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(continued)

Primer	SEQ NO.	Nucleotide Sequences (5'-> 3')
		TGA TGA TGC ATG GGA GGT TTT AGA AAA GCA TC
E474-6H-not	56	GTT ATA GCG GCC GCT CAT TAG TGG TGA TGG TGA TGA TGC TCC ATG GGA GGT TTT AGA AAA GC
T475-6H-not	57	GTT ATA GCG GCC GCT CAT TAG TGG TGA TGG TGA TGA TGT GTC TCC ATG GGA GGT TTT AG
E476-6H-not	58	GTT ATA GCG GCC GCT CAT TAG TGG TGA TGG TGA TGA TGT TCT GTC TCC ATG GGA GG
E476-not	59	GTT ATA GCG GCC GCT CAT TAT TCT GTC TCC ATG GGA GG

[0096] After finding the PH20 variant with increased enzymatic activity and thermal stability, the 6xHis-tag-free cDNA of the PH20 variant was also constructed.

[0097] When the cell density of ExpiCHO cells reached $6 \times 10^6/\text{mL}$, a plasmid comprising the wild-type or variant PH20 cDNA inserted in the pcDNA3.4-TOPO vector was transfected into the ExpiCHO cells by ExpiFectamine CHO reagent. As a cell culture medium, ExpiCHO expression medium (100 to 500 mL) was used. After transfection, the ExpiCHO cells were shake-cultured at 130 rpm for total 6 days, during which the cells were cultured at 37°C for 1 day and further cultured at lower temperature of 32°C for 5 days. After completion of the culture, the cell supernatant was collected by centrifugation at 10,000 rpm for 30 min.

[0098] The recombinant proteins of the C-terminal 6xHis-attached wild-type PH20 and variant PH20, produced in the ExpiCHO cells, were purified in three steps (performed using a HisTrap column, a Q Sepharose column and a Phenyl column, respectively) by an AKTA prime system.

[0099] For protein purification using the HisTrap column, buffer A (20 mM sodium phosphate, pH 7.5, 0.5 M NaCl) and buffer B (20 mM sodium phosphate, pH 7.5, 0.5 M NaCl, 0.5 M imidazole) were prepared. The protein was bound to the HisTrap column, and the column was flushed with 5 column volumes (CV) of buffer A to remove non-specifically bound proteins. It was confirmed that the conductivity was maintained at constant level, the column was flushed with 5 CV of 20% buffer B to elute the protein. The eluted protein was dialyzed with dialysis buffer (20 mM sodium phosphate, pH 7.5, 50 mM NaCl). For protein purification using the Q Sepharose column, buffer A (20 mM sodium phosphate, pH 7.5) and buffer B (20 mM sodium phosphate, pH 7.5, 0.5 M NaCl) were prepared. The protein was bound to the Q Sepharose column, and the column was flushed with 5 CV of buffer A to remove nonspecifically bound proteins, and then 5 CV of buffer B was flushed at concentration gradient of 0 to 100% to elute the protein.

[0100] For protein purification using the phenyl column, buffer A (20 mM sodium phosphate, pH 7.0, 1.5 M $(\text{NH}_4)_2\text{SO}_4$) and buffer B (20 mM sodium phosphate, pH 7.0) were prepared. The protein was bound to the phenyl column, and the column was flushed with 5 CV of buffer A to remove nonspecifically bound proteins, and then 5 CV of buffer B was flushed at concentration gradient of 0 to 100% to elute the protein.

[0101] The enzymatic activities of wild-type PH20 and variant PH20 were measured by turbidimetric assay, substrate-gel assay, and Morgan-Elson assay.

[0102] The turbidimetric assay is a method of measuring the absorbance in the precipitate produced when hyaluronic acid is mixed with albumin (BSA). When hyaluronic acid is hydrolyzed by PH20, the absorbance of the precipitate produced when mixed with albumin decreases. Hyaluronidase PH20 (Sigma) was diluted to 1, 2, 5, 7.5, 10, 15, 20, 30, 50 and 60 units/mL, and prepared in each tube. The purified protein sample was dissolved in enzyme diluent buffer (20 mM Tris-HCl, pH 7.0, 77 mM NaCl, 0.01% (w/v) bovine serum albumin) and diluted to 100X, 300X, 600X, 1200X and 2400X and prepared in each tube. In fresh tubes, the hyaluronic acid solution having a concentration of 3 mg/mL was diluted 10-fold to a concentration of 0.3 mg/mL so that the volume of each tube became 180 μL . 60 μL of enzyme was added to and mixed with the diluted hyaluronic acid solution and allowed to react at 37°C for 45 min. After completion of the reaction, 50 μL of the reacted enzyme and 250 μL of acidic albumin solution were added to each well of a 96-well plate and shaken for 10 min, and then the absorbance was measured at 600 nm by spectrophotometer.

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[0103] In the substrate-gel assay, the protein was electrophoresed on 10% SDS gel (including 0.17 mg/mL hyaluronic acid) for 1 h, and SDS was removed with 2.5% Triton X-100 (w/v) at 4°C for 2 h. Thereafter, an enzymatic reaction was performed in the buffer (50 mM sodium phosphate, pH 7.0, 150 mM NaCl) at 37°C (which is the optimum temperature for PH20) for 1 to 4 h, and the protein was stained with 0.5% Alcian blue reagent. Alcian blue reagent not bound to the hyaluronic acid was removed using de-staining solution. The SDS gel stained with Alcian blue was imaged, and then the band was quantified.

[0104] The thermal stability of the protein was measured by a method of measuring the aggregation temperature by dynamic light scattering (DLS), a method of measuring the melting temperature (T_m) in real-time PCR using Sypro-Orange dye, a method of measuring the enzymatic activity after leaving the protein to stand at predetermined temperature for a predetermined time, etc. In the method of measuring the aggregation temperature by DLS, the aggregation of molecules is measured using light scattering, and thus the sensitivity is high and the aggregation temperature is generally lower than the melting temperature of the protein.

[0105] The sequences of the substituted or cleaved amino acids in the PH20 variants constructed in the present invention are shown in Table 11 below.

[0106] Among the variants according to the present invention, the variant having the 6xHis-tag attached to the C-terminus of PH20 was named HM; the variant free of the 6xHis-tag was named HP; mature PH20 (L36 to S490) having the 6xHis-tag attached to the C-terminus was named WT; and mature wild-type PH20 (L36 to Y482) having the C-terminus cleaved after Y482 while being free of the 6xHis-tag was named HW2.

Table 11. Amino acid sequences of PH20 variants according to the present invention and substitution/cleavage characteristics thereof

Name	SEQ NO.	Substitution	Amino Acid Sequence
HM1	60	12 amino acids substitution of M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T and N363G.	<p>LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDM</p> <p>SLFSFIGSPRINATGQGVTFYVDRLGYYPYIDSI</p> <p>TGVTVNGGIPQKISLQDHLDAKAKDITFYMPVDNL</p> <p>GMAVIDWEEWRPTWARNWKPKDVYKNRSIELVQQQ</p> <p>NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLL</p> <p>RPNHLWGYYLFPDCYNHHYKPGYNGSCFNVEIKR</p> <p>NDDLSQLWNESTALYPSIYLNTQQSPVAATLYVRN</p> <p>RVREAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKF</p> <p>LSQDELVYTFGETVALGASGIVIWGTLSTRTKES</p> <p><u>COAIKEYMDTTLGPY</u>IINVTLAAKMCSQVLCQEQQ</p> <p>VCIRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGK</p> <p>PTLEDLEQFSEKFYCSYSTLSCKEKADVKTDAV</p> <p>DVCIADGVCIDAFKPPMETEEPQIFYNASPSTLS</p>
HM2	61	7 amino acids substitution of Y365F, I367L, L371S, A372G, K374L, M375L and V379A	<p>LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDM</p> <p>SLFSFIGSPRINATGQGVTFYVDRLGYYPYIDSI</p> <p>TGVTVNGGIPQKISLQDHLDAKAKDITFYMPVDNL</p> <p>GMAVIDWEEWRPTWARNWKPKDVYKNRSIELVQQQ</p> <p>NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLL</p> <p>RPNHLWGYYLFPDCYNHHYKPGYNGSCFNVEIKR</p> <p>NDDLSQLWNESTALYPSIYLNTQQSPVAATLYVRN</p> <p>RVREAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKF</p> <p>LSQDELVYTFGETVALGASGIVIWGTLSTRTKES</p> <p><u>CQAIKEYMDTTLNPFILNVTSGALLCSQALCQEQQ</u></p> <p>VCIRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGK</p> <p>PTLEDLEQFSEKFYCSYSTLSCKEKADVKTDAV</p> <p>DVCIADGVCIDAFKPPMETEEPQIFYNASPSTLS</p>

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Name	SEQ NO.	Substitution	Amino Acid Sequence
HM3	62	19 amino acids substitution of M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T, N363G, Y365F, I367L, L371S, A372G, K374L, M375L and V379A	<p>LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTFYVDRLGYYPYIDSI TGVTVNGGIPQKISLQDHLDAKAKDITFYMPVDNL GMAVIDWEEWRPTWARNWKPKDVYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLL RPNHLWGYYLFPDCYNHHYKPGYNGSCFNVEIKR NDDLSQLWNNESTALYPSIYLNTQQSPVAATLYVRN RVREAIRVSKI PDAKSPLPVFAYTRIVFTDQVLKF LSQDELVYTFGETVALGASGIVIWGTLSTTRTKES COAIKEYMDTTLGFILNVTSGALLCSQALCQEQQ VCIRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGK PTLEDLEQFSEKFYCSYSTLSCKEKADVKTDAV DVCIA DGVCIDAFLKPPMETEEPQIFYNASPSTLS</p>
HM4	63	17 amino acids substitution of G340V, T341S, L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T and N363G	<p>LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTFYVDRLGYYPYIDSI TGVTVNGGIPQKISLQDHLDAKAKDITFYMPVDNL GMAVIDWEEWRPTWARNWKPKDVYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLL RPNHLWGYYLFPDCYNHHYKPGYNGSCFNVEIKR NDDLSQLWNNESTALYPSIYLNTQQSPVAATLYVRN RVREAIRVSKI PDAKSPLPVFAYTRIVFTDQVLKF LSQDELVYTFGETVALGASGIVIWWSWENTTRTKES COAIKEYMDTTLGPIIINVTLAAKMCSQVLCQEQQ VCIRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGK PTLEDLEQFSEKFYCSYSTLSCKEKADVKTDAV DVCIA DGVCIDAFLKPPMETEEPQIFYNASPSTLS</p>
HM6	64	11 amino acids substitution of M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T	<p>LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTFYVDRLGYYPYIDSI TGVTVNGGIPQKISLQDHLDAKAKDITFYMPVDNL GMAVIDWEEWRPTWARNWKPKDVYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLL RPNHLWGYYLFPDCYNHHYKPGYNGSCFNVEIKR NDDLSQLWNNESTALYPSIYLNTQQSPVAATLYVRN RVREAIRVSKI PDAKSPLPVFAYTRIVFTDQVLKF LSQDELVYTFGETVALGASGIVIWGTLSTTRTKES COAIKEYMDTTLNPIIINVTLAAKMCSQVLCQEQQ VCIRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGK PTLEDLEQFSEKFYCSYSTLSCKEKADVKTDAV DVCIA DGVCIDAFLKPPMETEEPQIFYNASPSTLS</p>

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Name	SEQ NO.	Substitution	Amino Acid Sequence
HM7	65	16 amino acids substitution of G340V, T341S L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T	LNFRAPPV I PNV PFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTIFYVDRLGYYPYIDSI TGVTVNGGIPQKISLQDHLDAKAKDITFYMPVDNL GMAVIDWEEWRPTWARNWKPKDVYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLL RPNHLWGYYLFPDCYNHHYKPGYNGSCFNVEIKR NDDL SWLWNESTALYPSIYLNTQQSPVAATLYVRN RVREAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKF LSQDELVYTFGETVALGASGIVIW <u>VSWENT</u> <u>TKE</u> <u>S</u> <u>COAIKE</u> <u>YMDT</u> <u>T</u> LNPII INVTLAAKMCSQVLCQEQQ VCIRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGK PTLEDLEQFSEKFYCSYSTLSCKEKADVKTDAV DVC IADGVC IDAFLKPPMETEEPQIFYNASPSTLS
HM8	66	12 amino acids substitution of I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T	LNFRAPPV I PNV PFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTIFYVDRLGYYPYIDSI TGVTVNGGIPQKISLQDHLDAKAKDITFYMPVDNL GMAVIDWEEWRPTWARNWKPKDVYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLL RPNHLWGYYLFPDCYNHHYKPGYNGSCFNVEIKR NDDL SWLWNESTALYPSIYLNTQQSPVAATLYVRN RVREAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKF LSQDELVYTFGETVALGASGIVIWGTL <u>SNTR</u> <u>TKE</u> <u>S</u> <u>COAIKE</u> <u>YMDT</u> <u>T</u> LNPII INVTLAAKMCSQVLCQEQQ VCIRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGK PTLEDLEQFSEKFYCSYSTLSCKEKADVKTDAV DVC IADGVC IDAFLKPPMETEEPQIFYNASPSTLS
HM9	67	13 amino acids substitution of S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T	LNFRAPPV I PNV PFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTIFYVDRLGYYPYIDSI TGVTVNGGIPQKISLQDHLDAKAKDITFYMPVDNL GMAVIDWEEWRPTWARNWKPKDVYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLL RPNHLWGYYLFPDCYNHHYKPGYNGSCFNVEIKR NDDL SWLWNESTALYPSIYLNTQQSPVAATLYVRN RVREAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKF LSQDELVYTFGETVALGASGIVIWGTL <u>ENTR</u> <u>TKE</u> <u>S</u> <u>COAIKE</u> <u>YMDT</u> <u>T</u> LNPII INVTLAAKMCSQVLCQEQQ VCIRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGK PTLEDLEQFSEKFYCSYSTLSCKEKADVKTDAV DVC IADGVC IDAFLKPPMETEEPQIFYNASPSTLS

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Name	SEQ NO.	Substitution	Amino Acid Sequence
HM10	68	14 amino acids substitution of L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T	<p>LNFRAPPV I PNV PFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTIFYVDRLGYYPYIDSI TGVTVNGGIPQKISLQDHLDAKAKDITFYMPVDNL GMAVIDWEEWRPTWARNWKPKDVYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLL RPNHLWGYYLFPDCYNHHYKPGYNGSCFNVEIKR NDDL SWLWNESTALYPSIYLNTQQSPVAATLYVRN RVREAIRVSKI PDAKSPLPVFAYTRIVFTDQVLKF LSQDELVYTFGETVALGASGIVIWGT WENTRTKES COAIKEYMDTTLN PY I INVTLAAKMCSQVLCQEQQ VCIRKNWNSSDY LHLNPDNFAIQLEKGGKFTVRGK PTLEDLEQFSEKFYCSYSTLSCKEKADV KDTDAV DVC IADGVCIDAFLKPPMETEEPQIFYNASPSTLS</p>
HM11	69	13 amino acids substitution of M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T, Y365F and I367L	<p>LNFRAPPV I PNV PFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTIFYVDRLGYYPYIDSI TGVTVNGGIPQKISLQDHLDAKAKDITFYMPVDNL GMAVIDWEEWRPTWARNWKPKDVYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLL RPNHLWGYYLFPDCYNHHYKPGYNGSCFNVEIKR NDDL SWLWNESTALYPSIYLNTQQSPVAATLYVRN RVREAIRVSKI PDAKSPLPVFAYTRIVFTDQVLKF LSQDELVYTFGETVALGASGIVIWGTLSI TRTKES COAIKEYMDTTLN FILNVTLAAKMCSQVLCQEQQ VCIRKNWNSSDY LHLNPDNFAIQLEKGGKFTVRGK PTLEDLEQFSEKFYCSYSTLSCKEKADV KDTDAV DVC IADGVCIDAFLKPPMETEEPQIFYNASPSTLS</p>
HM12	70	15 amino acids substitution of M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T, Y365F, I367L, L371S and A372G	<p>LNFRAPPV I PNV PFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTIFYVDRLGYYPYIDSI TGVTVNGGIPQKISLQDHLDAKAKDITFYMPVDNL GMAVIDWEEWRPTWARNWKPKDVYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLL RPNHLWGYYLFPDCYNHHYKPGYNGSCFNVEIKR NDDL SWLWNESTALYPSIYLNTQQSPVAATLYVRN RVREAIRVSKI PDAKSPLPVFAYTRIVFTDQVLKF LSQDELVYTFGETVALGASGIVIWGTLSI TRTKES COAIKEYMDTTLN FILNVT SGAKMCSQVLCQEQQ VCIRKNWNSSDY LHLNPDNFAIQLEKGGKFTVRGK PTLEDLEQFSEKFYCSYSTLSCKEKADV KDTDAV DVC IADGVCIDAFLKPPMETEEPQIFYNASPSTLS</p>

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Name	SEQ NO.	Substitution	Amino Acid Sequence
HM13	71	11 amino acids substitution of M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, and truncation before F38 at the N-terminus	FRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGVTFYVDRLGYYPYIDSITG VTVNGGIPQKISLQDHLDAKAKDITFYMPVDNLGM AVIDWEEWRPTWARNWPKPDVYKNRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRP NHLWGYYLFPDCYNHHYKPGYNGSCFNVEIKRND DLSWLWNESTALYPSIYLNTQQSPVAATLYVRNRV REAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLS QDELVYTFGETVALGASGIVIGTLSI <u>TRTKES</u> <u>COAIKE</u> <u>YMDT</u> <u>T</u> LNPIIINVTLAAKMCSQVLCQEQQVC IRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGKPT LEDLEQFSEKFYCSYSTLSCKEKADVKTDAVDV CIADGVCIDAF LKPPMETEEPQIFYNASPSTLS
HM14	72	11 amino acids substitution of M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T and truncation after I465 at the C-terminus	LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTFYVDRLGYYPYIDSI TGVTVNGGIPQKISLQDHLDAKAKDITFYMPVDNL GMAVIDWEEWRPTWARNWPKPDVYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLL RPNHLWGYYLFPDCYNHHYKPGYNGSCFNVEIKR NDDLWLWNESTALYPSIYLNTQQSPVAATLYVRN RVREAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKF LSQDELVYTFGETVALGASGIVIGTLSI <u>TRTKES</u> <u>COAIKE</u> <u>YMDT</u> <u>T</u> LNPIIINVTLAAKMCSQVLCQEQQ VCIRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGK PTLEDLEQFSEKFYCSYSTLSCKEKADVKTDAV DVCIDAGVCI
HM15	73	11 amino acids substitution of M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, and truncation after F468 at the C-terminus	LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTFYVDRLGYYPYIDSI TGVTVNGGIPQKISLQDHLDAKAKDITFYMPVDNL GMAVIDWEEWRPTWARNWPKPDVYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLL RPNHLWGYYLFPDCYNHHYKPGYNGSCFNVEIKR NDDLWLWNESTALYPSIYLNTQQSPVAATLYVRN RVREAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKF LSQDELVYTFGETVALGASGIVIGTLSI <u>TRTKES</u> <u>COAIKE</u> <u>YMDT</u> <u>T</u> LNPIIINVTLAAKMCSQVLCQEQQ VCIRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGK PTLEDLEQFSEKFYCSYSTLSCKEKADVKTDAV DVCIDAGVCIDAF

