comprising bone marrow, spleen, and lymph nodes; and (2) a mucosal compartment comprising lymphoid tissues associated with mucosal surfaces (also called mucosa associated lymphoid tissue or the "MALT") in the gastrointestinal tract, genitourinary tract, and respiratory tract, along with external secretory glands. EX2122, S470. By December 28, 2012, POSAs would have known that despite being "anatomically separated [from each other], different regions of the MALT are functionally connected and crosstalk [with] each other." EX2138, 54-55; *see also* EX2138, 54 (stating that "[d]ifferent mucosal tissues are immunologically connected [with one another] to form the 'common mucosal

immune system'"). By that time, a POSA also would have known that within the MALT, there are different subcompartments: nasopharynx-associated lymphoid tissue (NALT), bronchus-associated lymphoid tissue (BALT), gut-associated lymphoid tissue (GALT), and genital-tract associated lymphoid tissue. EX2139, 594.

25. By December 28, 2012, various routes for administering vaccines were known in the art. These routes included intravenous (i.v.), intramuscular (i.m.), subcutaneous (s.c.), mucosal (*e.g.*, oral, intranasal, intravaginal, or sublingual). EX2138, 595; EX2122, S472 (discussing subcutaneous and parenteral immunization). POSAs would have known that antigens administered via a mucosal route (i.e., mucosal vaccines) were "capable of inducing protective immune responses both in the mucosal and systemic immune compartments." EX2138, 50. Mucosal vaccines were also recognized for their "lower costs, ease of administration, higher patient compliance, [and] needle-free administration" as compared with other routes of administration. EX2138, 50-51; *see also* EX2139, 592. Various mucosal vaccines, including nasal vaccines such as influenza vaccine, had received FDA approval in the U.S. by December 2012. EX2139, 594, Table 1.

26. By December 28, 2012, intranasal immunization with antigens was known to "preferentially induce[] antigen-specific immunity in [the] respiratory and reproductive tissues." EX2138, 55; EX2139, 592, 596 ("Intranasal vaccination

stimulates immune responses in the nasopharynx-associated lymphoid tissue (NALT) and is effective at inducing systemic and mucosal immunity in the … respiratory and genital tracts.") ("Moreover, intranasal immunization is effective at inducing antibody responses in the genital tract (FIG. 2).").

27. POSAs would have also known that "intranasal immunization of various species, including humans, was efficient at inducing antigen-specific antibody responses in the *female* genital tract." EX2122, Abstract (emphasis added). Prior-art studies showed that antigens administered through an intranasal route elicited strong antibody responses in the female reproductive tract in mammals (humans and other mammals) and the studies disclosed intranasal vaccination for eliciting antibody responses in the female reproductive tract. EX2122, S472; EX2140; EX2141; EX2142; EX2143; EX2145; EX2146. For example, Mestecky 1999 states that "[e]xperiments done in rodents, rhesus monkeys, chimpanzees, and humans convincingly demonstrated that viral or bacterial antigens instilled into the nasal cavity induce superior immune responses in local secretions, such as saliva and, surprisingly, also in female genital tract secretions." EX2122, S472. Rudin 1998 observed that in human females cholera toxin B subunit (CTB) administered by "[n]asal vaccination resulted in 5- to 6-fold CTB-specific IgA [antibody] and 20- to 30-fold specific IgG [antibody] increases in vaginal secretions" that was of "much longer duration than [] the oral route" and

suggested nasal vaccines for "eliciting antibody responses in the female genital tract." EX2140, Abstract, S472; *see also* EX2147, Abstract, 2680 (showing that nasal vaccination elicits an antibody response in vaginal secretions in human females); EX2146, 518 (noting that "in a recent study of humans, we have confirmed the induction of CTB-specific antibodies in the vaginal secretions after i.n. [(intranasal)] vaccination" and that "it appears that both vaginal and i.n. immunizations would be efficient administration routes for future STD vaccines in women" to trigger immune response in the female reproductive tract).

28. Similarly, rhesus macaque monkeys (another primate, like humans) when "intranasally vaccinated with [HIV-1 virosomes] elicited strong protective IgA antibody responses in the genital tract" that prevented HIV transmission. EX2139, 596-597. Studies in mice likewise showed that intranasal vaccines induced strong antibody responses in the female reproductive tract. For example, Johansson 1998 showed that among perorally, intraperitoneally, vaginally, and intranasally i.n. [i.e., intranasal] immunizations, the "strongest genital antibody responses … were induced after vaginal and i.n. immunizations." EX2146, Abstract; *see also* EX2145, Abstract ("Intranasal immunization induced [] IgA and IgG [antibodies] in vaginal washes of mice, whereas i.p. [(intraperitoneal)] immunization induced IgG, which appeared to be serum-derived."); EX2141; EX2142; EX2143.

29. By December 28, 2012, POSAs also would have known routine techniques for further improving antibody responses. These techniques included using a potent mucosal adjuvant or administering one or more booster doses after the initial vaccine dose. EX2139, 597; EX2138, 51; EX2146, Abstract. Adjuvants—i.e., "agents that can potentiate and modulate immune reactions against antigens"—were known to improve an immune response. EX2138, 51. Potent mucosal adjuvants (i.e., adjuvants that improve antibody responses to an antigen administered via the mucosal route) were well known in the art. EX2138, 55-59; EX2139, 598-600, Table 2; EX2146, Abstract, 519. Some of the potent mucosal adjuvants known in the prior art include Toll-like receptor (TLR) ligands (*e.g.*, flagellin), mutants or subunits of *E. coli* enterotoxin or cholera toxin lacking toxicity (*e.g.*, subunit B of cholera toxin), and mucoadhesives (*e.g.*, chitosan, lectins). EX2138, 55-59, Table 1; EX2139, 598-600, Table 2; EX2146, Abstract, 519. For example, POSAs would have known that "TLR ligand mucosal adjuvant [] flagellin," had "superior mucosal adjuvanticity [] over other TLR ligands," and that it had the ability to have "any given antigen, which is unable to stimulate significant immune reactions in the mucosal compartment, [be] convert[ed] to [an] effective mucosal vaccine[]." EX2138, 57-58. In fact, flagellin "FlaB is capable of having conventional injectable inactivated influenza vaccine be converted into a need[le]less nasal spray vaccine." EX2138, 58. And "mice [] intranasally

immunized with inactivated trivalent influenza vaccines (TIV) in combination with FlaB" showed that "influenza-specific IgG and IgA [antibody] responses in serum and mucosal secretions were significantly enhanced." EX2138, 58. Additionally, POSAs would have known that "CTB [(Cholera Toxin Subunit B)], with a strong binding affinity to mucosal surfaces, ha[d] proved to be an exceptionally efficient mucosal immunogen especially in humans, after either p.o. [(peroral)], i.n. [(intranasal)], rectal, or vaginal immunizations." EX2146, 519.

30. By December 28, 2012, administering one or more booster doses of a vaccine after its initial dose (priming dose) was a known, common technique for improving an antibody response against a vaccine's antigen. *See*, *e.g.*, EX2148, Abstract (disclosing that "2 doses provided additional protection"); EX2149, Abstract (disclosing that vaccine efficiency for "two doses in vaccine-naïve young children was 77%" and for "one dose against antigenically similar strains in vaccine-naive children was 60%"). The booster dose(s) re-expose(s) the subject's immune system to the vaccine's antigen and trigger higher levels of antibodies.

31. By December 28, 2012, POSAs would have also known of using different routes for the initial dose and booster doses. For example, POSAs would have known that "combining intranasal priming and intravaginal boosting immunizations could be an effective strategy to achieve strong immune protection in the genital tract." EX2139, 597; EX2150, 490 (demonstrating that antibody

responses in the reproductive tract of female mice "can be significantly boosted . . . by the intranasal or by the intravaginal route" following intranasal priming).

32. The "immune system is trained not to respond to self molecules (in order to avoid autoimmunity)." EX2151, 468. However, under certain conditions, an antibody response against self-antigens is desired, *e.g.*, to counter overexpression of the self-antigen in a disease (such as, TNF-α overexpression causing chronic inflammation in cachexia, Crohn's disease, and rheumatoid arthritis). EX2152, 55. By December 28, 2012, POSAs would have known of techniques to elicit a polyclonal antibody response against a self-antigen. *See, e.g.*, EX2152. One such technique included replacing some amino acids of the polypeptide self-antigen (*e.g.*, TNF-α) with helper T cell epitope peptide, *e.g.*, PADRE (pan DR-binding epitope) peptide, to generate a fusion self-antigen (*e.g.*, PADRE-TNF-α) for use as a vaccine to generate antibodies that neutralize the self-antigen (*e.g.*, TNF-α). *See*, *e.g.*, EX2152, Abstract.

33. By December 28, 2012, POSAs would have known that antibodies generated against a polypeptide antigen can cross-react with (bind to) polypeptides similar to the polypeptide antigen via the same or similar epitopes. EX2137, 260 ("Because antibodies recognize a relatively small component of an antigen, they can cross-react with similar epitopes on other antigens, but usually with less affinity."). POSAs would have also known that a polypeptide vaccine generates

polyclonal antibodies in a mammal (including humans), which comprise a collection of antibodies that bind to different epitopes on the polypeptide that stimulated the immune response. EX2137, 261 ("[P]olyclonal sera are a composite of antibodies with unique specificities."). Because a polypeptide similar to the polypeptide that stimulated the polyclonal antibodies would have the same or similar epitopes as the epitopes on the stimulating polypeptide, POSAs would have expected polyclonal antibodies to exhibit significant cross-reactivity with similar polypeptides. EX2137, 261 ("[B]ecause PAbs [polyclonal antibodies] are heterogeneous and recognize a host of antigenic epitopes, the effect of change on a single or small number of epitopes is less likely to be significant."). In other words, POSAs would have expected that in the collection of polyclonal antibodies generated by a particular polypeptide, there would be antibodies that would cross-react with the polypeptides similar to the polypeptide that stimulated the antibodies.

34. By December 28, 2012, polyclonal antibodies generated against a polypeptide antigen were known to cross-react with another polypeptide having as low as ~46 – 49% sequence identity to the stimulating polypeptide, irrespective of whether the polypeptides are from a different animal species. *See*, *e.g.*, EX2153; EX2154; EX2155; EX2156. For example, Dieude 2009 shows that mice immunized with *mycobacterial* heat shock protein 65 (HSP65) induced "anti-

HSP60 autoantibodies" against *mouse* heat shock protein 60 (HSP60) by breaking immune tolerance to self-HSP60. EX2153, 4. A comparison of mouse HSP60 amino acid sequence with the amino acid sequences of HSP65 from 3 mycobacterial species of mycobacteria using UniProt[1] (with default settings) showed 45.5 – 49.3% sequence identity between mycobacterial HSP65 and mouse HSP60. *See* Appendix A. Thus, Dieude 2009 shows that polyclonal antibodies generated in response to mycobacterial HSP65 bind to mouse HSP60 having 46 – 49% sequence identity to mycobacterial HSP65.

35. Oliver 2003 shows that mice immunized with the extracellular domain of human myelin oligodendrocyte glycoprotein (MOG) triggered a polyclonal antibody response in mice such that the generated antibodies reacted with the native MOG protein in mice causing experimental autoimmune encephalomyelitis in mice. EX2154, Abstract, FIG. 6. A comparison of the amino acid sequences of the extracellular domains of mouse MOG and human MOG using UniProt (with default settings) showed 90% sequence identity between mouse MOG domain and human MOG domain. *See* Appendix A. Thus, Oliver 2003 shows that polyclonal antibodies generated in response to the extracellular

[1] UniProt is a free comprehensive database of protein sequences available by December 28, 2012. It can be accessed at https://www.uniprot.org/.

domain of human MOG protein bind to mouse MOG protein having 90% sequence identity to the human protein.

36. Trentham 1977 shows that chicken, human, or rat type II collagen when injected into a rheumatoid arthritis mouse model induce inflammatory arthritis in mice, confirming antibody cross-reactivity between human, chicken, or rat type II collagen and mouse type II collagen as arthritis was caused by "antibodies to collagen in sera." EX2155, Abstract; *see also* EX2156, 666-668. A comparison of the amino acid sequences of the mouse, chicken, human, and rat type II collagen using UniProt (with default settings) showed that mouse type II collagen has ~90%, ~95%, and ~98% sequence identity with chicken, human, and rat type II collagen, respectively. *See* Appendix A. Thus, Trentham 1977 shows that polyclonal antibodies generated in response to chicken, human, and rat type II collagen bind to mouse type II collagen having 90%, ~95%, and ~98% sequence identity, respectively, to them.

37. Accordingly, POSAs would have expected that polyclonal antibodies generated in a subject against a polypeptide would cross-react with (bind to) polypeptides having as low as ~46 – 49% sequence identity, and a POSA would have expected such cross-reactivity across animal species.

VII. A POSA WOULD HAVE EXPECTED THAT POLYCLONAL ANTIBODIES GENERATED IN A HUMAN FEMALE AGAINST MODIFIED PH20 POLYPEPTIDES WOULD BIND TO THE WILD-TYPE HUMAN PH20 POLYPEPTIDE

38. I understand that PH20 is a sperm-associated protein having hyaluronidase activity and is involved in fertilization in mammals. I have been asked to opine on whether a human female vaccinated with any of the modified PH20 polypeptides (defined in ¶14 above) would have been expected to generate anti-PH20 polyclonal antibodies that bind to the mature wild-type PH20 polypeptide of human sperm introduced into the female reproductive tract.

39. I understand that mature, full-length, wild-type PH20 polypeptide of human sperm introduced into the female reproductive tract has the amino acid sequence of SEQ ID NO: 7. I understand that SEQ ID NOs: 3 and 32-66 are amino acid sequences of a series of C-terminal truncations of full-length human PH20 polypeptides (SEQ ID NO: 7), with SEQ ID NO: 32 being the most truncated polypeptide having 430 amino acids. Each of SEQ ID NOs: 3, 7, and 32-66 was provided by counsel and is included in Appendix B. *See* Appendix B.

40. A comparison of the amino acid sequences using UniProt (with default settings) showed that amino acid sequence of PH20 polypeptide with SEQ ID NO: 3 or SEQ ID NO: 32 is identical to the corresponding amino acid sequences (within the N-terminal portion) of the mature, full-length, wild-type human PH20 polypeptide, which has the amino acid sequence of SEQ ID NO: 7.

See Appendix B, pp. 1-2, 31. Because the remaining PH20 polypeptides with any of SEQ ID NOs: 33-66 have an amino acid sequence ranging between SEQ ID NOs: 3 and 32, their amino acid sequences would also be identical to the corresponding amino acid sequences (within the N-terminal portion) of the sequence of the wild-type human PH20 polypeptide with SEQ ID NO: 7.

41. The modified PH20 polypeptides, defined in ¶14 above, have amino acid sequences that are at least 91% identical to the amino acid sequence of any one of SEQ ID NO: 3, 7, and 32-66 (including a modification at position 309). Thus, the modified PH20 polypeptides have amino acid sequences that are at least 91% identical to the amino acid sequence of the wild-type human PH20 polypeptide of human sperm (SEQ ID NO: 7).

42. PH20 polypeptides with amino acid sequence of any of SEQ ID NOs: 3, 7, and 32-66 are at least 430 amino acids long. *See* Appendix B. Thus, POSAs would have expected that each of these polypeptides would present numerous epitopes to the host's immune system when administered as a vaccine to a human female. For the reasons discussed in Section VI, POSAs would have known that PH20 polypeptides having amino acid sequence of any of SEQ ID NOs: 3, 7, and 32-66 would generate a polyclonal antibody response, i.e., a collection of different antibodies that bind to different epitopes of the PH20 polypeptide, in the vaccinated subject. EX2137, 259, 261 ("[P]olyclonal sera are a composite of

antibodies with unique specificities.").

43. As I explain in Section VI, polyclonal antibodies were known to cross-react with (bind to) a polypeptide having as low as about 46 – 49% sequence identity with the polypeptide antigen that stimulated the antibody response. EX2154; EX2155; EX2156; EX2153, 4. Thus, given the high degree of sequence identity (at least 91%) between each of the modified PH20 polypeptides (as defined above in ¶14) and the wild-type PH20 polypeptide of sperm introduced into the human female reproductive tract (SEQ ID NO: 7), POSAs would have expected that polyclonal antibodies would have been generated in human females in response to vaccination with any one of the modified PH20 polypeptides and bind to the wild-type PH20 polypeptide of human sperm introduced into the female reproductive tract.

44. Moreover, given the high degree of amino acid sequence identity (at least 91%) between the administered modified PH20 polypeptides and the wild-type human PH20 polypeptide (SEQ ID NO: 7), even if some epitopes on the modified PH20 polypeptide were changed or disrupted (*e.g.*, an epitope in the active site of PH20 polypeptide) or the modified PH20 polypeptide underwent a conformational change (*e.g.*, due to intentional denaturation), POSAs still would have expected the vast majority of the epitopes on the modified PH20 polypeptides to be the same or similar to those on the wild-type human PH20 polypeptide (SEQ

ID NO: 7).