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Name	SEQ NO.	Substitution	Amino Acid Sequence
HM16	74	11 amino acids substitution of M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, and truncation after P471 at the C-terminus	<p>LNFRAPPV I PNV PFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTIFYVDRLGYYPYIDSI TGVTVNGGIPQKISLQDHLDKAKKDITFYMPVDNL GMAVIDWEEWRPTWARNWKPKDVYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLL RPNHLWGYYLFPDCYNHHYKPGYNGSCFNVEIKR NDDL SWLWNESTALYPSIYLNTQQSPVAATLYVRN RVREAIRVSKI PDAKSPLPVFAYTRIVFTDQVLKF LSQDELVYTFGETVALGASGIVIWGTL SI <u>TRTKES</u> <u>COAIKE</u>YMD<u>T</u>TLNPI I INVTLAAKMCSQVLCQEQQ VCIRKNWNSSDY LHLNPDNFAIQLEKGGKFTVRGK PTLEDLEQFSEKFCYSCYSTLSCKEKADV KDTDAV DVC IADGVCIDAFLKP</p>
HM17	75	Substitution of L36~V47 with FRGPLLPNR, and amino acids substitution of M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T	<p><u>FRGPLLPNR</u>PFLWAWNAPSEFCLGKFDEPLDMSLF SFIGSPRINATGQGVTIFYVDRLGYYPYIDSI TGV TVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGMA VIDWEEWRPTWARNWKPKDVYKNRSIELVQQQNVQ LSLTEATEKAKQEFKAGKDFLVETIKLGKLLRPN HLWGYYLFPDCYNHHYKPGYNGSCFNVEIKRND LSWLWNESTALYPSIYLNTQQSPVAATLYVRNRVR EAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQ DELVYTFGETVALGASGIVIWGTL SI <u>TRTKES</u><u>COA</u> <u>IKE</u>YMD<u>T</u>TLNPI I INVTLAAKMCSQVLCQEQQVCI RKNWNSSDY LHLNPDNFAIQLEKGGKFTVRGKPTL EDLEQFSEKFCYSCYSTLSCKEKADV KDTDAVDVC IADGVCIDAFLKPPMETEEPQIFYNASPSTLS</p>
HM18	76	Substitution of L36~A52 with FRGPLLPNRPFTTV, and amino acids substitution of M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T	<p><u>FRGPLLPNRPFTTV</u>WNA PSEFCLGKFDEPLDMSLF SFIGSPRINATGQGVTIFYVDRLGYYPYIDSI TGV TVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGMA VIDWEEWRPTWARNWKPKDVYKNRSIELVQQQNVQ LSLTEATEKAKQEFKAGKDFLVETIKLGKLLRPN HLWGYYLFPDCYNHHYKPGYNGSCFNVEIKRND LSWLWNESTALYPSIYLNTQQSPVAATLYVRNRVR EAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQ DELVYTFGETVALGASGIVIWGTL SI <u>TRTKES</u><u>COA</u> <u>IKE</u>YMD<u>T</u>TLNPI I INVTLAAKMCSQVLCQEQQVCI RKNWNSSDY LHLNPDNFAIQLEKGGKFTVRGKPTL EDLEQFSEKFCYSCYSTLSCKEKADV KDTDAVDVC IADGVCIDAFLKPPMETEEPQIFYNASPSTLS</p>

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Name	SEQ NO.	Substitution	Amino Acid Sequence
HM19	77	14 amino acids substitution of L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before F38 at the N-terminus, and truncation after K470 at the C-terminus	FRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGVTFIFYVDRLGYYPYIDSITG VTVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGM AVIDWEEWRPTWARNWPKPDVYKNRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRP NHLWGYLFPDCYNHHYKPGYNGSCFNVEIKRND DLSWLWNESTALYPSIYLNTQQSPVAATLYVRNRV REAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLS QDELVYTFGETVALGASGIVIWGT <u>WENTRTKESQ</u> <u>AIKEYMDTT</u> LNPIIINVTLAAKMCSQVLCQEQGVC IRKNWNSSDYLHLNPDNFIAIQLEKGGKFTVRGKPT LEDLEQFSEKFYCSCYSTLSCKEKADVKTDAVDV CIADGVCIDAF
HM20	78	14 amino acids substitution of L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before F38 at the N-terminus, and truncation after F468 at the C-terminus	FRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGVTFIFYVDRLGYYPYIDSITG VTVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGM AVIDWEEWRPTWARNWPKPDVYKNRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRP NHLWGYLFPDCYNHHYKPGYNGSCFNVEIKRND DLSWLWNESTALYPSIYLNTQQSPVAATLYVRNRV REAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLS QDELVYTFGETVALGASGIVIWGT <u>WENTRTKESQ</u> <u>AIKEYMDTT</u> LNPIIINVTLAAKMCSQVLCQEQGVC IRKNWNSSDYLHLNPDNFIAIQLEKGGKFTVRGKPT LEDLEQFSEKFYCSCYSTLSCKEKADVKTDAVDV CIADGVCIDAF

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Name	SEQ NO.	Substitution	Amino Acid Sequence
HM21	79	15 amino acids substitution of T341S, L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T	<p>LNFRAPPVIPNV PFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTIFYVDRLGYYPYIDSI TGVTVNGGIPQKISLQDHLDKAKKDITFYMPVDNL GMAVIDWEEWRPTWARNWKPKDVYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLL RPNHLWGYYLFPDCYNHHYKPGYNGSCFNVEIKR NDDL SWLWNESTALYPSIYLNTQQSPVAATLYVRN RVREAIRVSKI PDAKSPLPVFAYTRIVFTDQVLKF LSQDELVYTFGETVALGASGIVIWG <u>SWENTRTKES</u> <u>COAIKE</u>YMDTTLNPI I INVTLAAKMCSQVLCQEQQ VCIRKNWNSSDY LHLNPDNFAIQLEKGGKFTVRGK PTLEDLEQFSEKFYCSYSTLSCKEKADV KDTDAV DVC IADGVCIDAFLKPPMETEEPQIFYNASPSTLS</p>
HM24	80	11 amino acids substitution of M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, and truncation before A40 at the N-terminus	<p>APPVIPNV PFLWAWNAPSEFCLGKFDEPLDMSLF FIGSPRINATGQGVTIFYVDRLGYYPYIDSITGV TVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAV</p> <p>IDWEEWRPTWARNWKPKDVYKNRSIELVQQQNVQL SLTEATEKAKQEFKAGKDFLVETIKLGKLLRPNH LWGYYLFPDCYNHHYKPGYNGSCFNVEIKRNDL SWLWNESTALYPSIYLNTQQSPVAATLYVRNRVRE AIRVSKI PDAKSPLPVFAYTRIVFTDQVLKFLS QDELVYTFGETVALGASGIVIWGTLST <u>TRTKES</u> <u>COAIKE</u>YMDTTLNPI I INVTLAAKMCSQVLCQEQQVCIR KNWNSSDY LHLNPDNFAIQLEKGGKFTVRGKPTLE DLEQFSEKFYCSYSTLSCKEKADV KDTDAVDVCI ADGVC IADGVCIDAFLKPPMETEEPQIFYNASPSTLS</p>
HM25	81	11 amino acids substitution of M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before P42 at the N-terminus	<p>PVIPNV PFLWAWNAPSEFCLGKFDEPLDMSLF SFIGSPRINATGQGVTIFYVDRLGYYPYIDSITGV TVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAV IDWEEWRPTWARNWKPKDVYKNRSIELVQQQNVQL SLTEATEKAKQEFKAGKDFLVETIKLGKLLRPNHLW GYLFPDCYNHHYKPGYNGSCFNVEIKRNDL SWLWNESTALYPSIYLNTQQSPVAATLYVRNRVRE AIRVSKI PDAKSPLPVFAYTRIVFTDQVLKFLS QDELVYTFGETVALGASGIVIWGTLST <u>TRTKES</u> <u>COAIKE</u>YMDTTLNPI I INVTLAAKMCSQVLCQEQQVCIR KNWNSSDY LHLNPDNFAIQLEKGGKFTVRGKPTLE DLEQFSEKFYCSYSTLSCKEKADV KDTDAVDVCI ADGVC IADGVCIDAFLKPPMETEEPQIFYNASPSTLS</p>

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Name	SEQ NO.	Substitution	Amino Acid Sequence
HM29	82	14 amino acids substitution of L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before L36 at the N-terminus, and truncation after A467 at the C-terminus	LNFRAPPV I PNV PFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTIFYVDRLGYYPYIDSI TGVTVNGGIPQKISLQDHLDAKAKDITFYMPVDNL GMAVIDWEEWRPTWARNWPKPDVYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLL RPNHLWGYYLFPDCYNHHYKPGYNGSCFNVEIKR NDDL SWLWNESTALYPSIYLN TQQSPVAATLYVRN RVREAIRVSKI PDAKSPLPVFAYTRIVFTDQVLKF LSQDEL VYTFGETVALGASGIVIWGT <u>WENT</u> <u>R</u> <u>TKE</u> <u>S</u> <u>COAIKE</u> <u>YMD</u> <u>T</u> <u>T</u> LNPY I INVTLA AKMCSQVLCQE QG VCIRKNWNSSDY LHLNPDNF AIQLEKGGKFTVRGK PTLEDLEQFSEKFYCSYSTLSCKEKADV KDTDAV DVC IADGVCIDA
HM30	83	14 amino acids substitution of L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before L36 at the N-terminus, and truncation after C464 at the C-terminus	LNFRAPPV I PNV PFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTIFYVDRLGYYPYIDSI TGVTVNGGIPQKISLQDHLDAKAKDITFYMPVDNL GMAVIDWEEWRPTWARNWPKPDVYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLL RPNHLWGYYLFPDCYNHHYKPGYNGSCFNVEIKR NDDL SWLWNESTALYPSIYLN TQQSPVAATLYVRN RVREAIRVSKI PDAKSPLPVFAYTRIVFTDQVLKF LSQDEL VYTFGETVALGASGIVIWGT <u>WENT</u> <u>R</u> <u>TKE</u> <u>S</u> <u>COAIKE</u> <u>YMD</u> <u>T</u> <u>T</u> LNPY I INVTLA AKMCSQVLCQE QG VCIRKNWNSSDY LHLNPDNF AIQLEKGGKFTVRGK PTLEDLEQFSEKFYCSYSTLSCKEKADV KDTDAV DVC IADGVC
HM31	84	14 amino acids substitution of L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before L36 at the N-terminus, and truncation after D461 at the C-terminus	LNFRAPPV I PNV PFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTIFYVDRLGYYPYIDSI TGVTVNGGIPQKISLQDHLDAKAKDITFYMPVDNL GMAVIDWEEWRPTWARNWPKPDVYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLL RPNHLWGYYLFPDCYNHHYKPGYNGSCFNVEIKR NDDL SWLWNESTALYPSIYLN TQQSPVAATLYVRN RVREAIRVSKI PDAKSPLPVFAYTRIVFTDQVLKF LSQDEL VYTFGETVALGASGIVIWGT <u>WENT</u> <u>R</u> <u>TKE</u> <u>S</u> <u>COAIKE</u> <u>YMD</u> <u>T</u> <u>T</u> LNPY I INVTLA AKMCSQVLCQE QG VCIRKNWNSSDY LHLNPDNF AIQLEKGGKFTVRGK PTLEDLEQFSEKFYCSYSTLSCKEKADV KDTDAV DVC IAD

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Name	SEQ NO.	Substitution	Amino Acid Sequence
HM32	85	14 amino acids substitution of L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before L36 at the N-terminus, and truncation after C458 at the C-terminus	LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTFYVDRLGYYPYIDSI TGVTVNGGIPQKISLQDHLDAKAKDITFYMPVDNL GMAVIDWEEWRPTWARNWKPKDVYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLL RPNHLWGYYLFPDCYNHKKPGYNGSCFNVEIKR NDDLSQLWNESTALYPSIYLNTQQSPVAATLYVRN RVREAIRVSKI PDAKSPLPVFAYTRIVFTDQVLKF LSQDELVYTFGETVALGASGIVIWGT <u>WENTRTKES</u> <u>COAIKEYMDTT</u> LNPI I INVTLAAKMCSQVLCQEQQ VCIRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGK PTLEDLEQFSEKFYCSYSTLSCKEKADVKTDAV DVC
HM33	86	14 amino acids substitution of L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before L36 at the N-terminus, and truncation after V455 at the C-terminus	LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTFYVDRLGYYPYIDSI TGVTVNGGIPQKISLQDHLDAKAKDITFYMPVDNL GMAVIDWEEWRPTWARNWKPKDVYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLL RPNHLWGYYLFPDCYNHKKPGYNGSCFNVEIKR NDDLSQLWNESTALYPSIYLNTQQSPVAATLYVRN RVREAIRVSKI PDAKSPLPVFAYTRIVFTDQVLKF LSQDELVYTFGETVALGASGIVIWGT <u>WENTRTKES</u> <u>COAIKEYMDTT</u> LNPI I INVTLAAKMCSQVLCQEQQ VCIRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGK PTLEDLEQFSEKFYCSYSTLSCKEKADVKTDAV
HP34	87	15 amino acids substitution of T341S, L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before F38 at the N-terminus, and truncation after K470 at the C-terminus	FRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGVTFYVDRLGYYPYIDSITG VTVNGGIPQKISLQDHLDAKAKDITFYMPVDNLGM AVIDWEEWRPTWARNWKPKDVYKNRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRP NHLWGYYLFPDCYNHKKPGYNGSCFNVEIKRND DLSQLWNESTALYPSIYLNTQQSPVAATLYVRNRV REAIRVSKI PDAKSPLPVFAYTRIVFTDQVLKFLS QDELVYTFGETVALGASGIVIWG <u>SWENTRTKES</u> <u>COAIKEYMDTT</u> LNPI I INVTLAAKMCSQVLCQEQQVC IRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGKPT LEDLEQFSEKFYCSYSTLSCKEKADVKTDAVDV CIADGVCIDAFLK

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Name	SEQ NO.	Substitution	Amino Acid Sequence
HM35	88	14 amino acids substitution of L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before F38 at the N-terminus, and truncation after P472 at the C-terminus	FRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGVTFIFYVDRLGYYPYIDSITG VTVNGGIPQKISLQDHLDAKAKDITFYMPVDNLGM AVIDWEEWRPTWARNWPKPKDVYKNRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRP NHLWGYYLFPDCYNHHYKPKGYNGSCFNVEIKRND DLSWLWNESTALYPSIYLNTQQSPVAATLYVRNRV REAIRVSKI PDAKSPLPVFAYTRIVFTDQVLKFLS QDELVYTFGETVALGASGIVIWGT <u>WENTR</u> <u>TKE</u> <u>SCQ</u> <u>AIKE</u> <u>YMD</u> <u>T</u> <u>T</u> LNPI I INVTLAAKMCSQVLCQEQQVC IRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGKPT LEDLEQFSEKFYCSCYSTLSCKEKADVKTDAVDV CIADGVCIDAFLKPP
HM36	89	14 amino acids substitution of L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before F38 at the N-terminus, and truncation after M473 at the C-terminus	FRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGVTFIFYVDRLGYYPYIDSITG VTVNGGIPQKISLQDHLDAKAKDITFYMPVDNLGM AVIDWEEWRPTWARNWPKPKDVYKNRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRP NHLWGYYLFPDCYNHHYKPKGYNGSCFNVEIKRND DLSWLWNESTALYPSIYLNTQQSPVAATLYVRNRV REAIRVSKI PDAKSPLPVFAYTRIVFTDQVLKFLS QDELVYTFGETVALGASGIVIWGT <u>WENTR</u> <u>TKE</u> <u>SCQ</u> <u>AIKE</u> <u>YMD</u> <u>T</u> <u>T</u> LNPI I INVTLAAKMCSQVLCQEQQVC IRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGKPT LEDLEQFSEKFYCSCYSTLSCKEKADVKTDAVDV CIADGVCIDAFLKPPM
HM37	90	14 amino acids substitution of L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before F38 at the N-terminus, and truncation after E474 at the C-terminus	FRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGVTFIFYVDRLGYYPYIDSITG VTVNGGIPQKISLQDHLDAKAKDITFYMPVDNLGM AVIDWEEWRPTWARNWPKPKDVYKNRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRP NHLWGYYLFPDCYNHHYKPKGYNGSCFNVEIKRND DLSWLWNESTALYPSIYLNTQQSPVAATLYVRNRV REAIRVSKI PDAKSPLPVFAYTRIVFTDQVLKFLS QDELVYTFGETVALGASGIVIWGT <u>WENTR</u> <u>TKE</u> <u>SCQ</u> <u>AIKE</u> <u>YMD</u> <u>T</u> <u>T</u> LNPI I INVTLAAKMCSQVLCQEQQVC IRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGKPT LEDLEQFSEKFYCSCYSTLSCKEKADVKTDAVDV CIADGVCIDAFLKPPME