45. As a result, irrespective of (1) the location of an amino acid difference on any of the administered modified PH20 polypeptides compared to the wild-type PH20 polypeptide, (2) whether any of the administered modified PH20 polypeptides is enzymatically active, or (3) whether the administered modified PH20 polypeptide has conformational change (*e.g.*, due to intentional denaturation), POSAs would have expected the polyclonal antibodies generated against the administered modified PH20 polypeptide (enzymatically active or inactive) to include antibodies that bind to the wild-type PH20 polypeptide. *See* EX2137, 260 (stating that antibodies "can cross-react with similar epitopes on other antigens"), 260 (stating that because polyclonal antibodies "recognize multiple epitopes, some of which are likely to be linear" and because "conformational changes [in an antigen] may not influence all epitopes to the same degree," the "impact of conformational change [in an antigen] is of less concern" for polyclonal antibodies), 261 ("[B]ecause PAbs [(polyclonal antibodies)] are heterogeneous and recognize a host of antigenic epitopes, the effect of change on a single or small number of epitopes is less likely to be significant."); EX2167, Abstract, 448 (disclosing that intentionally denatured protein generate antibodies in the host (mice)).

46. Further, by December 28, 2012, POSAs would have known common

techniques for improving the immune response to modified PH20 polypeptide vaccines. As I explain above in Section VI, these techniques included one or more of the following well-known approaches for administering any of the modified PH20 polypeptides as vaccines: (1) mucosal (*e.g.*, intranasal) administration, which was known to elicit a strong antibody response in the female reproductive tract; (2) a potent mucosal adjuvant; (3) booster doses after the initial vaccine dose; and (4) if PH20 were expressed in human females (i.e., if PH20 were a self-antigen in human females), using known techniques to elicit an antibody response against it. *See* Section VI.

47. Thus, POSAs would have expected that polyclonal antibodies would be generated in a human female against any of the modified PH20 polypeptides (as defined in ¶14). POSAs would have also expected that such polyclonal antibodies would bind to the wild-type human PH20 polypeptide.

VIII. A POSA WOULD HAVE EXPECTED THAT POLYCLONAL ANTIBODIES GENERATED IN A NON-HUMAN FEMALE MAMMAL AGAINST MODIFIED PH20 POLYPEPTIDES WOULD BIND TO THE WILD-TYPE PH20 POLYPEPTIDE IN THE MAMMAL

48. I have been asked to opine on whether anti-PH20 polyclonal antibodies generated in non-human female mammals vaccinated with any of the modified PH20 polypeptides (defined in ¶14 above) would be expected to bind to the wild-type PH20 polypeptide of sperm introduced into the reproductive tract of

those female mammals. As explained above in Section VII, I understand that SEQ ID NOs: 3 and 32-66 are amino acid sequences of a series of C-terminal truncations of full-length human PH20 polypeptide (SEQ ID NO: 7), with SEQ ID NO: 32 being the most truncated polypeptide having 430 amino acids. Each of SEQ ID NOs: 3, 7, and 32-66 was provided by counsel and is included in Appendix B.

49. Specifically, I have been asked to consider the following non-human mammals: chimpanzee, Rhesus monkey, Cynomolgus monkey, cow, mouse, rat, rabbit, guinea pig, red fox, gibbon, marmoset, and orangutan. I understand that the mature, wild-type PH20 polypeptides of sperm of these animals have the following amino acid sequences: SEQ ID NOs: 10 and 870 (chimpanzee), SEQ ID NO: 12 (Rhesus monkey), SEQ ID NO: 14 (Cynomolgus monkey), SEQ ID NOs: 16 and 18 (cow), SEQ ID NO: 20 (mouse), SEQ ID NO: 22 (rat), SEQ ID NO: 24 (rabbit), SEQ ID NO: 29 (guinea pig), SEQ ID NO: 31 (red fox), SEQ ID NO: 857 (gibbon), SEQ ID NO: 859 (marmoset), and SEQ ID NO: 861 (orangutan). Each of SEQ ID NOs: 10, 870, 12, 14, 16, 18, 20, 22, 24, 29, 31, 857, 859, and 861 was provided by counsel and is provided in Appendix B. *See* Appendix B.

50. As shown in Appendix B, PH20 polypeptides having amino acid sequence of any of SEQ ID NOs: 3, 7, and 32-66 are at least 430 amino acids long. *See* Appendix B. Thus, POSAs would have expected that each of these

polypeptides would present numerous epitopes to the host's immune system when administered as a vaccine. For the reasons discussed in Section VI, POSAs would have known that PH20 polypeptides having amino acid sequence of any of SEQ ID NOs: 3 and 32-66 would generate a polyclonal antibody response, i.e., a collection of different antibodies that bind to different epitopes of the PH20 polypeptide, in the vaccinated subject. EX2137, 259, 261 ("[P]olyclonal sera are a composite of antibodies with unique specificities.").

51. A comparison of the amino acid sequences using UniProt (with default settings) showed that PH20 polypeptide with SEQ ID NO: 3, PH20 polypeptide with SEQ ID NO: 7, and PH20 polypeptide with SEQ ID NO: 32 have the below-listed respective % sequence identities:

- 98.9%, 99%, and 99.1% identity with the amino acid sequence of the wild-type chimpanzee PH20 polypeptide (SEQ ID NO: 10);
- 98.2%, 98.3%, and 98.4% identity with the amino acid sequence of the wild-type chimpanzee PH20 polypeptide (SEQ ID NO: 870);
- 89.3%, 86.1%, and 90% identity with the amino acid sequence of the wild-type Rhesus monkey PH20 polypeptide (SEQ ID NO: 12);
- 89.3%, 88.8%, and 90% identity with the amino acid sequence of the wild-type Cynomolgus monkey PH20 polypeptide (SEQ ID NO: 14);
- 62.4%, 60.4%, and 63.7% identity with the amino acid sequence of

the wild-type cow PH20 polypeptide (SEQ ID NO: 16);

- 65.5%, 65.5%, and 64.9% identity with the amino acid sequence of the wild-type cow PH20 polypeptide (SEQ ID NO: 18);
- 56.5%, 56.3%, and 58% identity with the amino acid sequence of the wild-type mouse PH20 polypeptide (SEQ ID NO: 20);
- 54.3%, 54%, and 55.5% identity with the amino acid sequence of the wild-type rat PH20 polypeptide (SEQ ID NO: 22);
- 69.4%, 66.2%, and 71.2% identity with the amino acid sequence of the wild-type rabbit PH20 polypeptide (SEQ ID NO: 24);
- 59.4%, 57%, and 60.1% identity with the amino acid sequence of the wild-type guinea pig PH20 polypeptide (SEQ ID NO: 29);
- 60.4%, 57.6%, and 61.6% identity with the amino acid sequence of the wild-type red fox PH20 polypeptide (SEQ ID NO: 31);
- 96.4%, 96.4%, and 96.7% identity with the amino acid sequence of the wild-type gibbon PH20 polypeptide (SEQ ID NO: 857);
- 88.4%, 86.8%, and 88.6% identity with the amino acid sequence of the wild-type marmoset PH20 polypeptide (SEQ ID NO: 859); and
- 97.1%, 94.3%, and 97.2% identity with the amino acid sequence of the wild-type orangutan PH20 polypeptide (SEQ ID NO: 861).

See Appendix B, pp. 32-33.

52. Because the remaining SEQ ID NOs: 33-66 have amino acid sequences ranging between SEQ ID NOs: 3 and 32, their % sequence identities with the wild-type PH20 polypeptides having SEQ ID NOs: 10, 870, 12, 14, 16, 18, 20, 22, 24, 29, 31, 857, 859, and 861 range between those of SEQ ID NOs: 3 and 32. *See* Appendix B. Accordingly, PH20 polypeptides with SEQ ID NOs: 3 and 32-66 have the following % sequence identities:

- 98.9% to 99.1% (at least 98.9%) with the amino acid sequence of the wild-type PH20 polypeptide of chimpanzee sperm (SEQ ID NO: 10);
- 98.2% to 98.4% (at least 98.2%) with the amino acid sequence of the wild-type PH20 polypeptide of chimpanzee sperm (SEQ ID NO: 870);
- 86.1% to 90% (at least 86.1%) with the amino acid sequence of the wild-type PH20 polypeptide of Rhesus monkey sperm (SEQ ID NO: 12);
- 88.8% to 90% (at least 88.8%) with the amino acid sequence of the wild-type PH20 polypeptide of Cynomolgus monkey sperm (SEQ ID NO: 14);
- 60.4% to 63.7% (at least 60.4%) with the amino acid sequence of the wild-type PH20 polypeptide of cow sperm (SEQ ID NO: 16);
- 64.9% to 65.5% (at least 64.9%) with the amino acid sequence of the wild-type PH20 polypeptide of cow sperm (SEQ ID NO: 18);
- 56.3% to 58% (at least 56.3%) with the amino acid sequence of the wild-type PH20 polypeptide of mouse sperm (SEQ ID NO: 20);

- 54% to 55.5% (at least 54%) with the amino acid sequence of the wild-type PH20 polypeptide of rat sperm (SEQ ID NO: 22);
- 66.2% to 71.2% (at least 66.2%) with the amino acid sequence of the wild-type PH20 polypeptide of rabbit sperm (SEQ ID NO: 24);
- 57% to 60.1% (at least 57%) with the amino acid sequence of the wild-type guinea pig PH20 polypeptide of guinea pig sperm (SEQ ID NO: 29);
- 57.6% to 61.6% (at least 57.6%) with the amino acid sequence of the wild-type PH20 polypeptide of red fox sperm (SEQ ID NO: 31);
- 96.4% to 96.7% (at least 96.4%) with the amino acid sequence of the wild-type PH20 polypeptide of gibbon sperm (SEQ ID NO: 857);
- 86.8% to 88.6% (at least 86.8%) with the amino acid sequence of the wild-type PH20 polypeptide of marmoset sperm (SEQ ID NO: 859); and
- 94.3% to 97.2% (at least 94.3%) with the amino acid sequence of the wild-type PH20 polypeptide of orangutan sperm (SEQ ID NO: 861).

53. The modified PH20 polypeptides, as defined above in ¶14, are polypeptides with at least 91% identity with the amino acid sequence of SEQ ID NO: 3, SEQ ID NO: 7, or SEQ ID NO: 32-66 (including a modification at position 309). Thus, the modified PH20 polypeptides have at most 9% difference in their amino acid sequence from the amino acid sequence of SEQ ID NO: 3, SEQ ID NO: 7, or SEQ ID NO: 32-66. Accordingly, the modified PH20 polypeptides have

the following % sequence identities:

- at least 89.9% (98.9% minus 9%) with the amino acid sequence of the wild-type PH20 polypeptide of chimpanzee sperm (SEQ ID NO: 10);
- at least 89.2% (98.2% minus 9%) with the amino acid sequence of the wild-type PH20 polypeptide of chimpanzee sperm (SEQ ID NOs: 870);
- at least 77.1% (86.1% minus 9%) with the amino acid sequence of the wild-type polypeptide of Rhesus monkey sperm (SEQ ID NO: 12);
- at least 79.8% (88.8% minus 9%) with the amino acid sequence of the wild-type PH20 polypeptide of Cynomolgus monkey sperm (SEQ ID NO: 14);
- at least 51.4% (60.4% minus 9%) with the amino acid sequence of the wild-type PH20 polypeptide of cow sperm (SEQ ID NO: 16);
- at least 55.9% (64.9% minus 9%) with the amino acid sequence of the wild-type PH20 polypeptide of cow sperm (SEQ ID NO: 18);
- at least 47.3% (56.3% minus 9%) with the amino acid sequence of the wild-type PH20 polypeptide of mouse sperm (SEQ ID NO: 20);
- at least 45% (54% minus 9%) with the amino acid sequence of the wild-type PH20 polypeptide of rat sperm (SEQ ID NO: 22);
- at least 57.2% (66.2% minus 9%) with the amino acid sequence of the wild-type PH20 polypeptide of rabbit sperm (SEQ ID NO: 24);
- at least 48% (57% minus 9%) with the amino acid sequence of the wild-type

PH20 polypeptide of guinea pig sperm (SEQ ID NO: 29);

- at least 48.6% (57.6% minus 9%) with the amino acid sequence of the wild-type PH20 polypeptide of red fox sperm (SEQ ID NO: 31);
- at least 87.4% (96.4% minus 9%) with the amino acid sequence of the wild-type PH20 polypeptide of gibbon sperm (SEQ ID NO: 857);
- at least 77.8% (86.8% minus 9%) with the amino acid sequence of the wild-type PH20 polypeptide of marmoset sperm (SEQ ID NO: 859); and
- at least 85.3% (94.3% minus 9%) with the amino acid sequence of the wild-type PH20 polypeptide of orangutan sperm (SEQ ID NO: 861).

54. Thus, the modified PH20 polypeptides have at least about 45% identity with the amino acid sequence of the wild-type PH20 polypeptides having SEQ ID NOs: 10, 870, 12, 14, 16, 18, 20, 22, 24, 29, 31, 857, 859, and 861.

55. As explained in Section VI, polyclonal antibodies were known to cross-react with a polypeptide having as low as about 46 – 49% sequence identity with the polypeptide that stimulated the polyclonal antibody response. EX2154; EX2155; EX2156; EX2153. Thus, given that the administered modified PH20 polypeptide(s) and the wild-type PH20 polypeptide of sperm in chimpanzee (SEQ ID NOs: 10 and 870), Rhesus monkey (SEQ ID NO: 12), Cynomolgus monkey (SEQ ID NO: 14), cow (SEQ ID NOs: 16 and 18), mouse (SEQ ID NO: 20), rat (SEQ ID NO: 22), rabbit (SEQ ID NO: 24), guinea pig (SEQ ID NO: 29), red fox

(SEQ ID NO: 31), gibbon (SEQ ID NO: 857), marmoset (SEQ ID NO: 859), and orangutan (SEQ ID NO: 861) have at least about 45% amino acid sequence identity, POSAs would have expected that polyclonal antibodies would have been generated in these animals against the administered modified PH20 polypeptides and bind to the wild-type PH20 polypeptide of sperm in these animals.

56. Moreover, given the % identities between any of the administered modified PH20 polypeptides and the wild-type PH20 polypeptides in the above-discussed animals, even if some epitopes on the administered modified PH20 polypeptides were changed or disrupted (such as an epitope in the active site of PH20 polypeptide) or the modified PH20 polypeptide undergoes a conformational change (*e.g.*, due to intentional denaturation), POSAs still would have expected many epitopes on the administered modified PH20 polypeptides to be the same or similar to those on the wild-type PH20 polypeptide in the animals.

57. As a result, irrespective of (1) the location where the amino acid difference is on any of the administered modified PH20 polypeptides compared to the wild-type PH20 polypeptide introduced via sperm into the vaccinated animal, (2) whether any of the administered modified PH20 polypeptides was enzymatically active, or (3) whether the administered modified PH20 polypeptide has conformational change (*e.g.*, due to intentional denaturation), POSAs would have expected the polyclonal antibodies generated against the administered

modified PH20 polypeptide to include antibodies that would bind to the wild-type PH20 polypeptide introduced via sperm into the vaccinated animals. *See* EX2137, 260 (stating that antibodies "can cross-react with similar epitopes on other antigens"), 260 (stating that because polyclonal antibodies "recognize multiple epitopes, some of which are likely to be linear" and because "conformational changes [in an antigen] may not influence all epitopes to the same degree," the "impact of conformational change [in an antigen] is of less concern" for polyclonal antibodies), 261 ("[B]ecause PAbs [(polyclonal antibodies)] are heterogeneous and recognize a host of antigenic epitopes, the effect of change on a single or small number of epitopes is less likely to be significant."); EX2167, Abstract, 448 (disclosing that intentionally denatured proteins generate antibodies in the host (mice)).

58. Further, by December 28, 2012, POSAs would have known of common techniques for improving the antibody response to modified PH20 polypeptide vaccines. As explained above in Section VI, these techniques included one or more of the following well-known approaches for administering any of the modified PH20 polypeptides as vaccines: (1) mucosal (*e.g.*, intranasal) administration, which was known to elicit a strong antibody response in the female reproductive tract; (2) a potent mucosal adjuvant; and (3) a booster dose(s) after the initial vaccine dose. *See* Section VI.

59. Thus, POSAs would have expected to generate polyclonal antibodies in a female mammal (such as chimpanzee, Rhesus monkey, Cynomolgus monkey, cow, mouse, rat, rabbit, guinea pig, red fox, gibbon, marmoset, and orangutan) against any of the modified PH20 polypeptides (as defined in ¶14) and that such antibodies would bind to the wild-type PH20 polypeptide.