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Name	SEQ NO.	Substitution	Amino Acid Sequence
HM38	91	14 amino acids substitution of L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before F38 at the N-terminus, and truncation after T475 at the C-terminus	FRAPPVIPNPVFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGVTFIFYVDRLGYYPYIDSITG VTVNGGIPQKISLQDHLDDKAKKDITFYMPVDNLGM AVIDWEEWRPTWARNWPKPDVYKNRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRP NHLWGYYLFPDCYNHHYKPKPGYNGSCFNVEIKRND DLSWLWNESTALYPSIYLNTQQSPVAATLYVRNRV REAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLS QDELVYTFGETVALGASGIVIWGTTWENTRTKESQ AIKEYMDTTLNPIINVTLAAKMCSQVLCQEQGVC IRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGKPT LEDLEQFSEKFYCSCYSTLSCKEKADVKTDAVDV CIADGVCIDAFLKPPMET
HM39	92	14 amino acids substitution of L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before F38 at the N-terminus, and truncation after E476 at the C-terminus	FRAPPVIPNPVFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGVTFIFYVDRLGYYPYIDSITG VTVNGGIPQKISLQDHLDDKAKKDITFYMPVDNLGM AVIDWEEWRPTWARNWPKPDVYKNRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRP NHLWGYYLFPDCYNHHYKPKPGYNGSCFNVEIKRND DLSWLWNESTALYPSIYLNTQQSPVAATLYVRNRV REAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLS QDELVYTFGETVALGASGIVIWGTTWENTRTKESQ AIKEYMDTTLNPIINVTLAAKMCSQVLCQEQGVC IRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGKPT LEDLEQFSEKFYCSCYSTLSCKEKADVKTDAVDV CIADGVCIDAFLKPPMETE
HM40	93	11 amino acids substitution of M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, and truncation before N37 at the N-terminus	NFRAPPVIPNPVFLWAWNAPSEFCLGKFDEPLDMS LFSFIGSPRINATGQGVTFIFYVDRLGYYPYIDSIT GVTVNGGIPQKISLQDHLDDKAKKDITFYMPVDNLG MAVIDWEEWRPTWARNWPKPDVYKNRSIELVQQQN VQLSLTEATEKAKQEFKAGKDFLVETIKLGKLLR PNHLWGYYLFPDCYNHHYKPKPGYNGSCFNVEIKRN DDLWLWNESTALYPSIYLNTQQSPVAATLYVRNR VREAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFL SQDELVYTFGETVALGASGIVIWGTLSTRTKESQ QAIKEYMDTTLNPIINVTLAAKMCSQVLCQEQGV CIRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGKP TLEDLEQFSEKFYCSCYSTLSCKEKADVKTDAVD VCIADGVCIDAFLKPPMETEETPQIFYNASPSTLS

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Name	SEQ NO.	Substitution	Amino Acid Sequence
HM41	94	11 amino acids substitution of M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, and truncation before R39 at the N-terminus	RAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSLF SFIGSPRINATGQGVTIFYVDRLGYYPYIDSITGV TVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGMA VIDWEEWRPTWARNWPKPDVYKNRSIELVQQQNVQ LSLATEATEKAKQEFKAGKDFLVETIKLGKLLRPN HLWGYLFPDCYNHYYKKPGYNGSCFNVEIKRND LSWLWNESTALYPSIYLNTQQSPVAATLYVRNRVR EAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLS QDELVYTFGETVALGASGIVIWGTLSTI <u>TRTKE</u> <u>SCQA</u> <u>IKE</u> <u>YMDT</u> <u>T</u> LNPIINVTLAAKMCSQVLCQEQGVC IRKNWNSSDYLHLNPDNFQAIQLEKGGKFTVRGKPTL EDLEQFSEKFYCSCYSTLSCKEKADVKTDAVDVC IADGVCIDAFLKPPMETEEPQIFYNASPSTLS
HM42	95	11 amino acids substitution of M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, and truncation before P41 at the N-terminus	PPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSLFSF IGSPRINATGQGVTIFYVDRLGYYPYIDSITGVTV NGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVI DWEEWRPTWARNWPKPDVYKNRSIELVQQQNVQLS LATEATEKAKQEFKAGKDFLVETIKLGKLLRPNHL WGYLFPDCYNHYYKKPGYNGSCFNVEIKRND DLWNESTALYPSIYLNTQQSPVAATLYVRNRVREA IRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDE LVYTFGETVALGASGIVIWGTLSTI <u>TRTKE</u> <u>SCQA</u> <u>IAIK</u> <u>E</u> <u>YMDT</u> <u>T</u> LNPIINVTLAAKMCSQVLCQEQGVCIRK NWNSSDYLHLNPDNFQAIQLEKGGKFTVRGKPTLED LEQFSEKFYCSCYSTLSCKEKADVKTDAVDVCIA DGVCIDAFLKPPMETEEPQIFYNASPSTLS
HM43	96	14 amino acids substitution of L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before F38 at the N-terminus, and truncation after I465 at the C-terminus	FRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGVTIFYVDRLGYYPYIDSITG VTVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGM AVIDWEEWRPTWARNWPKPDVYKNRSIELVQQQNV QLSLATEATEKAKQEFKAGKDFLVETIKLGKLLRP NHLWGYLFPDCYNHYYKKPGYNGSCFNVEIKRND DLWLWNESTALYPSIYLNTQQSPVAATLYVRNRV REAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLS QDELVYTFGETVALGASGIVIWGS <u>WENT</u> <u>RTKE</u> <u>SCQ</u> <u>AIKE</u> <u>YMDT</u> <u>T</u> LNPIINVTLAAKMCSQVLCQEQGVC IRKNWNSSDYLHLNPDNFQAIQLEKGGKFTVRGKPT LEDLEQFSEKFYCSCYSTLSCKEKADVKTDAVDV CIADGVC

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Name	SEQ NO.	Substitution	Amino Acid Sequence
HM44	97	14 amino acids substitution of L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before F38 at the N-terminus, and truncation after D466 at the C-terminus	FRAPPV I P N V P F L W A W N A P S E F C L G K F D E P L D M S L F S F I G S P R I N A T G Q G V T I F Y V D R L G Y P Y I D S I T G V T V N G G I P Q K I S L Q D H L D K A K K D I T F Y M P V D N L G M A V I D W E E W R P T W A R N W K P K D V Y K N R S I E L V Q Q Q N V Q L S L T E A T E K A K Q E F E K A G K D F L V E T I K L G K L L R P N H L W G Y Y L F P D C Y N H H Y K K P G Y N G S C F N V E I K R N D D L S W L W N E S T A L Y P S I Y L N T Q Q S P V A A T L Y V R N R V R E A I R V S K I P D A K S P L P V F A Y T R I V F T D Q V L K F L S Q D E L V Y T F G E T V A L G A S G I V I W G S <u>W E N T R T K E S C Q</u> <u>A I K E Y M D T T</u> L N P Y I I N V T L A A K M C S Q V L C Q E Q G V C I R K N W N S S D Y L H L N P D N F A I Q L E K G G K F T V R G K P T L E D L E Q F S E K F Y C S C Y S T L S C K E A D V K D T D A V D V C I A D G V C I D
HM45	98	14 amino acids substitution of L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before F38 at the N-terminus, and truncation after A467 at the C-terminus	FRAPPV I P N V P F L W A W N A P S E F C L G K F D E P L D M S L F S F I G S P R I N A T G Q G V T I F Y V D R L G Y P Y I D S I T G V T V N G G I P Q K I S L Q D H L D K A K K D I T F Y M P V D N L G M A V I D W E E W R P T W A R N W K P K D V Y K N R S I E L V Q Q Q N V Q L S L T E A T E K A K Q E F E K A G K D F L V E T I K L G K L L R P N H L W G Y Y L F P D C Y N H H Y K K P G Y N G S C F N V E I K R N D D L S W L W N E S T A L Y P S I Y L N T Q Q S P V A A T L Y V R N R V R E A I R V S K I P D A K S P L P V F A Y T R I V F T D Q V L K F L S Q D E L V Y T F G E T V A L G A S G I V I W G S <u>W E N T R T K E S C Q</u> <u>A I K E Y M D T T</u> L N P Y I I N V T L A A K M C S Q V L C Q E Q G V C I R K N W N S S D Y L H L N P D N F A I Q L E K G G K F T V R G K P T L E D L E Q F S E K F Y C S C Y S T L S C K E A D V K D T D A V D V C I A D G V C I D A
HP46	99	15 amino acids substitution of T341S, L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before F38 at the N-terminus, and truncation after F468 at the C-terminus	FRAPPV I P N V P F L W A W N A P S E F C L G K F D E P L D M S L F S F I G S P R I N A T G Q G V T I F Y V D R L G Y P Y I D S I T G V T V N G G I P Q K I S L Q D H L D K A K K D I T F Y M P V D N L G M A V I D W E E W R P T W A R N W K P K D V Y K N R S I E L V Q Q Q N V Q L S L T E A T E K A K Q E F E K A G K D F L V E T I K L G K L L R P N H L W G Y Y L F P D C Y N H H Y K K P G Y N G S C F N V E I K R N D D L S W L W N E S T A L Y P S I Y L N T Q Q S P V A A T L Y V R N R V R E A I R V S K I P D A K S P L P V F A Y T R I V F T D Q V L K F L S Q D E L V Y T F G E T V A L G A S G I V I W G S <u>W E N T R T K E S C Q</u> <u>A I K E Y M D T T</u> L N P Y I I N V T L A A K M C S Q V L C Q E Q G V C I R K N W N S S D Y L H L N P D N F A I Q L E K G G K F T V R G K P T L E D L E Q F S E K F Y C S C Y S T L S C K E A D V K D T D A V D V C I A D G V C I D A F

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Name	SEQ NO.	Substitution	Amino Acid Sequence
HM47	100	14 amino acids substitution of L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before F38 at the N-terminus, and truncation after P478 at the C-terminus	FRAPPV I P N V P F L W A W N A P S E F C L G K F D E P L D M S L F S F I G S P R I N A T G Q G V T I F Y V D R L G Y Y P Y I D S I T G V T V N G G I P Q K I S L Q D H L D K A K K D I T F Y M P V D N L G M A V I D W E E W R P T W A R N W K P K D V Y K N R S I E L V Q Q Q N V Q L S L T E A T E K A K Q E F E K A G K D F L V E T I K L G K L L R P N H L W G Y Y L F P D C Y N H H Y K K P G Y N G S C F N V E I K R N D D L S W L W N E S T A L Y P S I Y L N T Q Q S P V A A T L Y V R N R V R E A I R V S K I P D A K S P L P V F A Y T R I V F T D Q V L K F L S Q D E L V Y T F G E T V A L G A S G I V I W G T <u>W E N T R T K E S C Q</u> <u>A I K E Y M D T T</u> L N P Y I I N V T L A A K M C S Q V L C Q E Q G V C I R K N W N S S D Y L H L N P D N F A I Q L E K G G K F T V R G K P T L E D L E Q F S E K F Y C S C Y S T L S C K E K A D V K D T D A V D V C I A D G V C I D A F L K P P M E T E E P
HM48	101	14 amino acids substitution of L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before F38 at the N-terminus, and truncation after I480 at the C-terminus	FRAPPV I P N V P F L W A W N A P S E F C L G K F D E P L D M S L F S F I G S P R I N A T G Q G V T I F Y V D R L G Y Y P Y I D S I T G V T V N G G I P Q K I S L Q D H L D K A K K D I T F Y M P V D N L G M A V I D W E E W R P T W A R N W K P K D V Y K N R S I E L V Q Q Q N V Q L S L T E A T E K A K Q E F E K A G K D F L V E T I K L G K L L R P N H L W G Y Y L F P D C Y N H H Y K K P G Y N G S C F N V E I K R N D D L S W L W N E S T A L Y P S I Y L N T Q Q S P V A A T L Y V R N R V R E A I R V S K I P D A K S P L P V F A Y T R I V F T D Q V L K F L S Q D E L V Y T F G E T V A L G A S G I V I W G T <u>W E N T R T K E S C Q</u> <u>A I K E Y M D T T</u> L N P Y I I N V T L A A K M C S Q V L C Q E Q G V C I R K N W N S S D Y L H L N P D N F A I Q L E K G G K F T V R G K P T L E D L E Q F S E K F Y C S C Y S T L S C K E K A D V K D T D A V D V C I A D G V C I D A F L K P P M E T E E P Q I
HM49	102	14 amino acids substitution of L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before F38 at the N-terminus, and truncation after Y482 at the C-terminus	FRAPPV I P N V P F L W A W N A P S E F C L G K F D E P L D M S L F S F I G S P R I N A T G Q G V T I F Y V D R L G Y Y P Y I D S I T G V T V N G G I P Q K I S L Q D H L D K A K K D I T F Y M P V D N L G M A V I D W E E W R P T W A R N W K P K D V Y K N R S I E L V Q Q Q N V Q L S L T E A T E K A K Q E F E K A G K D F L V E T I K L G K L L R P N H L W G Y Y L F P D C Y N H H Y K K P G Y N G S C F N V E I K R N D D L S W L W N E S T A L Y P S I Y L N T Q Q S P V A A T L Y V R N R V R E A I R V S K I P D A K S P L P V F A Y T R I V F T D Q V L K F L S Q D E L V Y T F G E T V A L G A S G I V I W G T <u>W E N T R T K E S C Q</u> <u>A I K E Y M D T T</u> L N P Y I I N V T L A A K M C S Q V L C Q E Q G V C I R K N W N S S D Y L H L N P D N F A I Q L E K G G K F T V R G K P T L E D L E Q F S E K F Y C S C Y S T L S C K E K A D V K D T D A V D V C I A D G V C I D A F L K P P M E T E E P Q I F Y

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Name	SEQ NO.	Substitution	Amino Acid Sequence
HM50	103	14 amino acids substitution of L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before F38 at the N-terminus, and truncation after A484 at the C-terminus	FRAPPV I P N V P F L W A W N A P S E F C L G K F D E P L D M S L F S F I G S P R I N A T G Q G V T I F Y V D R L G Y P Y I D S I T G V T V N G G I P Q K I S L Q D H L D K A K K D I T F Y M P V D N L G M A V I D W E E W R P T W A R N W K P K D V Y K N R S I E L V Q Q Q N V Q L S L T E A T E K A K Q E F E K A G K D F L V E T I K L G K L L R P N H L W G Y Y L F P D C Y N H H Y K K P G Y N G S C F N V E I K R N D D L S W L W N E S T A L Y P S I Y L N T Q Q S P V A A T L Y V R N R V R E A I R V S K I P D A K S P L P V F A Y T R I V F T D Q V L K F L S Q D E L V Y T F G E T V A L G A S G I V I W G T <u>W E N T R T K E S C Q</u> <u>A I K E Y M D T T</u> L N P Y I I N V T L A A K M C S Q V L C Q E Q G V C I R K N W N S S D Y L H L N P D N F A I Q L E K G G K F T V R G K P T L E D L E Q F S E K F Y C S C Y S T L S C K E K A D V K D T D A V D V C I A D G V C I D A F L K P P M E T E E P Q I F Y N A
HM51	104	14 amino acids substitution of L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before F38 at the N-terminus, and truncation after P486 at the C-terminus	FRAPPV I P N V P F L W A W N A P S E F C L G K F D E P L D M S L F S F I G S P R I N A T G Q G V T I F Y V D R L G Y P Y I D S I T G V T V N G G I P Q K I S L Q D H L D K A K K D I T F Y M P V D N L G M A V I D W E E W R P T W A R N W K P K D V Y K N R S I E L V Q Q Q N V Q L S L T E A T E K A K Q E F E K A G K D F L V E T I K L G K L L R P N H L W G Y Y L F P D C Y N H H Y K K P G Y N G S C F N V E I K R N D D L S W L W N E S T A L Y P S I Y L N T Q Q S P V A A T L Y V R N R V R E A I R V S K I P D A K S P L P V F A Y T R I V F T D Q V L K F L S Q D E L V Y T F G E T V A L G A S G I V I W G T <u>W E N T R T K E S C Q</u> <u>A I K E Y M D T T</u> L N P Y I I N V T L A A K M C S Q V L C Q E Q G V C I R K N W N S S D Y L H L N P D N F A I Q L E K G G K F T V R G K P T L E D L E Q F S E K F Y C S C Y S T L S C K E K A D V K D T D A V D V C I A D G V C I D A F L K P P M E T E E P Q I F Y N A S P
HM52	105	14 amino acids substitution of L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before F38 at the N-terminus, and truncation after T488 at the C-terminus	FRAPPV I P N V P F L W A W N A P S E F C L G K F D E P L D M S L F S F I G S P R I N A T G Q G V T I F Y V D R L G Y P Y I D S I T G V T V N G G I P Q K I S L Q D H L D K A K K D I T F Y M P V D N L G M A V I D W E E W R P T W A R N W K P K D V Y K N R S I E L V Q Q Q N V Q L S L T E A T E K A K Q E F E K A G K D F L V E T I K L G K L L R P N H L W G Y Y L F P D C Y N H H Y K K P G Y N G S C F N V E I K R N D D L S W L W N E S T A L Y P S I Y L N T Q Q S P V A A T L Y V R N R V R E A I R V S K I P D A K S P L P V F A Y T R I V F T D Q V L K F L S Q D E L V Y T F G E T V A L G A S G I V I W G T <u>W E N T R T K E S C Q</u> <u>A I K E Y M D T T</u> L N P Y I I N V T L A A K M C S Q V L C Q E Q G V C I R K N W N S S D Y L H L N P D N F A I Q L E K G G K F T V R G K P T L E D L E Q F S E K F Y C S C Y S T L S C K E K A D V K D T D A V D V C I A D G V C I D A F L K P P M E T E E P Q I F Y N A S P S T

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Name	SEQ NO.	Substitution	Amino Acid Sequence
HM53	106	15 amino acids substitution of T341G, L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before L36 at the N-terminus, and truncation after S490 at the C-terminus	LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTIFYVDRLGYYPYIDSI TGVTVNGGIPQKISLQDHLDAKAKDITFYMPVDNL GMAVIDWEEWRPTWARNWPKPDVYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLL RPNHLWGYYLFPDCYNHHYKPGYNGSCFNVEIKR NDDLSQLWNESTALYPSIYLNTQQSPVAATLYVRN RVREAIRVSKI PDAKSPLPVFAYTRIVFTDQVLKF LSQDELVYTFGETVALGASGIVIWG GWENTRTKES COAIKEYMDTTL NPYIINVTLAAKMCSQVLCQEQG VCIRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGK PTLEDLEQFSEKFYCSYSTLSCKEKADVKTDAV DVCIA DGVCIDAFLKPPMETEEPQIFYNASPSTLS
HM54	107	15 amino acids substitution of T341A, L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before L36 at the N-terminus, and truncation after S490 at the C-terminus	LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTIFYVDRLGYYPYIDSI TGVTVNGGIPQKISLQDHLDAKAKDITFYMPVDNL GMAVIDWEEWRPTWARNWPKPDVYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLL RPNHLWGYYLFPDCYNHHYKPGYNGSCFNVEIKR NDDLSQLWNESTALYPSIYLNTQQSPVAATLYVRN RVREAIRVSKI PDAKSPLPVFAYTRIVFTDQVLKF LSQDELVYTFGETVALGASGIVIWG AWENTRTKES COAIKEYMDTTL NPYIINVTLAAKMCSQVLCQEQG VCIRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGK PTLEDLEQFSEKFYCSYSTLSCKEKADVKTDAV DVCIA DGVCIDAFLKPPMETEEPQIFYNASPSTLS
HM55	108	15 amino acids substitution of T341C, L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before L36 at the N-terminus, and truncation after S490 at the C-terminus	LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTIFYVDRLGYYPYIDSI TGVTVNGGIPQKISLQDHLDAKAKDITFYMPVDNL GMAVIDWEEWRPTWARNWPKPDVYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLL RPNHLWGYYLFPDCYNHHYKPGYNGSCFNVEIKR NDDLSQLWNESTALYPSIYLNTQQSPVAATLYVRN RVREAIRVSKI PDAKSPLPVFAYTRIVFTDQVLKF LSQDELVYTFGETVALGASGIVIWG CWENTRTKES COAIKEYMDTTL NPYIINVTLAAKMCSQVLCQEQG VCIRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGK PTLEDLEQFSEKFYCSYSTLSCKEKADVKTDAV DVCIA DGVCIDAFLKPPMETEEPQ109IFYNASPS TLS