IX. A POSA WOULD HAVE EXPECTED TO SUCCESSFULLY DELIVER MONOCLONAL ANTIBODIES INTO THE VAGINAL CAVITY OF HUMAN FEMALES

60. By December 28, 2012, antibodies were considered for therapy. EX2135, Abstract. In fact, by December 2012, at least 19 monoclonal antibodies were in clinical use as therapeutics. EX2135, Abstract. POSAs would have known of routine techniques, such as hybridoma technology, to produce monoclonal antibodies. EX2135, 18-19; EX2157; EX2158, 117-135. POSAs would have also known of strategies for producing human monoclonal antibodies, for example, using "transgenic mice containing human immunoglobulin germ line locus." EX2135, 20, 22; EX2158, 137-148. The strategy involved immunizing the transgenic mice with an antigen (such as a human protein) to obtain B cells producing human antibodies to the antigen, i.e., a "human antibody response, from which hybridomas that produce human antibodies can be generated, as in traditional hybridoma technology." EX2135, 20, 22.

61. Further, POSAs would have known of systems for successfully

delivering monoclonal antibodies into the vaginal cavity, *e.g.*, via buffers, gels, films, disks, and rings. For example, Zeitlin 1996 discloses that monoclonal antibodies against herpes simplex virus (HSV-2) delivered to the murine vaginal cavity in phosphate buffer saline "provided approximately 50% protection" (1–5 ng antibodies) or "completely protected mice from genital herpes infection" (400 ng antibodies). EX2159, Abstract. Zeitlin further states that "[t]hese results suggest that topical applications of human monoclonal antibodies [via vaginal delivery] may be useful in developing new methods for preventing sexually transmitted disease" and that "several days of protection may be provided by a single dose of antibody in humans." EX2159, Abstract, 215. Similarly, Sherwood 1996 discloses that anti-HSV-2 antibodies delivered using "polymeric controlled-release devices" called "vaginal disks" provided "significant protection against HSV-2 infection" such that "no mice receiving [the] disks became infected." EX2160, Abstract. Thus, POSAs would have selected any of the well-known, routine systems to deliver monoclonal antibodies into the vaginal cavity of human females.

62. To improve the effect of the delivered antibodies, POSAs would have selected any of the well-known, routine systems to deliver a combination of different monoclonal antibodies into the female vaginal cavity, with each antibody binding to a different epitope on the target polypeptide. For example, Veselinovic 2012 discloses delivering to the vaginal cavity in mice a combination of four

monoclonal antibodies against HIV-1 via a "gel" such that "mice receiving the four [] antibody combination were protected against HIV-1 challenge." EX2161, Abstract, 3-4. Sherwood 1996 suggests that "hundreds of different MAbs [(monoclonal antibodies)] could be incorporated into the same intravaginal device" for humans and such devices may be used to deliver "a variety of antibodies against STD pathogens as well as antisperm antibodies for contraception." EX2160, 270.

63. Thus, POSAs would have expected to successfully deliver a monoclonal antibody(ies) to a human female's vaginal cavity to specifically target antigens in the reproductive tract using delivery systems known in the art by December 28, 2012.

X. CONCLUSION

64. As I explain in Sections VII and VIII, by December 28, 2012, POSAs would have expected that the modified PH20 polypeptides (which were at least 91% identical in amino acid sequence to human SEQ ID NO: 3, 7, and 32-66 and included a modification at position 309) would generate polyclonal antibodies in female mammals (including humans, chimpanzee, Rhesus monkey, Cynomolgus monkey, cow, mouse, rat, rabbit, guinea pig, red fox, gibbon, marmoset, and orangutan) that would bind to the wild-type PH20 polypeptide of sperm in the females.

65. As I explain in Section IX, by December 28, 2012, POSAs would have expected to successfully deliver monoclonal antibody(ies) to the vaginal cavity of human females to specifically target antigens in the female reproductive tract.

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 21 day of December, 2025.

James J. Moon, Ph.D.

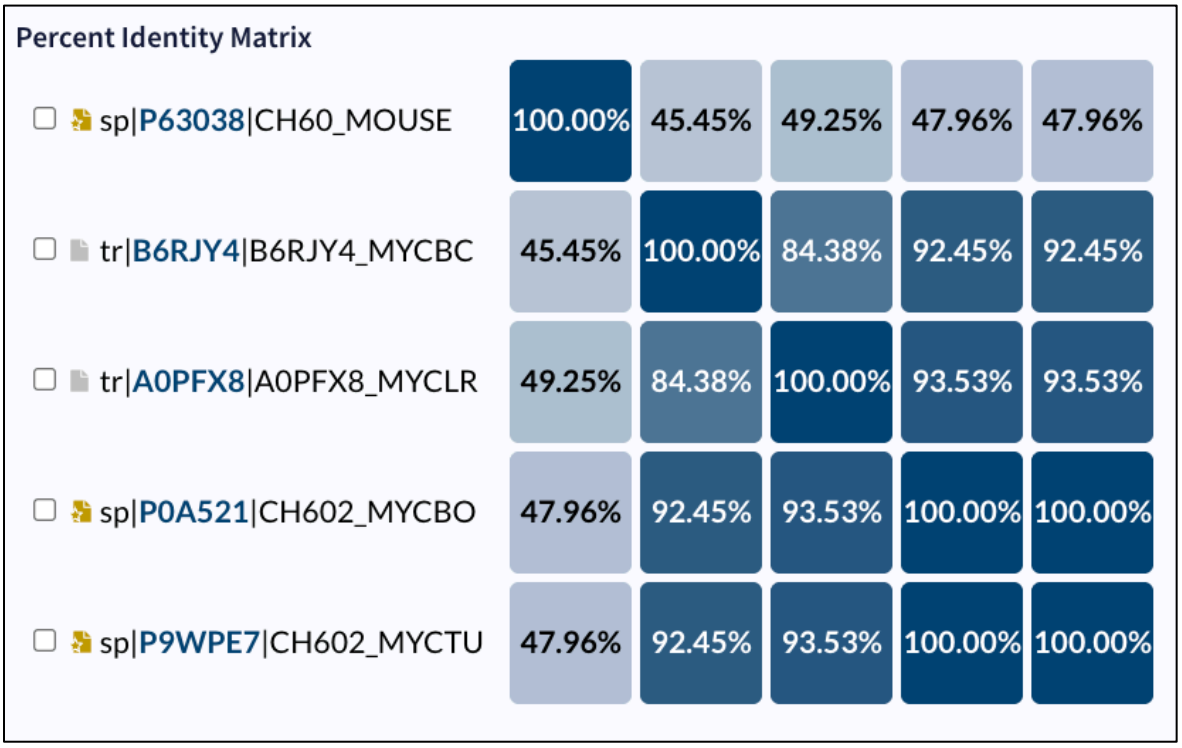
26024566

Moon Declaration Appendix A

I. Sequence comparison between mouse HSP60 and mycobacterial HSP65

Sequences analyzed

- Mouse Hsp60/HSPD1 (UniProt P63038)
- *Mycobacterium tuberculosis* Hsp65 (UniProt P9WPE7)
- *Mycobacterium bovis* Hsp65 (UniProt P0A521)
- *Mycobacterium leprae* Hsp65 (UniProt A0PFX8)
- *Mycobacterium bouchedurhonense* Hsp65 (UnitProt B6RJY4)

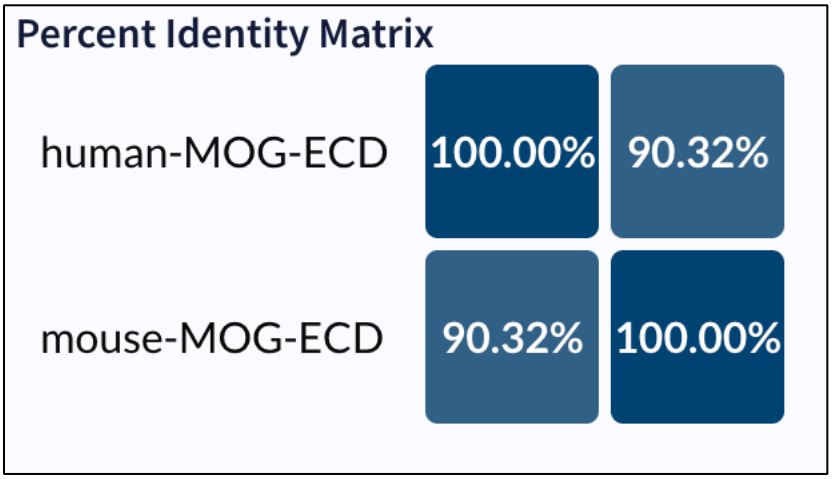


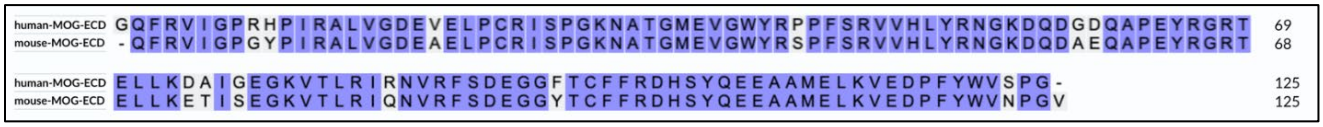
sp|P63038|CH60_MOUSE
tr|B6RJY4|B6RJY4_MYCBC
tr|A0PFX8|A0PFX8_MYCLR
sp|P0A521|CH602_MYCBO
sp|P9WPE7|CH602_MYCTU
P63038:Transit peptide