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Name	SEQ NO.	Substitution	Amino Acid Sequence
HM56	109	15 amino acids substitution of T341D, L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before L36 at the N-terminus, and truncation after S490 at the C-terminus	LNFRAPPV I PNV PFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGV T IFYVDRLGYYPYIDSI TGVTVNGGIPQKISLQDHLDKAKKDITFYMPVDNL GMAVIDWEEWRPTWARNWKPKDVYKNRSIELVQQQ NVQLSLTEATEKAKQEF EKAGKDFLVETIKLGKLL RPNHLWGYYLFPDCYNH HYKPGYNGSCFNVEIKR NDDL SWLWNESTALYPSIYLNTQQSPVAATLYVRN RVREAIRVSKI PDAKSPLPVFAYTRIVFTDQVLKF LSQDELVYT FGETVALGASGIVIWG <u>DWENTRTKES</u> <u>COAIKE</u> YMD <u>TT</u> LN PY I INVTLAAKMCSQVLCQE QG VCIRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGK PTLEDLEQFSEKFYCSCYSTLSCKEKADV KDTDAV DVC IADGVCIDAF LKPPMETEEPQIFYNASPSTLS
HP57	110	12 amino acids substitution of I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before F38 at the N-terminus, and truncation after F468 at the C-terminus	FRAPPV I PNV PFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGV T IFYVDRLGYYPYIDSI TG VTVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGM AVIDWEEWRPTWARNWKPKDVYKNRSIELVQQQNV QLSLTEATEKAKQEF EKAGKDFLVETIKLGKLLRP NHLWGYYLFPDCYNH HYKPGYNGSCFNVEIKRND DLSWLWNESTALYPSIYLNTQQSPVAATLYVRNRV REAIRVSKI PDAKSPLPVFAYTRIVFTDQVLKFLS QDELVYT FGETVALGASGIVIWGTL <u>SNTRTKES</u> <u>CO</u> <u>AIKE</u> YMD <u>TT</u> LN PY I INVTLAAKMCSQVLCQE QGVC IRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGKPT LEDLEQFSEKFYCSCYSTLSCKEKADV KDTDAVDV CIADGVCIDAF
HP58	111	13 amino acids substitution of S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before F38 at the N-terminus, and truncation after F468 at the C-terminus	FRAPPV I PNV PFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGV T IFYVDRLGYYPYIDSI TG VTVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGM AVIDWEEWRPTWARNWKPKDVYKNRSIELVQQQNV QLSLTEATEKAKQEF EKAGKDFLVETIKLGKLLRP NHLWGYYLFPDCYNH HYKPGYNGSCFNVEIKRND DLSWLWNESTALYPSIYLNTQQSPVAATLYVRNRV REAIRVSKI PDAKSPLPVFAYTRIVFTDQVLKFLS QDELVYT FGETVALGASGIVIWGTL <u>ENTRTKES</u> <u>CO</u> <u>AIKE</u> YMD <u>TT</u> LN PY I INVTLAAKMCSQVLCQE QGVC IRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGKPT LEDLEQFSEKFYCSCYSTLSCKEKADV KDTDAVDV CIADGVCIDAF

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Name	SEQ NO.	Substitution	Amino Acid Sequence
HP59	112	15 amino acids substitution of T341A, L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before F38 at the N-terminus, and truncation after F468 at the C-terminus	FRAPPV I P N V P F L W A W N A P S E F C L G K F D E P L D M S L F S F I G S P R I N A T G Q G V T I F Y V D R L G Y Y P Y I D S I T G V T V N G G I P Q K I S L Q D H L D K A K K D I T F Y M P V D N L G M A V I D W E E W R P T W A R N W K P K D V Y K N R S I E L V Q Q Q N V Q L S L T E A T E K A K Q E F E K A G K D F L V E T I K L G K L L R P N H L W G Y Y L F P D C Y N H H Y K K P G Y N G S C F N V E I K R N D D L S W L W N E S T A L Y P S I Y L N T Q Q S P V A A T L Y V R N R V R E A I R V S K I P D A K S P L P V F A Y T R I V F T D Q V L K F L S Q D E L V Y T F G E T V A L G A S G I V I W G <u>A W E N T R T K E S C Q</u> <u>A I K E Y M D T T</u> L N P Y I I N V T L A A K M C S Q V L C Q E Q G V C I R K N W N S S D Y L H L N P D N F A I Q L E K G G K F T V R G K P T L E D L E Q F S E K F Y C S C Y S T L S C K E K A D V K D T D A V D V C I A D G V C I D A F
HP60	113	15 amino acids substitution of T341G, L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before F38 at the N-terminus, and truncation after F468 at the C-terminus	FRAPPV I P N V P F L W A W N A P S E F C L G K F D E P L D M S L F S F I G S P R I N A T G Q G V T I F Y V D R L G Y Y P Y I D S I T G V T V N G G I P Q K I S L Q D H L D K A K K D I T F Y M P V D N L G M A V I D W E E W R P T W A R N W K P K D V Y K N R S I E L V Q Q Q N V Q L S L T E A T E K A K Q E F E K A G K D F L V E T I K L G K L L R P N H L W G Y Y L F P D C Y N H H Y K K P G Y N G S C F N V E I K R N D D L S W L W N E S T A L Y P S I Y L N T Q Q S P V A A T L Y V R N R V R E A I R V S K I P D A K S P L P V F A Y T R I V F T D Q V L K F L S Q D E L V Y T F G E T V A L G A S G I V I W G <u>G W E N T R T K E S C Q</u> <u>A I K E Y M D T T</u> L N P Y I I N V T L A A K M C S Q V L C Q E Q G V C I R K N W N S S D Y L H L N P D N F A I Q L E K G G K F T V R G K P T L E D L E Q F S E K F Y C S C Y S T L S C K E K A D V K D T D A V D V C I A D G V C I D A F
HP61	114	16 amino acids substitution of A40G, T341S, L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before F38 at the N-terminus, and truncation after F468 at the C-terminus	F R G P P V I P N V P F L W A W N A P S E F C L G K F D E P L D M S L F S F I G S P R I N A T G Q G V T I F Y V D R L G Y Y P Y I D S I T G V T V N G G I P Q K I S L Q D H L D K A K K D I T F Y M P V D N L G M A V I D W E E W R P T W A R N W K P K D V Y K N R S I E L V Q Q Q N V Q L S L T E A T E K A K Q E F E K A G K D F L V E T I K L G K L L R P N H L W G Y Y L F P D C Y N H H Y K K P G Y N G S C F N V E I K R N D D L S W L W N E S T A L Y P S I Y L N T Q Q S P V A A T L Y V R N R V R E A I R V S K I P D A K S P L P V F A Y T R I V F T D Q V L K F L S Q D E L V Y T F G E T V A L G A S G I V I W G <u>S W E N T R T K E S C Q</u> <u>A I K E Y M D T T</u> L N P Y I I N V T L A A K M C S Q V L C Q E Q G V C I R K N W N S S D Y L H L N P D N F A I Q L E K G G K F T V R G K P T L E D L E Q F S E K F Y C S C Y S T L S C K E K A D V K D T D A V D V C I A D G V C I D A F

(continued)

Name	SEQ NO.	Substitution	Amino Acid Sequence
HP62	115	Removal of P42, 15 amino acids substitution of T341S, L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T, truncation before F38 at the N-terminus, and truncation after F468 at the C-terminus	FRGPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGVTFYVDRLGYYPYIDSITG VTVNGGIPQKISLQDHLDDAKKDITFYMPVDNLGM AVIDWEEWRPTWARNWPKPDVYKNRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRP NHLWGYYLFPDCYNHHYKPGYNGSCFNVEIKRND DLSWLWNESTALYPSIYLNTQQSPVAATLYVRNRV REAIRVSKI PDAKSPLPVFAYTRIVFTDQVLKFLS QDELVYTFGETVALGASGIVIWGSWENTRTKESQ <u>AIKEYMDTTL</u> NPYI INVTLAAKMCSQVLCQEQQVC IRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGKPT LEDLEQFSEKFYCSCYSTLSCKEKADVKTDAVDV CIADGVCIDAF

Example 2. Construction of PH20 Variants HM1 and HM6

[0107] As shown in FIG. 1B, amino acid residues M345 to N363 of PH20 correspond to the alpha-helix 8 region and the linker region between alpha-helix 7 and alpha-helix 8 in the protein tertiary structure model. Among the amino acids of alpha-helix 8, C351 forms a disulfide bond with C60 of alpha-helix 1; Y357 forms hydrophobic interaction with F315 of alpha-helix 7; and N363 forms a hydrogen bond with D69 of alpha-helix 1, thereby stabilizing secondary structures adjacent to alpha-helix 8 (FIG. 1C).

[0108] In order to construct variants having higher enzymatic activity and thermal stability than WT by substituting amino acids located in the alpha-helix 8 region of PH20 and the linker region between alpha-helix 7 and alpha-helix 8, the following variants were constructed: the variant HM1 in which 12 amino acids in the M345 to N363 region were substituted; the variant HM2 in which 7 amino acids in the Y365 to V379 region were substituted; and the variant HM3 in which 19 amino acids in the M345 to V379 region were substituted. Among the amino acids located in alpha-helix 8 of PH20, C351, which is involved in disulfide bonding, and Y357 which is involved in hydrophobic interaction, were not substituted. The substituted amino acid sequences in the variants HM1, HM2 and HM3 are shown in Table 11 above. When ExpiCHO cells were transfected with the pcDNA3.4-TOPO plasmid comprising the gene of the variant HM1, HM2 or HM3, the variant HM1 was expressed in the ExpiCHO cells (FIG. 3A), and the variants HM2 and HM3 were not expressed in the cells. Whether the protein would be expressed was confirmed not only by measurement of the enzymatic activity, but also by Western blot analysis using an antibody (Abcam, ab193009) against human PH20. The epitope of the antibody is Q173 to P222 region. These experimental results suggest that amino acid substitution of Y365 to V379 region of the amino acid sequence of alpha-helix 8, used in construction of the variants HM2 and HM3, causes a serious effect on the protein structure; thus the proteins of the variants HM2 and HM3 were not expressed. The expression level of the variant HM1 was 3.4-fold higher than that of wild-type WT (FIG. 2). The variant HM1 is one in which the hydrogen bond between N363 of alpha-helix 8 and D69 of alpha-helix 1 was removed by substituting N363 with glycine (FIG. 1C). To restore the hydrogen bond between N363 and D69, G363 in HM1 was substituted with asparagine, thereby constructing the variant HM6. The substituted amino acids in the variant HM6 are shown in Table 11 above.

[0109] The variant HM6 was expressed in ExpiCHO cells, and the expression level thereof was similar to that of the variant HM1 (the expression level was 3.4-fold higher than that of WT) (FIG. 2). When the enzymatic activity was measured by turbidimetric assay, it was shown that the enzymatic activity of the variant HM6 was 1.3-fold higher than that of WT (FIG. 3B). In the substrate-gel assay, generally, SDS is removed with 2.5% Triton X-100 (w/v) after SDS-PAGE, and enzymatic reaction is performed at 37°C for 1 to 4 h, during which the extent to which hyaluronidase hydrolyzes hyaluronic acid is measured using Alcian blue dye. It is known that when SDS is removed from the substrate gel, protein folding immediately occurs, and the substrate does not affect the protein folding. When the enzymatic activities of WT and the variants HM1 and HM6 were measured by the substrate-gel assay at 37°C for 1 to 4 h, HM6 exhibited higher enzymatic activity than those of WT and the variant HM1 (FIG. 3C). This result suggests that protein folding of the variants HM1 and HM6 and the resulting renaturation were faster than those of WT and that the constructed variants exhibit higher enzymatic activity than WT. When the signal peptide of PH20 itself was used, the expression level of the

protein in ExpiCHO cells was low, and to solve this problem, the signal peptide sequence of human serum albumin or human Hyall was used. As shown in FIG. 3C, when each of the signal peptides of human serum albumin and human Hyall was used as the signal peptide of the variant HM1, the expression of the protein increased, and there was no significant difference between the two signal peptides. When the enzymatic activity was measured by the substrate-gel assay, WT having the signal peptide of human serum albumin and the variant HM1 having the signal peptide of human serum albumin or Hyall exhibited enzymatic activity at the pH ranging from 5 to 8 (FIG. 3D). In the present invention, the signal peptide of human serum albumin was used as the signal peptide of the variant constructed after HM1.

[0110] When the thermal stabilities of WT and the variants HM1 and HM6 were compared based on the aggregation temperatures, the aggregation temperatures were 46.5°C, 53.0°C and 50.5°C, respectively, indicating that the aggregation temperatures of the variants HM1 and HM6 were 6.5°C and 4.0°C higher, than that of WT, respectively (FIG. 10). The results of measuring the aggregation temperatures were consistent with the protein refolding results shown in the substrate-gel assay. These results suggest for the first time that the hydrogen bond formed by the N363 residue of alpha-helix 8 plays an important role in the thermal stability and enzymatic activity of PH20.

[0111] In addition, when the hydrophilic/hydrophobic natures of WT and the variants HM1 and HM6 were compared using a phenyl column chromatography, HM1 and HM6 were all eluted earlier than WT. This suggests that the variants HM1 and HM6 have a more hydrophilic nature than WT due to the substitution of the amino acids. However, the variants HM1 and HM6 eluted from the phenyl column showed two peaks, unlike WT, and exhibited the same molecular weight when treated with PNGase F. This appears to be a difference caused by N-glycosylation (Fig. 3E).

Example 3. Construction of PH20 Variants HM4, HM7, HM8, HM9, HM10, HM11 and HM12

[0112] It is believed that the amino acid substitution of the M345 to N363 and M345 to I361 regions by construction of the variants HM1 and HM6 in Example 2 resulted in an increase in both the enzymatic activity and thermal stability of PH20, has made great advances in terms of protein engineering. Thus, based on the variants HM1 and HM6, other amino acids in the N-terminal and C-terminal directions were additionally substituted.

[0113] First, the variants HM4 and HM7 were constructed, which comprise the substituted amino acids in the variants HM1 and HM6 and in which the amino acids between G340 and I344 were additionally substituted with G340V, T341S, L342W, S343E and I344N. The sequences of the substituted amino acid sequences in the variants HM4 and HM7 are shown in Table 11 above. The variants HM4 and HM7 were expressed in ExpiCHO cells. The results of protein purification for HM7 are shown in FIG. 5A. HM4 and HM7 showed an increase in protein expression of 6.3-fold compared to WT, and showed increases in aggregation temperature of 10°C and 11.5°C, respectively, compared to WT. However, the enzymatic activities of HM4 and HM7, measured by turbidimetric assay, were about 15% of that of WT (FIG. 5B). Enzymatic activity and thermal stability generally have a trade-off relationship, but in the present invention, it appeared that the substitution introduced in the variants HM1 and HM6 increased the thermal stability of the variants while maintaining the enzymatic activity, and the enzymatic activities of the variants HM4 and HM7 decreased due to an excessive increase in the thermal stability. An increase in aggregation temperature of 11.5°C, which appeared in the variants HM4 and HM7 is a very significant result in terms of protein engineering. When the structural flexibilities of the proteins were analyzed by a Stern-Volmer plot, it was shown that the structural flexibilities of HM1, HM6, HM4 and HM7, obtained by substituting alpha-helix 8 and its linker region, were all higher than that of WT (FIG. 11A). This result suggests that the increase in local thermal stability resulted in an increase in the flexibility of the entire protein structure.

[0114] The difference between the variants HM6 and HM7 is amino acids between G340 and I344. In order to identify amino acids which are involved in the increased thermal stability of the variant HM7, the following variants were constructed based on the variant HM6: HM8 in which I344N was substituted; HM9 in which S343 and I344N were substituted; HM10 in which L342W, S343E and I344N were substituted; and HM21 in which T341S, L342W, S343E and I344N were substituted. The sequences of the substituted amino acids in the variants HM8, HM9, HM10 and HM21 are shown in Table 11 above. The variants HM8, HM9, HM10 and HM21 were expressed in ExpiCHO cells (FIG. 5A). As I344N, S343E and L342W were introduced in the N-terminal direction loop of alpha-helix 8 based on the variant HM6, the aggregation temperatures of the variants HM8, HM9 and HM10 increased to 52.5°C, 53°C and 55.5°C, respectively (FIG. 10). However, the variants HM8, HM9 and HM10 maintained enzymatic activities similar to that of WT (FIG. 5B). This result suggests that the amino acid substitution introduced in the variants HM8, HM9 and HM10 had a local effect on the thermal stabilities of the enzymes, but had no significant effect on the enzymatic activities. However, HM21 showed reduced thermal stability compared to HM10, but showed approximately 2-fold higher enzymatic activity compared to WT at pH 7.0. When WT and each variant were allowed to react with the substrate for 1 h in the substrate-gel assay, the enzymatic activity was reduced in the order of HM21 > HM10 > HM9 > HM8 > HM6 > WT (FIG. 5C).

[0115] When the physical properties of the variants HM7, HM8, HM9, HM10 and HM21 were examined using a phenyl column chromatography, these PH20 variants were eluted earlier than WT, suggesting that these variants all have a hydrophilic nature. However, the pattern of the main peak at the amino acid substitution position appeared differently (FIG. 5D).

[0116] The variant HM7 also showed two peaks in the phenyl column chromatography, like the variants HM1 and HM6, suggesting that two different types were present.

[0117] In order to examine the patterns of migration of WT and the variants depending on their isoelectric points, isoelectric focusing (hereinafter referred to as IEF) analysis was performed (FIG. 5E). On IEF gel, WT and the variant HM6 and HM8 showed similar migration patterns, and the variants HM9, HM10, HM21 and HM7 comprising the S343E mutation migrated to a more acidic region. This result suggests that a change in the isoelectric point of the protein occurs due to the introduction of glutamic acid by S343E substitution of the amino acid between G340 and I344.

[0118] In addition, based on the variant HM6, other amino acids in the C-terminal regions of alpha-helix 8 were substituted, thereby constructing the variants HM11 and HM12. The sequences of the substituted amino acids in the variants HM11 and HM12 are shown in Table 11 above. The variant HM11 was expressed in ExpiCHO cells, but the expression level thereof was lower than that of WT (FIG. 2), and the variant HM12 was not expressed in ExpiCHO cells. The variant HM11 exhibited an activity corresponding to 32% of that of WT (FIG. 6B).

Example 4. Construction of N-terminal amino acid-truncated PH20 variants based on HM6

[0119] The C-terminal region of PH20 is already well known to play an important role in the expression and enzymatic activity of PH20, but the role of the N-terminal region of PH20 is not well known. In order to examine the effect of cleavage of the amino acid at the N-terminal region of PH20 on the enzymatic activity, variants HM40, HM13, HM41, HM24, HM42 and HM25 having the N-terminus cleaved at N37, F38, R39, A40, P41 or P42 were constructed based on the variant HM6 (Table 11). Furthermore, HP61 and HP62 with modifications at the N-terminal amino acids were additionally constructed.

[0120] The variants HM40, HM13, HM41, HM24, HM42, HP61 and HP62 were expressed in ExpiCHO cells, but HM25 was not expressed (FIGS. 7A and 7B). The N-terminal truncated PH20 variants showed a difference in enzyme activity depending on the position where the N-terminus started. The variants HM40, HM13 and HM41, in which one to three amino acids were cleaved, showed enzymatic activity similar to that of the template HM6, but HM24 and HM42, in which four to five amino acids were cleaved, showed slightly lower activity than HM6 (FIG. 7C). However, HM25 in which six amino acids were cleaved were little expressed in ExpiCHO cells, and the enzymatic activity was also significantly low (3.5 U/ μ g). It appears that changes in the enzymatic activities of HP61 and HP62 with modifications at N-terminal amino acids are not significant.

[0121] Regarding the enzymatic activities of the N-terminal cleaved PH20 variants, measured by the substrate-gel assay (1 h of reaction), the enzymatic activities of HM40, HM13 and HM41 were similar to that of the HM6 variant, but the enzymatic activities of HM24 and HM42 were lower than that of HM6 (FIG. 7D). HM25 in which six amino acids were cleaved could not be analyzed, because the amount of the protein produced was small.

[0122] When the physical properties of the variants HM40, HM13, HM41, HM24 and HM42 were analyzed using a phenyl column chromatography, these variants were eluted from the column earlier than WT, suggesting that these variants have a hydrophilic nature (FIG. 7E). This result suggests that the variants HM40, HM13, HM41, HM24 and HM42 constructed based on the variant HM6 maintained the hydrophilic nature of HM6 when considering the characteristics of L36 to A40 residues.

[0123] The aggregation temperatures of the N-terminal cleaved PH20 variants, measured by DLS, were different among the variants depending on the position where the amino acid started (FIG. 7F). Although the N-terminal amino acid residues of the variants HM40, HM13, HM41 and HM42 were cleaved, they showed an aggregation temperature of 50°C or higher, indicating that the characteristics of the template HM6 were remained intact. Among these variants, the variants HM40 and HM42 exhibited an aggregation temperature which was 3 to 4°C higher than that of HM6, indicating that the thermal stability of these variants increased. In addition, in order to examine the effect of substitution of the N-terminal amino acids of PH20 on protein expression and enzymatic activity, the following variants were constructed: the variant HM17 in which N-terminal amino acid residues 36 to 47 (LNFRAPPVIPNV) of PH20 were substituted with FRGPLLPNR; and the variant HM18 in which N-terminal amino acid residues 36 to 52 (LNFRAPPVIPNVPFLWA) of PH20 were substituted with FRGPLLPNRPFTTV. The sequences of the substituted amino acids in the variants HM17 and HM18 are shown in Table 11 above. The variants HM17 and HM18 were not expressed in ExpiCHO cells. This suggests that, even when up to five amino acids located at the N-terminus were cleaved, the variants showed protein expression and enzymatic activity; however, substitution of more amino acid residues, such as 36 to 47 residues or 36 to 52 residues, had an effect on protein folding.

Example 5. Construction of the C-terminal amino acid-truncated HM6-based variants HM14, HM15 and HM16 of PH20

[0124] The C-terminal region of PH20 is known to play an important role in protein expression and enzymatic activity. In the present invention, the variants HM14, HM15 and HM16, in which the C-terminal amino acids were cleaved at

1465, F468 and K471, respectively, were constructed based on the variant HM6. The sequences of the substituted amino acids in these variants HM14, HM15 and HM16 are shown in Table 11 above. These variants HM14, HM15 and HM16 were expressed in ExpiCHO cells (FIG. 8A), and the protein expression levels thereof were in the order of HM16 > HM15 > HM14, indicating that the protein expression levels decreased as the number of C-terminal amino acids cleaved increased (FIG. 8A). However, the enzymatic activities of the variants HM14, HM15 and HM16 were in the order of HM16 > HM14 ($\approx$ WT) > HM15 (FIG. 8B). According to Frost et al., the C-terminal 477-483 region of PH20 is necessary for soluble expression, and when the C-terminus is cleaved at 467, the enzymatic activity of the variant is only 10% of a PH20 variant whose C-terminus was cleaved at residues 477 to 483, and when the C-terminus is cleaved before residue 467, the variant has no enzymatic activity. However, the C-terminal cleaved variants HM14, HM15 and HM16 constructed based on the variant HM6 in the present invention showed increased protein folding due to amino acid substitution of the M345 to I361 region, and thus the thermal stability thereof increased. For this reason, even when the C-terminus was cleaved after 1465, F468 or P471, the variant showed enzymatic activity similar to that of WT, and the enzymatic activity thereof did not significantly decrease.

[0125] The structural flexibilities of WT and the variants HM14, HM15 and HM16 were examined by fluorescence quenching using acrylamide (FIG. 11B). The variants HM14, HM15 and HM16 were all structurally more flexible than WT. This result suggests that the C-terminal cleaved variants constructed using the variant HM6 also maintained their structural flexibility.

[0126] The enzymatic activities of the variants HM14, HM15 and HM16, measured by turbidimetric assay, were also confirmed in substrate-gel assay (FIG. 8C).

[0127] When the physical properties of the C-terminal cleaved variants were analyzed using a phenyl column chromatography, the variants HM14, HM15 and HM16 were all eluted earlier than WT, indicating that they had a hydrophilic nature. In addition, the hydrophobicities of these variants were in the order of HM16 > HM14 > HM15 (FIG. 8D).

Example 6. Construction of the HM10-Based Variants HM19 and HM20 Comprising N-Terminal and C-Terminal Amino Acid Cleavage

[0128] The PH20 variants constructed in the present invention were based on HM6, and HM8, HM9 and HM10, in which amino acid residues G340 to I344 were additionally substituted, exhibited better performance than WT in terms of protein expression levels, enzymatic activities and thermal stabilities. The variants HM19 and HM20 were constructed which had an N-terminus cleaved at F38 and a C-terminus cleaved at F468 based on HM10 having high enzymatic activity and thermal stability among variants HM8, HM9 and HM10. HM19 and HM20 were all expressed in ExpiCHO cells and purified using a HisTrap column chromatography (FIG. 9A). When the enzymatic activities of these variants were measured by turbidimetric assay, HM19 and HM20 exhibited an enzymatic activity which was 10% higher than that of WT (FIG. 9B). In substrate-gel assay, HM19 and HM20 also exhibited higher enzymatic activity than WT (FIG. 9C).

Example 7. Characterization of HM10-Based PH20 Variants

[0129] The expression levels of HM10-based C-terminal truncated variants in ExpiCHO cells showed a tendency to decrease as the length of the C-terminal region became shorter, and these variants were not expressed when the C-terminus was truncated at C464 or shorter (FIG. 12). C464 is necessary because it forms a disulfide bond with C437 and is important for maintaining the protein structure.

[0130] In order to examine whether the variant is not expressed in ExpiCHO cells when the C-terminus is cleaved at residue 464 or shorter, Western blot analysis was performed. As shown in FIG. 13, the HM30, HM31, HM32 and HM33 variants were not detected in Western blots.

[0131] The enzymatic activities of the HM10-based C-terminal truncated variants, measured by turbidimetric assay, are shown in FIGS. 14A and 14B. The C-terminal truncated PH20 variants exhibited an enzymatic activity of $\pm 20\%$ compared to WT. When the C-terminus was cleaved after 1480, the enzyme activity increased overall. In addition, the variants HP19 and HP20, obtained by removing the 6xHis-tag from HM19 and HM20, showed decreases in enzymatic activity of 23% and 9.6%, respectively, compared to when the 6xHis-tag was present. This suggests that the 6xHis-tag has an effect on the enzymatic activity.

[0132] When the enzymatic activities of the HM10-based C-terminal truncated variants were measured by substrate-gel assay, these variants exhibited higher enzymatic activity than WT, and showed enzymatic activity similar to that of the template HM10, indicating that the difference in enzymatic activity depending on the length of the C-terminal region was not significant (FIG. 14C).

Example 8. Characterization of HM21-Based PH20 Variants

[0133] The variant HP34 was purified by four-step column chromatography (FIG. 15A), and the variant HP46 was

purified by three-step column chromatography (FIG. 15B). The amounts of HP34 and HP46 produced were 1.73 mg/L and 25.6 mg/L, respectively. HP34 and HP46 are 6xHis-tag-free variants, and the process of purifying these variants differs from the process of purifying variants having the 6xHis-tag, and thus it is difficult to compare the expression levels of the proteins.

5 [0134] In turbidimetric assay, the activities of HP34 and HP46 were 45.6 U/ μ g and 47.2 U/ μ g, respectively, which were about 2-fold higher than that of WT and were about 10% higher than that of the template HM21 (FIG. 16A).

[0135] The kinetics of each variant was measured by Morgan-Elson assay, and the results of the measurement are shown in FIG. 16B. The catalytic efficiencies (k_{cat}/K_m) of HP34 and HP46 were 1.7 to 2 times higher than that of wild-type HW2. This result is consistent with the result that the specific activity was higher than that of WT. The Michaelis constant (K_m) was lower in these variants than in HW2, indicating the substrate affinities of these variants increased. From these results, it can be concluded that the HM21, HP34 and HP46 variants bind strongly to the substrate and have the property of converting the substrate into a product with high efficiency. This property is attributable to the effect of substitution of T341 with serine. When threonine located at position 341 is substituted with an amino acid, such as alanine, glycine, aspartic acid or the like, the effect of the substitution on the enzymatic activity can be predicted.

10 [0136] The aggregation temperatures of HP34 and HP46, measured by DLS, were 51.5°C and 51.0°C, respectively, which were similar to that of the template HM21 and were about 5°C higher than that of HW2, indicating that these variants were thermally stable (FIG. 17A). The enzymatic activity of HP20, measured by substrate-gel assay, was similar to that of HP20, whereas HP46 exhibited higher enzymatic activity than HP20, indicating that the protein folding of HM21 as a template was better than that of HM10 (FIG. 17B).

20 [0137] Wild-type HW2 and the variant HP46 were left to stand overnight at pH 7.0 and pH 3.0, and then the enzymatic activities thereof were compared by substrate-gel assay. As a result, it was shown that HP46 exhibited high activity not only at pH 7.0 but also at pH 3.0, indicating that it had excellent stability (FIG. 17C).

[0138] HM53, HM54, HM55, HM56, HP59 and HP60 are variants having a mutation at the amino acid at position 341, among HM21-based variants. It was confirmed that the mutation of the amino acid at position 341 had various effects on the expression level and activity of the variants (FIGS. 17D and 17E).

Example 9. *In Vitro* Immunogenicity Assay of PH20 Variant

30 [0139] Biopharmaceuticals with higher molecular weights than those of low-molecular-weight synthetic chemicals have a risk of triggering unintended immune responses when they enter the human body. An outside contact surface, created by folding or interaction with adjacent domains in the secondary structure or tertiary structure of a large-molecular-weight biomaterial, can promote immune response to the biomaterial by providing an epitope to the immune system in the human body. This immune response can produce an anti-drug antibody (ADA), and this response can inhibit the drug's effectiveness, or cause hypersensitivity to the drug, or promote clearance of the drug in the human body. The immune response to the drug may therefore affect the results in clinical trials, and may cause serious abnormal reactions upon long-term use. This immune response can be influenced by various factors, and triggered by the specific response to the drug itself or disease, or by factors that depend on the method of drug administration or individual patients. Factors caused by the drug itself include the similarity or dissimilarity of the biopharmaceuticals to human peptides, posttranslational modification, impurities, aggregate formation, and the characteristics of the formulation. Factors that varies among individual patients include sex, reactivity with other drugs being taken, and genetic factors depending on the type of human leukocyte antigen (HLA).

40 [0140] This immunogenic response is triggered by CD4 + T cells or CD8 + T cells that recognize epitopes regardless of the cause of the immune response. Because of HLA class II gene diversity in individuals, epitopes of CD4 + T cells are different among individuals, and therefore the responsiveness to biopharmaceuticals in CD4+ T cells in each blood provided by the healthy donor can be a very important criterion for evaluating immune responses that may arise in clinical processes. CD4 + T cells are activated by antigen presenting cells (APCs) recognizing the antigens presented through their type II MHC (major histocompatibility complex). Activated CD4 + T cells release cytokines that activate macrophages, cytotoxic T cells, and B cells, resulting in high levels of antibody production. On the contrary, CD8 + T cells have direct cytotoxicity and directly remove cells infected with antigens, damaged cells, or cells that lost their function. CD8 + T cells have T cell receptors that can recognize specific antigen peptides bound to type I MHC molecules located on the surface of every cell. CD8 + T cells can also be activated by recognizing antigens presented by antigen presenting cells, and this activation can be further enhanced by cytokines of CD4 + T cells. Therefore, when the activation level of CD4 + T cells and CD8 + T cells by new biomaterials is measured *in vitro*, it is possible to predict immunogenic responses that can be induced in clinical processes. In this example, in order to predict the immunogenicity of the PH20 variant in comparison with a control, CD4+ T cells and CD8+ T cells were isolated from PBMCs, and then treated with 1.5 ng/mL and 15 ng/mL of the control PH20 and the PH20 variant (HP46), and then the distributions of activated CD4+ T cells and CD8+ T cells were measured. The activation level of each type of T cells was measured using Stimulating Index, and Stimulating Index (SI) is defined as follows:

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[0141] Stimulating Index (SI) = (T-cell activation level after treatment with test sample) / (T-cell activation level after treatment with vehicle)

[0142] If the SI value of cells is 2 or more, it can be determined that the cells were activated at the significant level.

[0143] Immunogenic responses may vary depending on the HLA type. Therefore, experiments for measuring responses in more various HLA types were performed using T cells isolated from PBMCs provided from 10 healthy donors. The HLA types of the 10 PBMCs used are shown in Table 12 below.

Table 12. HLA types of tested PBMCs

No.	HLAA		HLAB		HLAC1		DRB1		DQB1		DPB1	
1	0206	3303	3501	5801	0302	0801	1405	1501	0303	0602	0201	0301
2	0201	0207	4601	5101	0102	1502	0803	1101	0301	0601	0201	0202
3	0206	3101	1501	3501	0304	0401	0803	0901	0303	0601	0201	0501
4	0101	3101	1501	1517	0303	0701	1302	1501	0602	0604	0401	0501
5	0201	3101	5101	6701	0702	1402	0401	0403	0301	0302	0201	0401
6	0201	1101	1501	3901	0401	0702	0102	0901	0402	0501	0101	1401
7	0201	0206	4002	5502	0102	0304	0802	1454	0302	0502	0402	0501
8	0201	0201	1501	4001	0303	0304	0802	1406	0301	0302	0501	1301
9	1101	2402	4006	5101	0801	1502	0701	0901	0202	0303	0201	1301
10	2602	3101	4002	5101	0304	1502	0405	1501	0401	0602	0201	0501

[0144] The results of measuring the activation levels of CD4+ and CD8+ T cells treated with each of PH20 and the PH20 variant are summarized in Table 13 below. When looking at the results of measuring the activation levels of CD4+ and CD8+ T cells, it appears that PH20 and the PH20 variant all show relatively low activation levels. In the case of PH20, the activation level of CD4+ T cells was measured to be 2 or more in two experiments, and in the case of the PH20 variant, the activation of CD4+ T cells was not detected. In the case of PH20, the activation of CD8+ T cells was detected in one experiment, and in the case of the PH20 variant, the activation of CD8+ T cells was also detected in one experiment. However, in the case of PH20, the SI value was measured to be 2 or more at both 1.5 ng/mL and 15 ng/mL, but in the case of the PH20 variant, an SI value of 2 or less at 1.5 ng/mL and an SI value of 2 or more at 15 ng/mL were measured (see FIGS. 18 and 19).

[0145] Therefore, at the lower concentration, the activation level of CD8+ T cells was observed to be low in the case of the PH20 variant, and it is determined that the activation level of CD8+ T cells by PH20 is higher than the activation level of CD8+ T cells by the PH20 variant. The conclusions drawn from the above results are as follows:

- 1) the activation levels of CD4+ T cells and CD8+ T cells by PH20 and the PH20 variant are relatively low; and
- 2) the possibility of activation of CD4+ T cells and CD8+ T cells by the PH20 variant is lower than that by PH20.

[0146] From these results, it is expected that the PH20 variant will have a lower possibility of triggering an immunogenic response in clinical processes than PH20.