II. Sequence comparison between the extracellular domains of human MOG protein and mouse MOG protein

Sequences analyzed

- Human MOG (Q16653) (Extracellular domain (ECD, Ig-like domain): residues 30–154)
- Mouse MOG (Q61885) (Extracellular domain (ECD, Ig-like domain): residues 30-154)

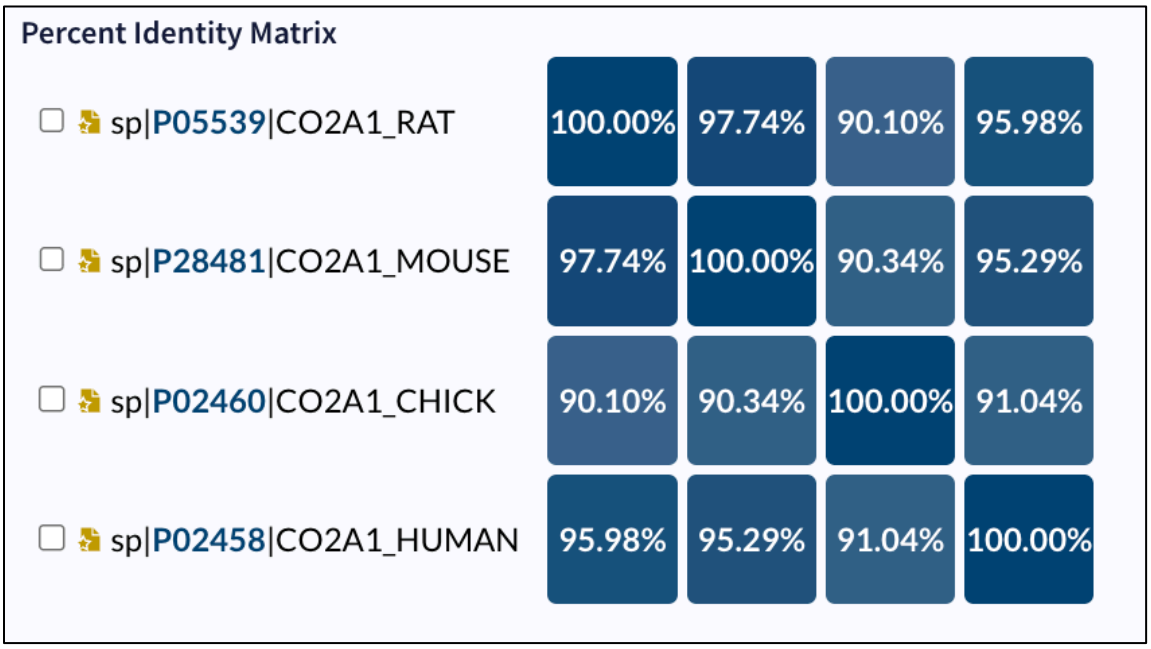




III. Sequence comparison between chicken, human, rat, and mouse type II collagen

Sequences analyzed

- Mouse Col2a1: UniProt ID P28481
- Human COL2A1: UniProt ID P02458
- Chichen COL2A1: UniProt ID P02460
- Rat COL2A1: UniProt ID P05539



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Moon Declaration Appendix B

I. PH20 polypeptide sequences

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 EEPQIFY 447

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 430

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 PSTLSATMFI VSILFLIISS VASL 474

SEQ ID NO: 10 (mature chimpanzee PH20)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINVTG QDVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE STALYPSIYL NTQQSPVAAT 240

LYVRNRVQEA IRVSKIPDAK SPLPVFVYTR IVFTDQVLKF LSQDELVYTF GETVALGASG 300

IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAKM CSQVLCQEQG VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE KADVKDTDAV 420

DVCIADGVCI DAFLKPPMET EESQIFYNAS PSTLSATMFI VSILFLIISS VASL 474

SEQ ID NO: 870 (mature chimpanzee PH20)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDTSLFSF IGSPRINVTG QDVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE STALYPSIYL NTQQSPVAAT 240

LYARNRVQEA IRVSKIPDAK SPLPVFVYTR IVFTDQVLKF LSQDELVYTF GETVALGASG 300

IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAKM CSQVLCQEQG VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE KADVKDTDAV 420

DVCIADGVYI DAFLKPPMET EESQIFYNAS PSTLSATMFI VSILFLIISS VASL 474

SEQ ID NO: 12 (mature Rhesus monkey PH20)

LNFRAPPIIP NVPFLWAWNA PSEFCLGKFN EPLDMSLFTL MGSPRINITG QGVTIFYVDR 60

LGYYPYIDLT TGVTVHGGIP QKVSLQDHLD KSKQDILFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLPQAT DKAKQEFEKA GKDFMLETIK LGRSLRPNHL 180

WGYYLFPDCY NHHYRKPGYN GSCFDVEIKR NDDLSWLWNE STALYPSIYL NTQQSVVVAT 240

LYVRNRVREA IRVSKIPDAK NPLPVFVYAR LVFTDQVLKF LSREELVSTL GETVALGASG 300

IVIWGSLSIT RSMKSCLLLD TYMETILNPY IINVTLAAKM CSQVLCQEQG VCIRKDWNSS 360

DYLHLNPDNF DIRLEKGGKF TVHGKPTVED LEEFSEKFYC SCYTNLSCKE KADVKDTDAV 420

DVCIADGVCI DASLKPPVET EGSPPIFYNT SSSTVSTTMF IWRLEVWDQG ISRIGFF 477

SEQ ID NO: 14 (mature Cynomolgus monkey PH20)

LNFRAPPIIP NVPFLWAWNA PSEFCLGKFN EPLDMSLFTL MGSPRINVTG QGVTIFYVDR 60

LGYYPYIDLT TGVTVHGGIP QKVSLQDHLD KSKQDILFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLPQAT DKAKQEFEKA GKDFMLETIK LGRSLRPNHL 180

WGYYLFPDCY NHHYRKPGYN GSCFDVEIKR NDDLSWLWNE STALYPSIYL NTQQSVVVAT 240

LYVRNRVREA IRVSKIPDAK NPLPVFVYAR LVFTDQVLKF LSREELVSTL GETVALGASG 300

IVIWGSLSIT RSMKSCLLLD TYMETILNPY IINVTLAAKM CSQVLCQEQG VCIRKDWNSS 360

DYLHLNPDNF DIRLEKGGKF TVHGKPTVED LEEFSEKFYC SCYTNLSCKE KADVKDTDAV 420

DVCIADGVCI DASLKPPVET EGSPPIFYNT SSSTVSTTMF IVNILFLIIS SVASL 475

SEQ ID NO: 16 (mature cow PH20)

LDFRAPPLIS NTSFLWAWNA PVERCVNRRF QLPPDLRLFS VKGSPQKSAT GQFITLFYAD 60

RLGYYPHIDE KTGKTVFGGI PQLGNLKSHM EKAKNDIAYY IPNDSVGLAV IDWENWRPTW 120

ARNWKPKDVY RDESVELVLQ KNPQLSFPEA SKIAKVDFET AGKSFMQETL KLGKLLRPNH 180

LWGYYLFPDC YNHNHNQPTY NGNCPDVEKR RNDDLEWLWK ESTALFPSVY LNIRLKSTQN 240

AALYVRNRVQ EAIRLSKIAS VESPLPVFVY ARPVFTDGSS TYLSQGDLVN SVGEIVSLGA 300

SGIIMWGSLN LSLSMQSCMN LGTYLNTTLN PYIINVTLAA KMCSQVLCHN EGVCTRKHWN 360

SSDYLHLNPM NFAIQTGEGG KYTVPGTVTL EDLQKFSDTF YCSCYANIHC KKRVDIKNVH 420

SVNVCMAEDI CIDSPVKLQP SDHSSSQEAS TTTFSSISPS TTTATVSPCT PEKHSPECLK 480

VRCSEVIPNV TQKACQSVKL KNISYQSPIQ NIKNQTTY 518

SEQ ID NO: 18 (mature cow PH20)