Table 13. Stimulating Index (SI) measured from *in vitro* immunogenicity assay results

PBMC No.	CD4				CD8			
	PH20 (ng/mL)		PH20 variant (ng/mL)		PH20 (ng/mL)		PH20 variant (ng/mL)	
	1.5	15	1.5	15	1.5	15	1.5	15
1	1.03	0.859	0.728	1.176	1.38	1.42	1.22	1.60
2	1.05	0.09	0.596	0.922	1.20	1.11	1.00	1.07
3	1.90	1.44	1.56	1.12	1.43	1.31	1.59	1.35
4	2.51	2.79	0.788	1.82	1.28	1.90	0.579	0.974
5	1.27	1.47	1.09	1.14	0.987	0.932	0.972	1.02

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(continued)

PBMC No.	CD4				CD8			
	PH20 (ng/mL)		PH20 variant (ng/mL)		PH20 (ng/mL)		PH20 variant (ng/mL)	
	1.5	15	1.5	15	1.5	15	1.5	15
6	0.825	0.834	0.998	0.946	0.904	1.13	1.09	0.986
7	2.07	2.07	1.43	1.90	2.08	2.34	1.30	2.46
8	0.898	1.079	0.967	0.822	0.926	1.06	0.896	0.813
9	0.882	0.957	0.895	0.941	0.853	0.993	0.950	1.09
10	0.983	0.970	1.12	1.13	1.15	1.08	1.15	1.24

ADVANTAGEOUS EFFECTS

[0147] The PH20 variants or fragments thereof according to the present invention have increased protein expression levels and show an increase in protein aggregation temperature of 4-11.5°C or so when expressed in CHO (ExpiCHO) cells so that they can be efficiently produced while having high thermal stability, compared to the mature wild-type PH20.

[0148] Further, as the result of substrate-gel assay, one of tests to measure the activity of hyaluronidase, the PH20 variants or fragments thereof according to the present invention have improved protein refolding so that they are re-natured faster than that of the mature wild-type PH20, and the original enzymatic activity is maintained regardless of the C-terminal cleavage position.

[0149] Furthermore, the PH20 variants or fragments thereof according to the present invention have low immunogenicity so that they can be repeatedly administered to the human body.

Reference

[0150]

Arming, S., Strobl, B., Wechselberger, C., and Kreil, G. (1997). In vitro mutagenesis of PH-20 hyaluronidase from human sperm. Eur J Biochem 247, 810-814.

Bookbinder, L.H., Hofer, A., Haller, M.F., Zepeda, M.L., Keller, G.A., Lim, J.E., Edgington, T.S., Shepard, H.M., Patton, J.S., and Frost, G.I. (2006). A recombinant human enzyme for enhanced interstitial transport of therapeutics. J Control Release 114, 230-241.

Chao, K.L., Muthukumar, L., and Herzberg, O. (2007). Structure of human hyaluronidase-1, a hyaluronan hydrolyzing enzyme involved in tumor growth and angiogenesis. Biochemistry 46, 6911-6920.

Frost, G.I. (2007). Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration. Expert Opin Drug Deliv 4, 427-440.

Sequence List (Free Text)

[0151] The electronic file is attached.

Claims

1. An PH20 variant or fragment thereof, which comprises one or more amino acid residue substitutions selected from the group consisting of T341A, T341C, T341G, S343E, M345T, K349E, L353A, L354I, N356E and I361T in wild-type PH20 having the amino acid sequence of SEQ ID NO: 1.
2. The PH20 variant or fragment thereof of claim 1, which comprises one or more amino acid residue substitutions selected from the group consisting of T341A, T341C, L354I and N356E.
3. The PH20 variant or fragment thereof of claim 1, which further comprises one or more amino acid residue substitutions in the region corresponding to an alpha-helix region and/or its linker region in wild-type PH20 having the amino acid sequence of SEQ ID NO: 1.

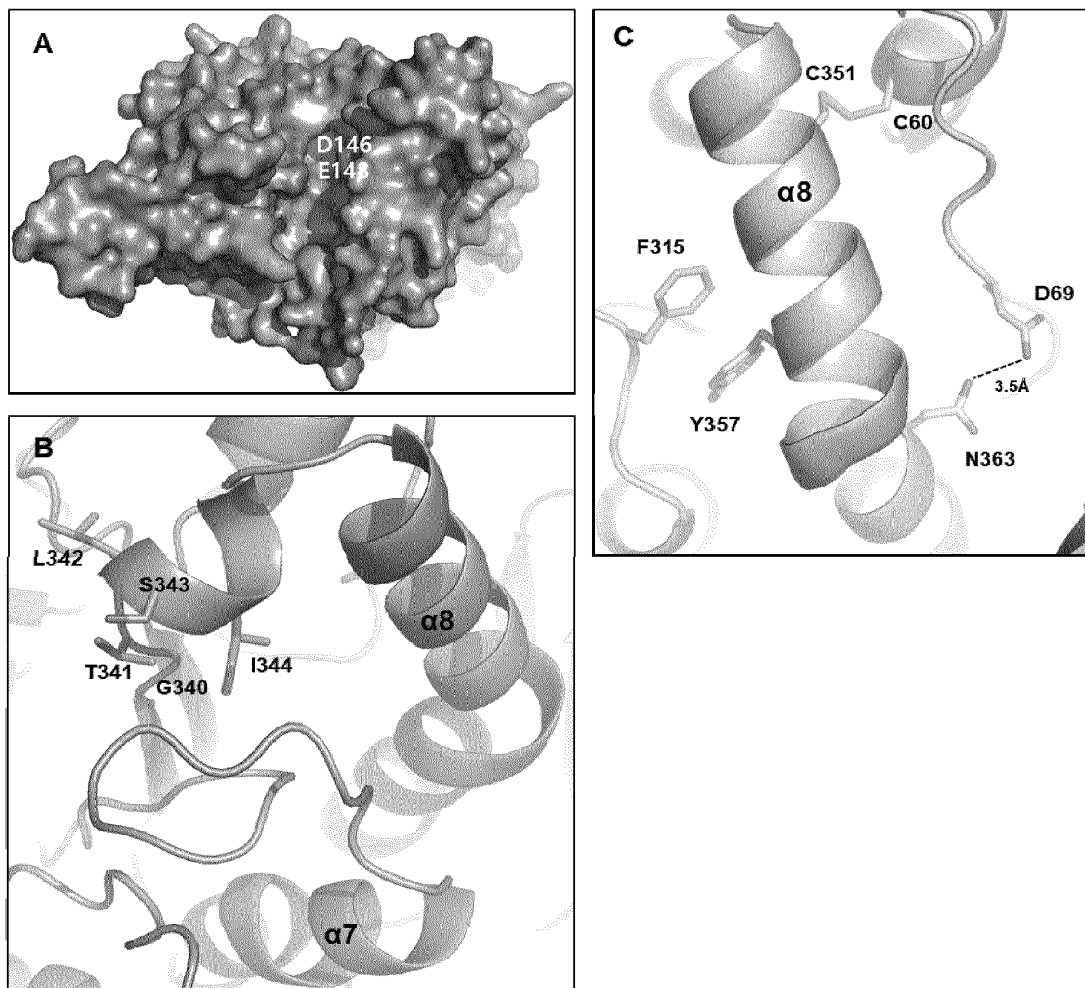
EP 3 636 752 A1

4. The PH20 variant or fragment thereof of claim 3, wherein the alpha-helix region is an alpha-helix 8 region (S347 to C381), and its linker region is a linker region (A333 to R346) between alpha-helix 7 and alpha-helix 8.
5. The PH20 variant or fragment thereof of claim 4, wherein the region corresponding to the alpha-helix region and the its linker region is T341 to N363, T341 to I361, L342 to I361, S343 to I361, I344 to I361, M345 to I361, or M345 to N363.
6. The PH20 variant or fragment thereof of claim 4, wherein the alpha-helix 8 region (S347 to C381) and/or the linker region (A333 to R346) between alpha-helix 7 and alpha-helix 8 are/is substituted with one or more amino acid residues of the corresponding region of Hyal1.
7. The PH20 variant or fragment thereof of claim 1, which comprises amino acid residue substitutions of L354I and/or N356E, and further comprises an amino acid residue substitution at one or more positions selected from the group consisting of T341, L342, S343, I344, M345, S347, M348, K349, L352, L353, D355, E359, I361 and N363.
8. The PH20 variant or fragment thereof of claim 7, which comprises amino acid residue substitutions of L354I and/or N356E, and further comprises one or more amino acid residue substitutions selected from the group consisting of T341A, T341C, T341D, T341G, T341S, L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, D355K, E359D, I361T and N363G.
9. The PH20 variant or fragment thereof of claim 7, which comprises M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T.
10. The PH20 variant or fragment thereof of claim 9, which further comprises one or more amino acid residue substitutions selected from the group consisting of T341A, T341C, T341D, T341G, T341S, L342W, S343E, I344N and N363G.
11. The PH20 variant or fragment thereof of claim 10, which comprises any one amino acid residue substitution selected from the following amino acid residue substitution groups:
 - (a) T341S, L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T;
 - (b) L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T;
 - (c) M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T and N363G;
 - (d) T341G, L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T;
 - (e) T341A, L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T;
 - (f) T341C, L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T;
 - (g) T341D, L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T;
 - (h) I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T; and
 - (i) S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D and I361T.
12. The PH20 variant or fragment thereof of any one of claims 1 to 11, wherein further one or more of the N-terminal or C-terminal amino acid residues are deleted.
13. The PH20 variant or fragment thereof of claim 12, wherein cleavage occurs before an amino acid residue selected from the group consisting of M1 to P42 at the N-terminus, so that one or more amino acid residues at the N-terminus are deleted.
14. The PH20 variant or fragment thereof of claim 13, wherein cleavage occurs before an amino acid residue L36, N37, F38, R39, A40, P41, or P42 at the N-terminus, so that one or more amino acid residues at the N-terminus are deleted.
15. The PH20 variant or fragment thereof of claim 12, wherein cleavage occurs after an amino acid residue selected from the group consisting of V455 to L509 at the C-terminus, so that one or more amino acid residues at the C-terminus are deleted.

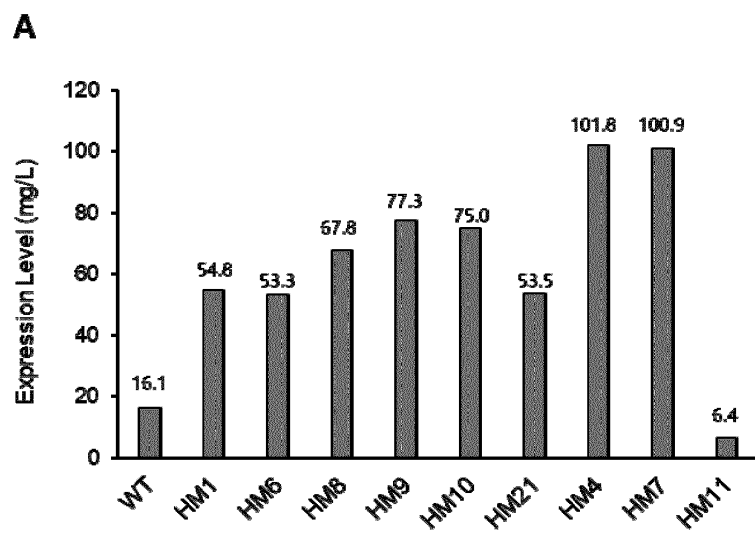
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16. The PH20 variant or fragment thereof of claim 15, wherein cleavage occurs after an amino acid residue selected from the group consisting of V455 to S490 at the C-terminus, so that one or more amino acid residues at the C-terminus are deleted.
- 5 17. The PH20 variant or fragment thereof of claim 16, wherein cleavage occurs after an amino acid residue V455, C458, D461, C464, I465, D466, A467, F468, K470, P471, P472, M473, E474, T475, E476, P478, I480, Y482, A484, P486, T488, or S490 at the C-terminus, so that one or more amino acid residues at the C-terminus are deleted.
- 10 18. The PH20 variant or fragment thereof of any one of claims 1 to 17, wherein the N-terminus comprises a human growth hormone-derived signal peptide having an amino acid sequence MATGSRTSLLLAFLGLCLPWLQEGSA of SEQ ID NO: 3, a human serum albumin-derived signal peptide having an amino acid sequence MKWVTFISLLFLFSSAYS of SEQ ID NO: 4, or a human Hyal1-derived signal peptide having an amino acid sequence MAAHLLPICALFLTLDDMAQG of SEQ ID NO: 5.
- 15 19. The PH20 variant or fragment thereof of any one of claims 1 to 11, wherein the PH20 variant or fragment thereof is selected from the group consisting of amino acid sequences of SEQ ID NOs: 60 to 115.
- 20 20. The PH20 variant or fragment thereof of claim 19, which has an amino acid sequence of SEQ ID NO: 99.
21. A composition for treating cancer, which comprises the PH20 variant or fragment thereof of any one of claims 1 to 20.
22. The composition for treating cancer of claim 21, wherein the composition is used for combined treatment with other anticancer drugs.
- 25 23. The composition for treating cancer of claim 22, wherein the other anticancer drugs are immuno-oncologic agents.
24. The composition for treating cancer of claim 23, wherein the immuno-oncologic agents are immune checkpoint inhibitors.
- 30 25. A nucleic acid encoding the PH20 variant or fragment thereof of any one of claims 1 to 20
26. A recombinant expression vector comprising the nucleic acid of claim 25.
27. A host cell transformed with the recombinant expression vector of claim 26.
- 35 28. The host cell of claim 27, wherein the host cell is selected from the group consisting of animal cells, plant cells, yeasts, *E. coli*, and insect cells.
- 40 29. A method for producing a PH20 variant or fragment thereof, the method comprising a step of culturing the host cell of claim 28.