LDFRAPPLIS NTSFLWAWNA PVERCVNRRF QLPPDLRLFS VKGSPQKSAT GQFITLFYAD 60

RLGYYPHIDE KTGKTVFGGI PQLGNLKSHL EKAKNDIAYY IPNDSVGLAV IDWENWRPTW 120

ARNWKPKDVY RDESVELVLQ KNPQLSFPEA SKIAKVDFET AGKSFMQETL KLGKLLRPNH 180

LWGYYLFPDC YNHNHNQPTY NGNCPDVEKR RNDDLEWLWK ESTALFPSVY LNIRLKSTQN 240

AALYVRNRVQ EAIRLSKIAS VESPLPVFVY ARPVFTDGSS TYLSQGDLVN SVGEIVSLGA 300

SGIIMWGSLN LSLSVQSCMN LGTYLNTTLN PYIINVTLAA KMCSQVLCHD GGVCTRKHWN 360

SSDYLHLNPM NFAIQTGEGG KYTVPGTLTL EDLQKFSDTF YCSCYSNLSC KKRVDIKNVH 420

SVDVCMAEDV CIDAFLKPP 439

SEQ ID NO: 20 (mature mouse PH20)

VDYRAAPILS NTTFLWIWNV PTERCVGNVN DPIDLSFFSL IGSPRKTATG QPVTLFYVDR 60

LGLYPHIDAN QAEHYGGIPQ RGDYQAHLRK AKTDIEHYIP DDKLGLAIID WEEWRPTWLR 120

NWKPKDNYRN KSIELVQSTN PGLSITEATQ KAIQQFEEAG RKFMEGTLHL GKFLRPNQLW 180

GYYLFPDCYN NKFQDPKYDG QCPAVEKKRN DNLKWLWKAS TGLYPSVYLK KDLKSNRQAT 240

LYVRYRVVEA IRVSKVGNAS DPVPIFVYIR LVFTDRTSEY LLEDDLVNTI GEIVALGTSG 300

IIIWDAMSLA QRAAGCPILH KYMQTTLNPY IVNVTLAAKM CSQTLCNEKG MCSRRKESSD 360

VYLHLNPSHF DIMLTETGKY EVLGNPRVGD LEYFSEHFKC SCFSRMTCKE TSDVKNVQDV 420

NVCVGDNVCI KAKVEPNPAF YLLPGKSLLF MTTLGHVLYH LPQDIFVFPR KTLVSTP 477

SEQ ID NO: 22 (mature rat PH20)

VDYRATPVLS DTTFVWVWNV PTEACVENVT EPIDLSFFSL IGSPRKTAIG QPVTLFYVDR 60

LGNYPHIDAQ QTEHHGGIPQ KGDLTTHLVK AKEDVERYIP TDKLGLAIID WEEWRPTWMR 120

NWTPKDIYRN KSIELVQAAD PAINITEATV RAKAQFEGAA KEFMEGTLKL GKHIRPKHLW 180

GFYLFPDCYN NKFQVDNYDG QCPDVEKKRN DDLDWLWKES TGLYPSVYLK KDLKSSRKAT 240

LYVRYRVLES IRVSKVSDES NPVPIFVYIR LVFTDHVSEY LLEDDLVNTI GEIVAQGTSG 300

IIIWDAMSLA QRSAGCPILR QYMKTTLNPY IVNVTLAAKM CSQTLCKEKG MCSRKTESSD 360

AYLHLDPSSF SINVTEAGKY EVLGKPEVKD LEYFSEHFKC SCFSKMTCEE TSDMRSIQDV 420

NVCMGDNVCI KATLGPNSAF HLLPGKGLLL MTTLAHILHH LPHDIFVFPW KMLVSTP 477

SEQ ID NO: 24 (mature rabbit PH20)

ANFRAPPVIP NVPFLWAWNA PTEFCLGKSG EPLDMSLFSL FGSPRKNKTG QGITIFYVDR 60

LGYYPYIDPH TGAIVHGRIP QLGPLQQHLT KLRQEILYYM PKDNVGLAVI DWEEWLPTWL 120

RNWKPKDIYR IKSIELVKSQ HPQYNHSYAT EKAKRDFEKA GKDFMEETLK LGRLLRPNHL 180

WGYYLFPDCY NHHYDKPNLY KGSCFDIEKK RNDDLSWLWK ESTALFPSVY LTSRARSATA 240

LSKLYVVRNR VHEAIRVSKI PDDKSPLPNF VYTRLVFTDQ IFQFLSHHDL VYTIGEIVAL 300

GASGIVVWGS QSLARSMKSC LHLDNYMKTI LNPYLINVTL AAKMCNQVLC QEQGVCTRKN 360

WNPNDYLHLN PGNFAIQLGS NGTYKVDGKP TLTDLEQFSK NFQCSCYTNL NCKERTDMNN 420

VRTVNVCAVE NVCIDTNVGP QAVTYAPKEK KDVAHILSNT TSINSSTTMS LPFPRKHVSG 480

CLLVLCMYSQ YLNICYRLVA IGIQHGYYLK 510

SEQ ID NO: 29 (mature guinea pig PH20)

DKRAPPLIPN VPLLWVVWNAP TEFCIGGTNQ PLDMSFFSIV GTPRKNITGQ SITLYYVDRL 60

GYYPYIDPHT GAIVHGGLPQ LMNLQQHLRK SRQDILFYMP TDSVGLAVID WEEWRPTWTR 120

NWRPKDIYRN KSIELVKSQH PQYNHSYAVA VAKRDFERTG KAFMLETLKL GKSLRPSSLW 180

GYYLFPDCYN THFTKPNYDG HCPPIELQRN NDLQWLWNDS TALYPSVYLT SRVRSSQNGA 240

LYVRNRVHES IRVSKLMDDK NPLPIYVYIR LVFTDQTTTF LELDDLVHSV GEIVPLGVSG 300

IIIWGSLSLT RSLVSCIGLE NYMKGTLLPY LINVTLAAKM CGQVLCKNQG ICTRKDWNTN 360

TYLHLNATNF DIELQQNGKF VVHGKPSLED LQEFSKNFHC SCYTNVACKD RLDVHNVRSV 420

NVCTANNICI DAVLNFPSLD DDDEPPITDD TSQNQDSISD ITSSAPPSSH ILPKDLSWCL 480

FLLSIFSQHW KYLL 494

SEQ ID NO: 31 (mature red fox PH20)

QEFRAPPFIP NVSFLWGWNA PTELCAKRFN VQLDLNLFSL IGSPLKTVVG QGIAIFYADR 60

LGYYPHINKT TGKHVNGGIP QLGSLKKHLD KAKKDISHYI ETDSMGLAVI DWDSWRPNWA 120

RNWRPKHIYK EQSIDLAQQQ HIHLNLTEVT QIAQADFEKA ARCFMQETLK LGKFLRPNYL 180

WGFYLYPDCY NYNYKNPNYN GSCYDIEERR NDEIDWLWKE STALFPSIYL KSKLKSSPFT 240

ALYVRNRVLE AIRVSKVKDI KHPLPIFVYA RPVFTDVLLT YLTEDDLVNT IGESVSLGVS 300

GIVMWGSLNL TENVQICTEL DTYIKNKLNP YIINVTLAAK MCSQVLCQDE GVCIRKHWNS 360

NDYLHLNPVN FAIQLERSGR YTVQGKPTLE DLQQFSKKFY CACYANTHCR ERVDMTDIHT 420

IKVCVGEDVC IDVYLNLVPS GHLPVWKGKY VTSSNIFSVM PPATGPPCVP GRDLNRCLKA 480

RFIVEDNSKT TQTGYQSIYI KNKKQ 505

SEQ ID NO: 857 (mature gibbon PH20)

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSL TGSPRINVTG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKQDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLAEAT EKAKQEFEKA GKDFMVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE STALYPSIYL NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFVYAR IVFTDQVLKF LSRDELVYTL GETVALGASG 300

IVIWGSLSIV RSMKSCLLLD NYMETILNPY IINVTLAAKM CSQVLCQEQG VCIRKDWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTPED LEQFSEKFYC SCYSTLSCKE KADVKDTDAV 420

DVCIADGVCI DAFLKPPKET EESQIFYNAS PSTLSATMFI VSILFLIISS VVSL 474

SEQ ID NO: 859 (mature marmoset PH20)

LNFRAPPIIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSL IGSPRINVTG QGVTIFYVDR 60