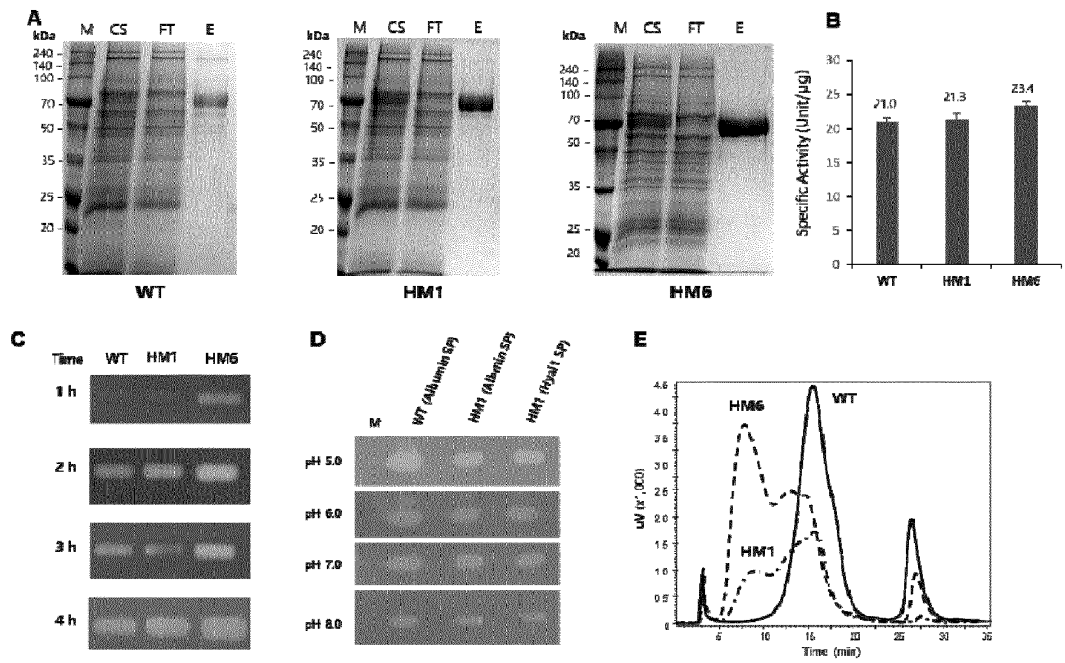
【Fig. 1】



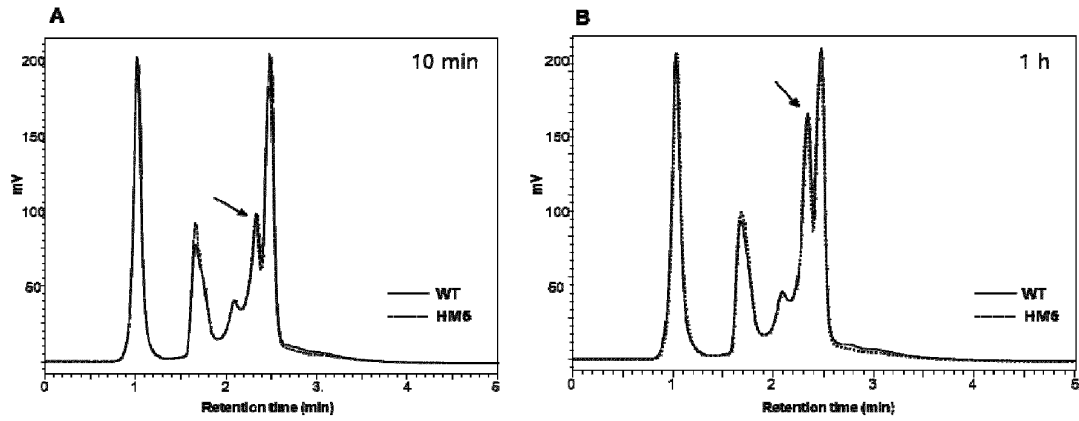
【Fig. 2】



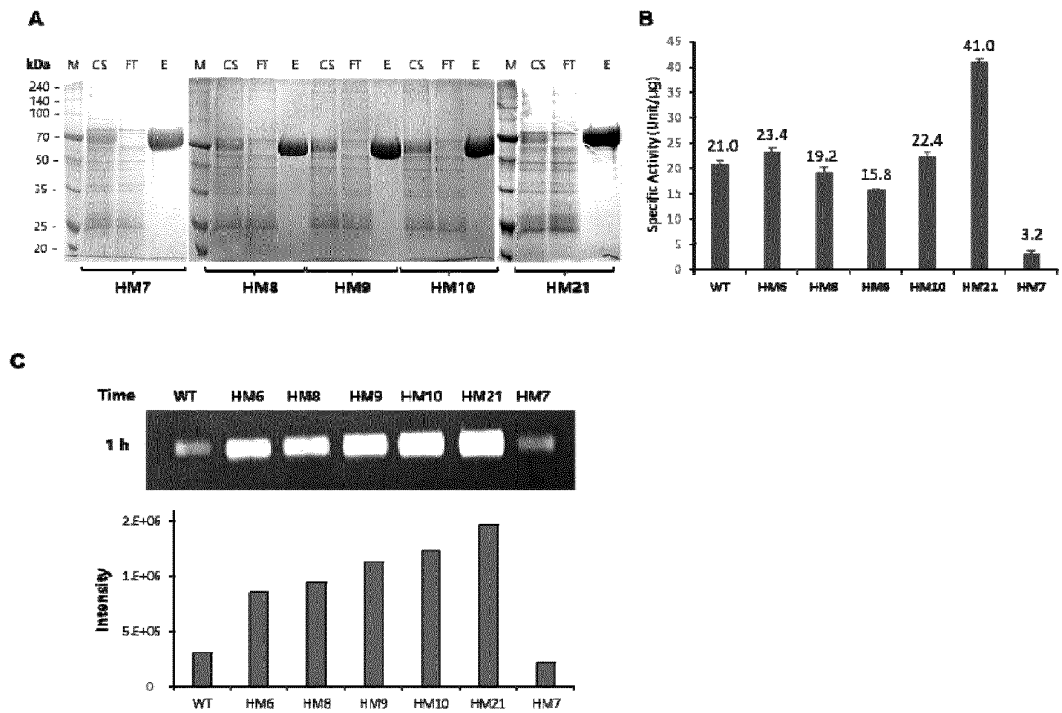
【Fig. 3】

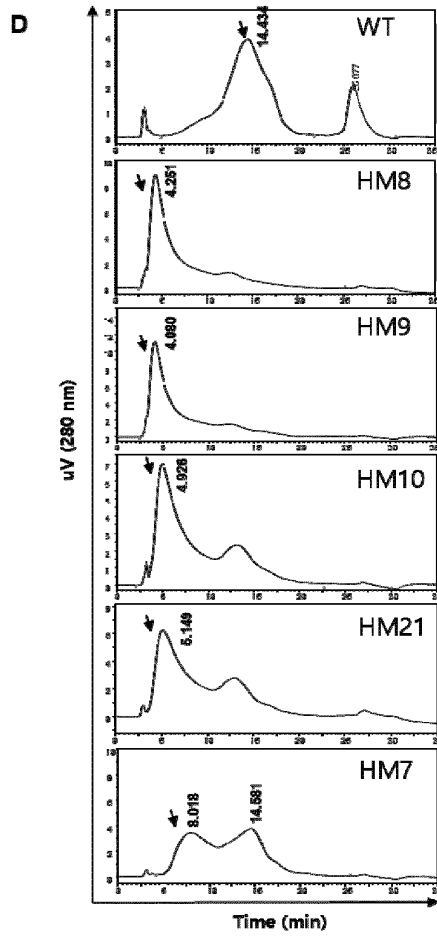
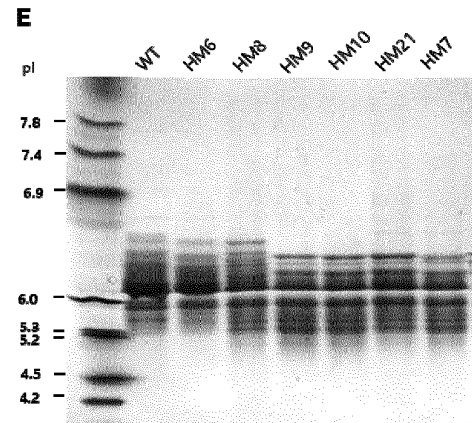


【Fig. 4】

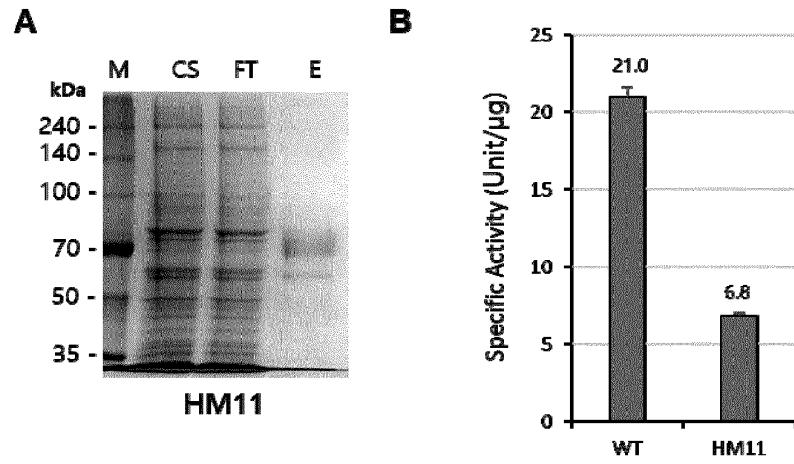


【Fig. 5】

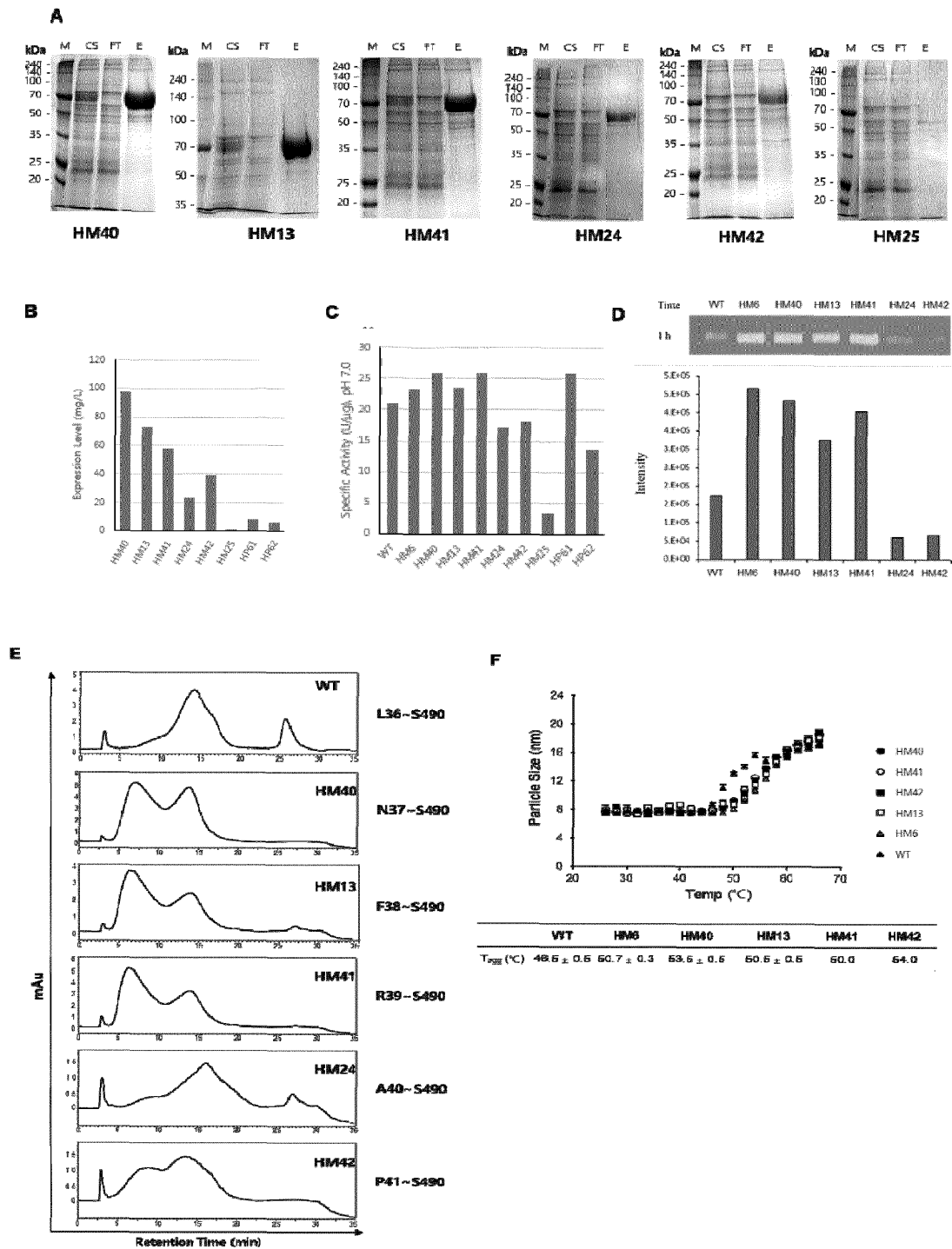




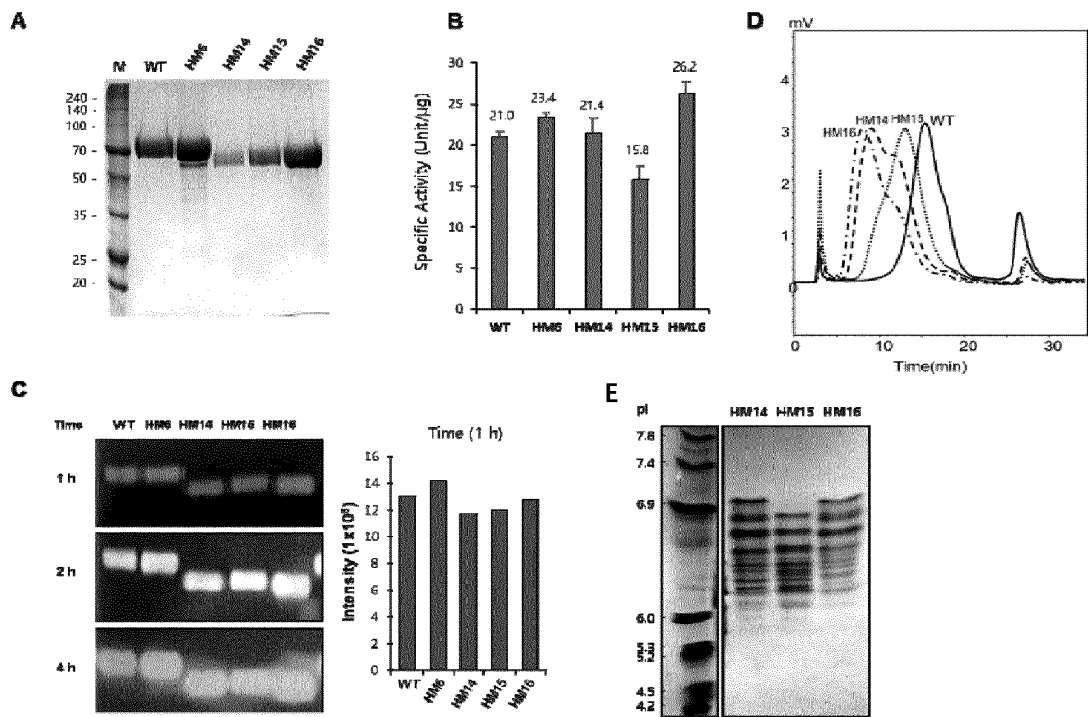
【Fig. 6】



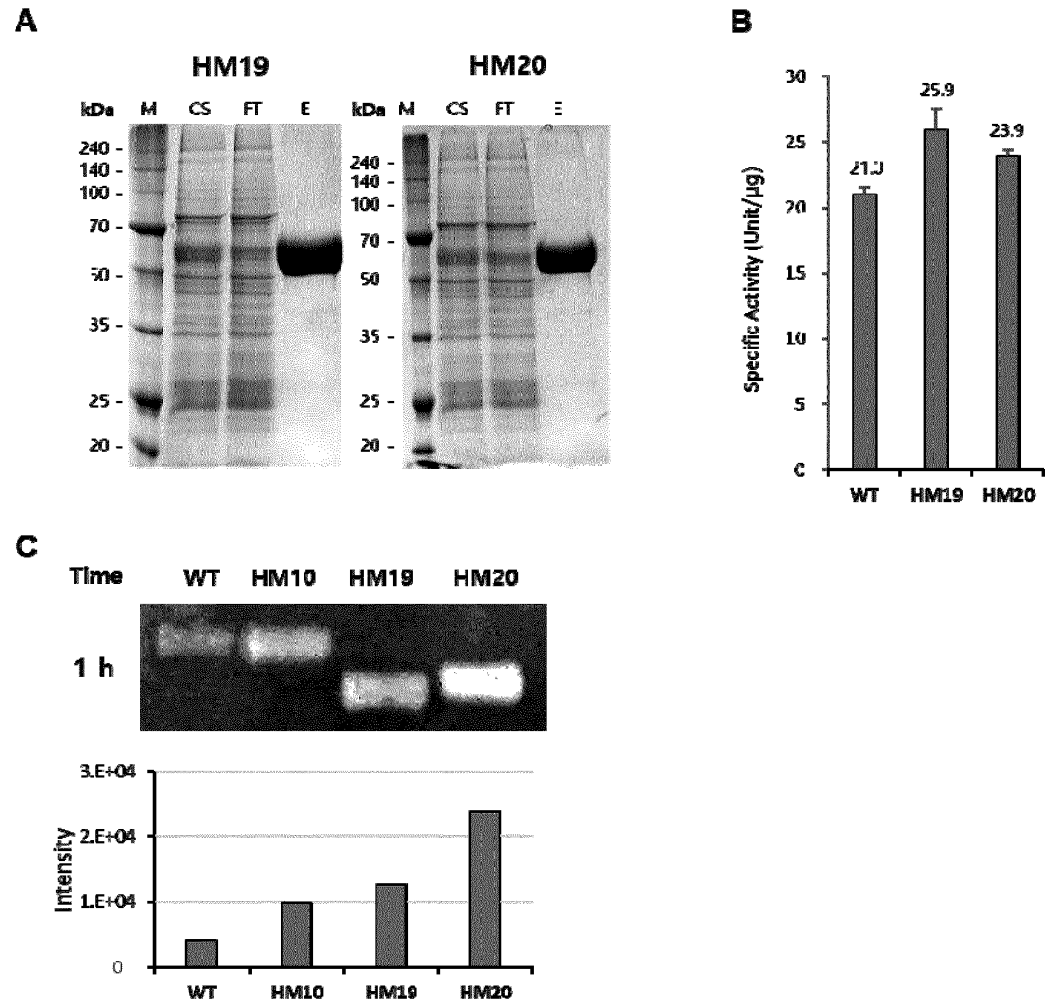
【Fig. 7】



【Fig. 8】



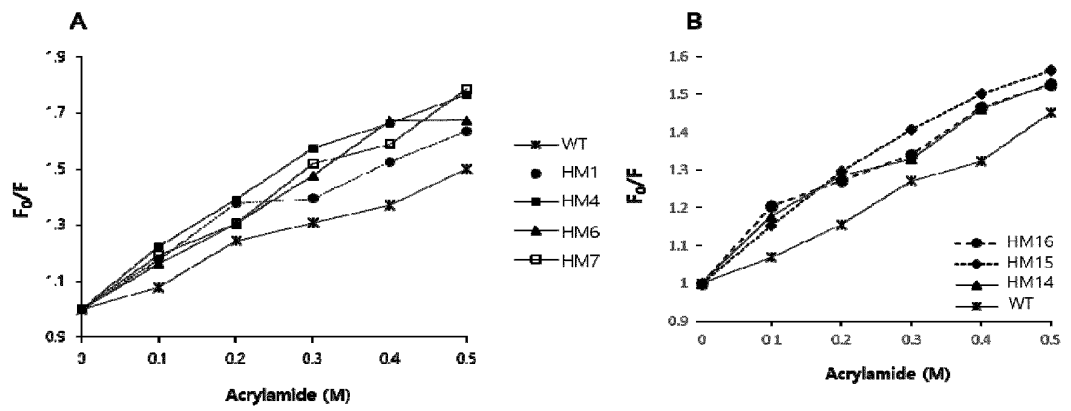
【Fig. 9】



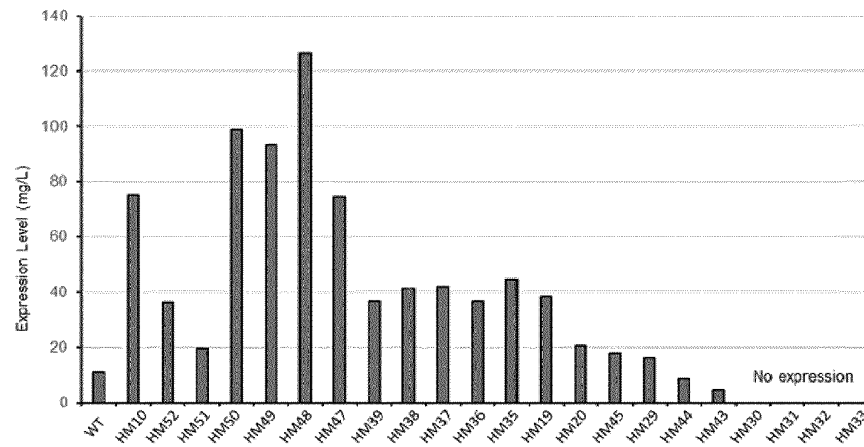
【Fig. 10】

	$T_{agg.} (^{\circ}\text{C})$
WT	46.5 ± 0.5
HM1	53.0 ± 1.2
HM4	56.5 ± 1.5
HM6	50.5 ± 0.5
HM7	58.0 ± 1.0
HM8	52.5 ± 0.5
HM9	53.0 ± 1.0
HM10	55.5 ± 0.5
HM13	50.5 ± 0.5
HM14	51.0 ± 1.0
HM15	49.0 ± 1.0
HM16	51.0 ± 1.0
HM19	53.0 ± 1.0
HM20	51.0 ± 1.0
HM21	51.7 ± 0.7