LGYYPYIDPT TGAVVNGGIP QKIALQDHLD KVRKDIIFYM PVDNLGMGVI DWEEWRPTWA 120

RNWKPKDIYK NKSIEMVQQR NVQLNLTQAT DIAKQEFEKA AKDFMLETIK LGKALRPNHL 180

WGYYLFPDCY NHHYKKPDYN GSCFNIEIKR NNDLSWLWNE STALYPSIYL NTQQSAVAAM 240

LYVRNRVQEA IRVSKTPNAN SPLPVFVYAR LVFTDQVLRF LSQDELVYTL GETVALGASG 300

IVIWGSLSIM RSMKSCLLLD TYMETVLNPY IINTTLAAKM CSQVLCQEQG VCIRKDWNSS 360

DYLHLNPDNF AIETEKGGKF TVRGKPTYED LEQFSEKFYC SCYTSLSCKV KADVKDTDAV 420

DVCIADGVCI DASLKPPKET EESSQIFYNP SSSTPSAAIF IVAILFFISC VVSL 474

SEQ ID NO: 861 (mature orangutan PH20)

LNFRAPPIIP NMPFLWAWNA PSEFCLGKFD EPLDMSLFSL IGSPRINVTG QAVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDILFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLNLTEAT EKAKQEFEKA GKDFMVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE STALYPSIYL NTQQSPVAAT 240

LYVRNRVREA IRVSKIPDAK SPLPVFVYAR IVFTDQVLKF LSQDELVYTF GETVALGASG 300

IVIWGSLSIM RSMKSCLLLD NYMETILNPY IINVTLAAKM CSQVLCQEQG VCIRKDWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE KADVKDTDAV 420

DVCIADGVCI DAFLKPPMET EESQIFYNAS PSTLSATMFI WRLEVWDQGI SRMGFF 476

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 D 431

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 DA 432

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 DAF 433

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 DAFL 434

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 DAFLK 435

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 DAFLKP 436

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 DAFLKPP 437

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 DAFLKPPM 438

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 DAFLKPPME 439

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 440

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 E 441

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 EE 442

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 EEP 443

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 EEPQ 444

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 EEPQI 445

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 EEPQIF 446

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 EEPQIFYN 448

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 EEPQIFYNA 449

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 450

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 P 451

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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
QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 PST 453

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 PSTL 454

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 PSTLS 455

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 PSTLSA 456

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 PSTLSAT 457

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 PSTLSATM 458

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 PSTLSATMF 459

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 PSTLSATMFI 460

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG
QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI
DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK
LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 PSTLSATMFI V 461

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 PSTLSATMFI VS 462

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 PSTLSATMFI VSI 463

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE 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 PSTLSATMFI VSIL 464

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

LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG QGVTIFYVDR 60

LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM PVDNLGMAVI DWEEWRPTWA 120

RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT EKAKQEFEKA GKDFLVETIK LGKLLRPNHL 180

WGYYLFPDCY NHHYKKPGYN GSCFNVEIKR NDDLSWLWNE STALYPSIYL NTQQSPVAAT 240

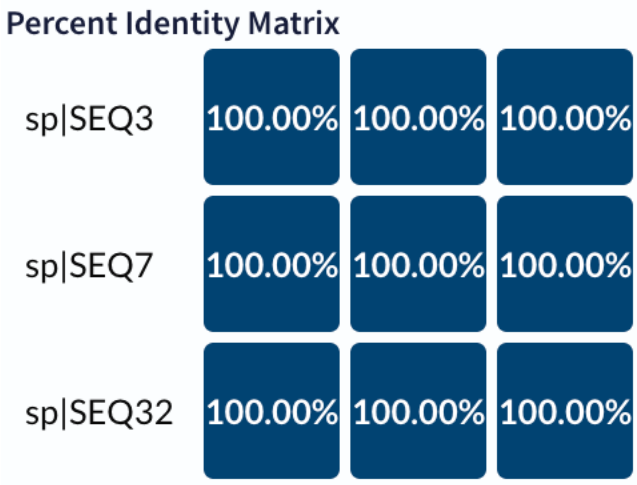
LYVRNRVREA IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF GETVALGASG 300

IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAKM CSQVLCQEQG VCIRKNWNSS 360

DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC SCYSTLSCKE KADVKDTDAV 420

DVCIADGVCI DAFLKPPMET EEPQIFYNAS PSTLSATMFI VSILF 465

II. Sequence comparison between SEQ ID NOs 3, 7, and 32



III. Sequence comparison between SEQ ID NOs 3, 32, 10, 870, 12, 14, 16, 18, 20, 22, 24, 29, 31, 857, 859, and 861*

Percent Identity Matrix

	SEQ-3	SEQ-32	SEQ-7	SEQ-10	SEQ-870	SEQ-12	SEQ-14	SEQ-16	SEQ-18	SEQ-20	SEQ-22	SEQ-24	SEQ-29	SEQ-31	SEQ-857	SEQ-859	SEQ-861
SEQ-3	100.00%	100.00%	100.00%	98.88%	98.21%	89.26%	89.26%	62.44%	65.45%	56.50%	54.26%	69.35%	59.37%	60.41%	96.42%	88.37%	97.09%
SEQ-32	100.00%	100.00%	100.00%	99.07%	98.37%	90.00%	90.00%	63.72%	64.88%	58.04%	55.48%	71.16%	60.14%	61.63%	96.74%	88.60%	97.21%
SEQ-7	100.00%	100.00%	100.00%	98.95%	98.31%	86.08%	88.79%	60.39%	65.45%	56.25%	54.02%	66.24%	57.02%	57.60%	96.39%	86.81%	94.30%
SEQ-10	98.88%	99.07%	98.95%	100.00%	99.37%	86.08%	89.01%	60.60%	65.68%	56.25%	54.02%	66.24%	57.24%	57.82%	96.60%	87.45%	94.73%
SEQ-870	98.21%	98.37%	98.31%	99.37%	100.00%	85.44%	88.37%	60.17%	65.22%	55.80%	53.57%	65.61%	56.59%	57.39%	95.97%	86.81%	94.09%
SEQ-12	89.26%	90.00%	86.08%	86.08%	85.44%	100.00%	97.05%	59.28%	64.30%	55.90%	53.45%	66.67%	60.73%	56.72%	88.37%	84.57%	90.13%
SEQ-14	89.26%	90.00%	88.79%	89.01%	88.37%	97.05%	100.00%	59.31%	64.30%	55.90%	53.45%	66.53%	60.78%	57.17%	90.66%	86.20%	87.76%
SEQ-16	62.44%	63.72%	60.39%	60.60%	60.17%	59.28%	59.31%	100.00%	96.58%	55.26%	52.63%	57.81%	55.39%	59.52%	60.60%	58.15%	60.77%
SEQ-18	65.45%	64.88%	65.45%	65.68%	65.22%	64.30%	64.30%	96.58%	100.00%	57.67%	55.38%	62.33%	59.73%	63.93%	65.68%	62.93%	65.90%
SEQ-20	56.50%	58.04%	56.25%	56.25%	55.80%	55.90%	55.90%	55.26%	57.67%	100.00%	78.83%	52.88%	52.60%	51.64%	56.25%	54.12%	56.70%
SEQ-22	54.26%	55.48%	54.02%	54.02%	53.57%	53.45%	53.45%	52.63%	55.38%	78.83%	100.00%	52.45%	52.60%	52.52%	54.02%	52.56%	54.46%
SEQ-24	69.35%	71.16%	66.24%	66.24%	65.61%	66.67%	66.53%	57.81%	62.33%	52.88%	52.45%	100.00%	65.50%	55.06%	66.67%	64.56%	66.60%
SEQ-29	59.37%	60.14%	57.02%	57.24%	56.59%	60.73%	60.78%	55.39%	59.73%	52.60%	52.60%	65.50%	100.00%	52.38%	57.51%	58.67%	57.85%
SEQ-31	60.41%	61.63%	57.60%	57.82%	57.39%	56.72%	57.17%	59.52%	63.93%	51.64%	52.52%	55.06%	52.38%	100.00%	58.03%	57.51%	58.42%
SEQ-857	96.42%	96.74%	96.39%	96.60%	95.97%	88.37%	90.66%	60.60%	65.68%	56.25%	54.02%	66.67%	57.51%	58.03%	100.00%	87.53%	94.50%
SEQ-859	88.37%	88.60%	86.81%	87.45%	86.81%	84.57%	86.20%	58.15%	62.93%	54.12%	52.56%	64.56%	58.67%	57.51%	87.53%	100.00%	87.29%
SEQ-861	97.09%	97.21%	94.30%	94.73%	94.09%	90.13%	87.76%	60.77%	65.90%	56.70%	54.46%	66.60%	57.85%	58.42%	94.50%	87.29%	100.00%

* The columns are arranged in the same order as the rows.