【Fig. 11】

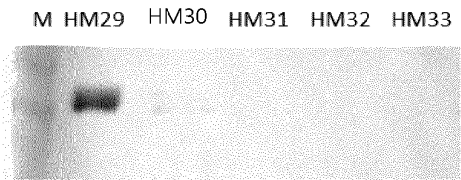


【Fig. 12】

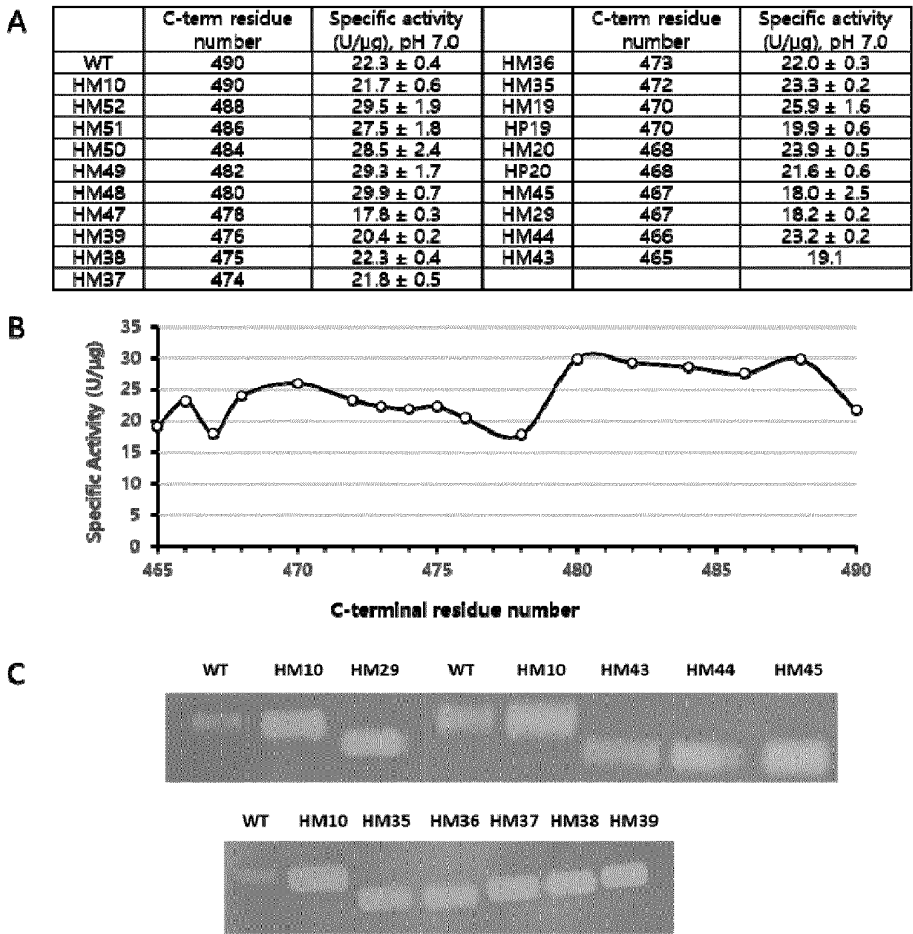
A**B**

	Total length	Expression level (mg/L)		Total length	Expression level (mg/L)		Total length	Expression level (mg/L)
WT	L36~S490	16.1	HM39	F38~E476	36.7	HM29	L36~A467	16.3
HM10	L36~S490	75.0	HM38	F38~T475	41.4	HM44	F38~D466	8.5
HM52	F38~T488	36.2	HM37	F38~E474	41.9	HM43	F38~I465	4.7
HM51	F38~P486	19.7	HM36	F38~M473	36.6	HM30	L36~C464	No
HM50	F38~A484	98.9	HM35	F38~P472	44.8	HM31	L36~D461	No
HM49	F38~Y482	93.4	HM19	F38~K470	38.3	HM32	L36~C458	No
HM48	F38~I480	126.5	HM20	F38~F468	20.8	HM33	L36~V455	No
HM47	F38~P478	74.4	HM45	F38~A467	17.9			

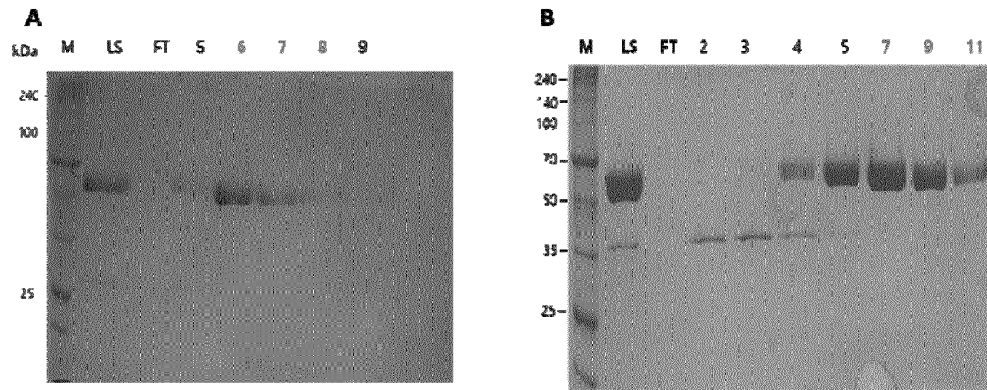
【Fig. 13】



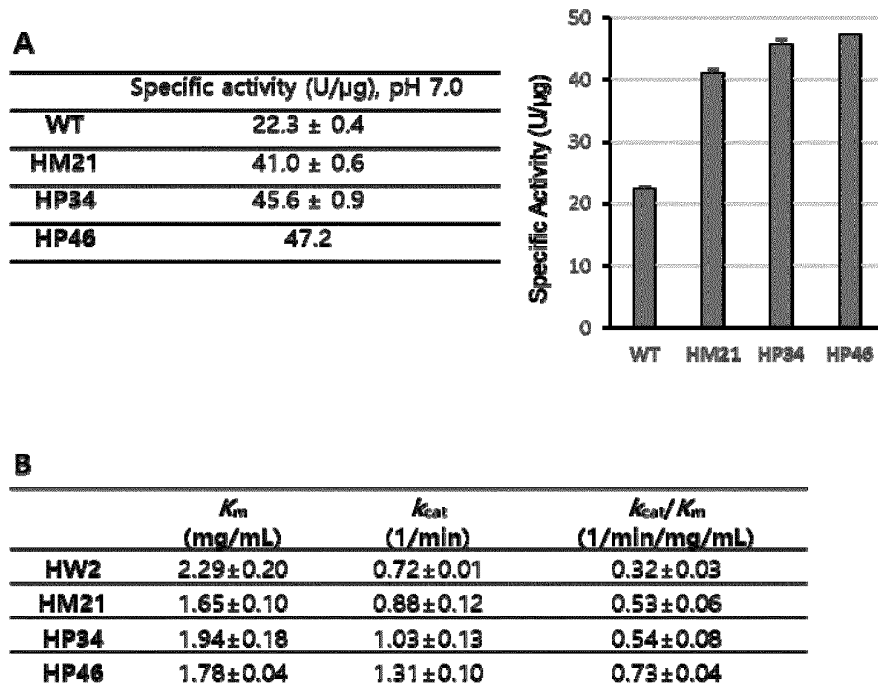
【Fig. 14】



【Fig. 15】



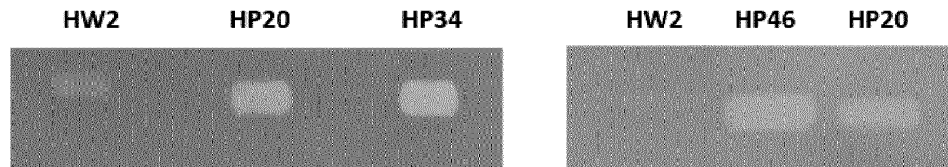
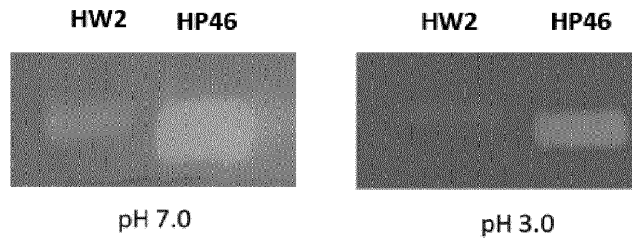
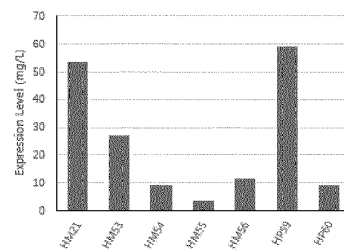
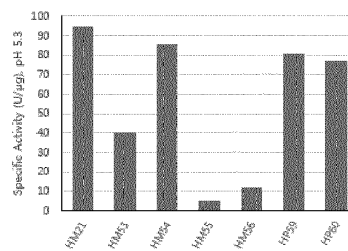
【Fig. 16】



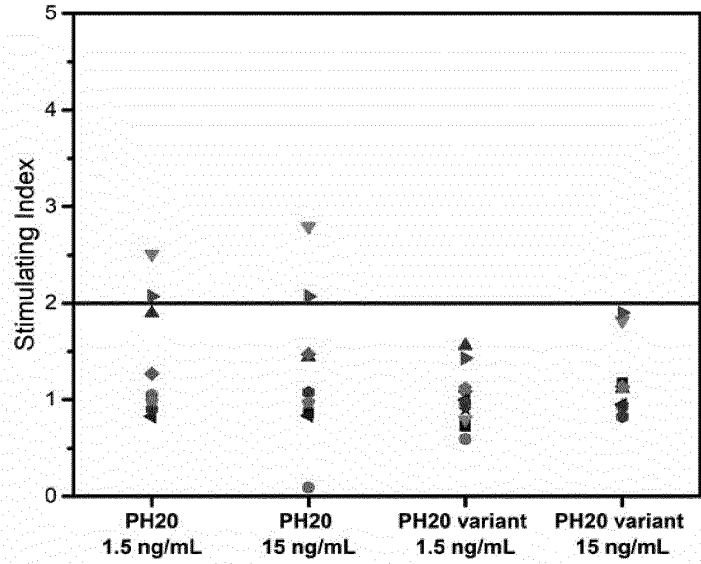
【Fig. 17】

A

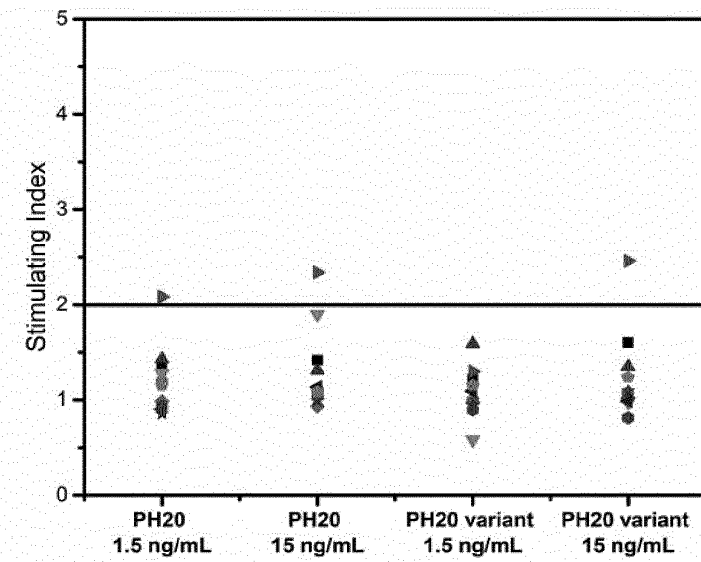
	T_{agg} (°C)
HW2	46.5
HM21	51.7
HP34	51.5
HP46	51.0

B**C****D****E**

【Fig. 18】



【Fig. 19】



INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR2019/009215

A. CLASSIFICATION OF SUBJECT MATTER

C12N 9/26(2006.01); A61K 38/16(2006.01); A61K 45/06(2006.01); A61P 35/00(2006.01);

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C12N 9/26; A61K 31/337; A61K 38/46; A61K 38/47; A61K 38/16; A61K 45/06; A61P 35/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models: IPC as above

Japanese utility models and applications for utility models: IPC as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS (KIPO internal) & Keywords: Hyaluronidase, variation, substitution, enzyme activity, cancer

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2015-0010529 A1 (WEI, Ge) 08 January 2015 See paragraphs [0005], [0009]; and figure 1.	1-17,19,20
A	KR 10-2013-0116386 A (HALOZYME, INC.) 23 October 2013 See the entire document.	1-17,19,20
A	US 2010-0143457 A1 (WEI, Ge et al.) 10 June 2010 See the entire document.	1-17,19,20
A	WO 2013-102144 A2 (HALOZYME, INC.) 04 July 2013 See the entire document.	1-17,19,20
A	MCATEE, Caitlin O. et al. Emerging roles for hyaluronidase in cancer metastasis and therapy. Advances in Cancer Research. 2014, vol. 123, pages 1-34 See the entire document.	1-17,19,20

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

29 OCTOBER 2019 (29.10.2019)

Date of mailing of the international search report

29 OCTOBER 2019 (29.10.2019)

Name and mailing address of the ISA/KR


 Korean Intellectual Property Office
 Government Complex Daejeon Building 4, 189, Cheongsa-ro, Seo-gu,
 Daejeon, 35208, Republic of Korea
 Facsimile No. +82-42-481-8578

Authorized officer

Telephone No.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR2019/009215

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 22-24, 26-29
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 22-24 and 26-29 refer to a claim violating PCT Rule 6.4(a). Thus, claims 22-24 and 26-29 are unclear.
3. ☒ Claims Nos.: 18, 21, 25
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2015)

EP 3 636 752 A1

INTERNATIONAL SEARCH REPORT Information on patent family members

International application No.

PCT/KR2019/009215

Patent document cited in search report	Publication date	Patent family member	Publication date
US 2015-0010529 A1	08/01/2015	TW 201534726 A WO 2015-003167 A1	16/09/2015 08/01/2015
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INTERNATIONAL SEARCH REPORT Information on patent family members

International application No.

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REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

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- **FROST et al.** *the C-terminal 477-483 region of PH20 is essential for soluble expression*, 2007 [0014]
- **ARMING, S. ; STROBL, B. ; WECHSELBERGER, C. ; KREIL, G.** In vitro mutagenesis of PH-20 hyaluronidase from human sperm. *Eur J Biochem*, 1997, vol. 247, 810-814 [0150]
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Wei <i>et al.</i>	Art Unit	: 1656
Serial No.	: 16/824,572	Examiner	: Not Yet Assigned
Filed	: March 19, 2020	Conf. No.	: 1431
		Cust. No.	: 13565
Title	: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

COPY

**INFORMATION DISCLOSURE STATEMENT IN
ACCORDANCE WITH 37 C.F.R. §§ 1.97-1.98**

Dear Sir:

Because this Information Disclosure Statement is filed before the receipt of a First Office Action on the Merits for the above-captioned application, a fee is not required. However, should it be determined that a fee for filing these papers is required, the Commissioner is authorized to charge Deposit Account No. 50-0911.

In accordance with the duty of disclosure imposed by 37 C.F.R. § 1.56 to inform the Patent Office of all information known by Applicant or Applicant's representative that may be material to the examination of the subject application, Applicant's representative hereby provides this Information Disclosure Statement that is prepared in accordance with 37 C.F.R. §§ 1.97-1.98. Forms PTO-1449 (24 pages) and copies of the cited non-U.S. patent documents are provided herewith in connection with the above-captioned application. In accordance with 37 C.F.R. § 1.98(d), copies of the references listed on the Forms PTO-1449 that are marked with a double asterisk (**) are not provided herewith as they have been previously provided in connection with U.S. Application Serial No. 13/694,731 and/or 15/226,489, which are relied upon for an earlier filing date in accordance with 35 U.S.C. § 120.

The documents cited on the Forms PTO-1449 are in the English language, with the exception of the items noted below. Item FP (CN 102065886A) is in the Chinese language and an English language equivalent (Item GD, WO 2009/128917) was previously provided in connection with U.S. Application Serial No. 13/694,731. Item FU (JP 2007-153797) is in the Japanese language and an English Derwent Abstract (Item HY) for Japanese Publication No. JP 2007-153797 was previously provided in connection with U.S. Application Serial No.

CERTIFICATE OF TRANSMISSION VIA EFS-WEB

I hereby certify that this paper is being transmitted via the Electronic Filing System (EFS-WEB) to the United States Patent and Trademark Office on May 15, 2020.

/Hyun Jeung Ji/
Hyun Jeung Ji

Applicant : Wei *et al.*
erial No. : 16/824,572
Filed : March 19, 2020

Attorney Docket No.: 33320.03087.US26/3087C
Information Disclosure Statement

13/694,731. Item FV (KR 10-2020-0017538) is in the Korean language and a machine generated English translation was previously provided in connection with U.S. Application Serial No. 15/226,489. Hence, in accordance with the requirements of 37 C.F.R. § 1.98, no further explanation of the listed items is necessary.

Applicant also makes known to the Examiner the following pending U.S. Applications that have one or more common inventors and/or an owner in common:

U.S.S.N.	Filing Date	Publ. No.	Publ. Date	Docket No.
16/373,562	04/02/2019	2019-0224286	7/25/2019	3051L
15/444,151	02/27/2017	2017/0218069 2018/0044419	08/03/2017 02/15/2018	3087B

Although these documents and applications are made known to the Patent and Trademark Office in compliance with Applicant's duty of disclosure, such disclosure is not to be construed as an admission by Applicant or Applicant's representative that any of the documents, singly or in any combination thereof, is effective as prior art against the subject application. In accordance with 37 C.F.R. § 1.97(g) and (h), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 C.F.R. § 1.56(b) exists.

Applicant respectfully requests that the Examiner review the foregoing documents and they be made of record in the file history of the above-captioned application.

Respectfully submitted,

/Stephanie Seidman/
Stephanie Seidman
Reg. No. 33,779

Attorney Docket No.: 33320.03087.US26/3087C
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COPY

Substitute Form PTO-1449 (Modified) List of Patents and Publications for Applicant's Information Disclosure Statement (37 CFR §1.98(b))	U.S. Department of Commerce Patent and Trademark Office		Attorney Docket No. 33320.03087.US26/ 3087C	Application No. 16/824,572
	Applicant Wei <i>et al.</i>			
	Filing Date March 19, 2020		Group Art Unit 1656	

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Examiner Initial	Desig . ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
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	AB	3,598,123	08/10/1971	Zaffaroni	424	435	04/01/1969
	AC	3,630,200	12/28/1971	Higuchi	424	427	06/09/1969
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	AE	3,845,770	11/05/1974	Theeuwes et al.	424	427	06/05/1972
	AF	3,916,899	11/04/1975	Theeuwes et al.	424	424	02/07/1974
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	AH	4,008,719	02/22/1977	Theeuwes et al.	424	427	02/02/1976
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	AM	4,769,027	09/06/1988	Baker et al.	424	493	02/24/1987
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Examiner Signature	Date Considered
EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

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	Applicant Wei <i>et al.</i>			
	Filing Date March 19, 2020		Group Art Unit 1656	

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	BG	5,766,581	06/16/1998	Bartley et al.	424	85.1	03/30/1995
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	BJ	5,854,046	12/29/1998	Au-Young et al.	435	201	01/20/1998
	BK	5,900,461	05/04/1999	Harris	525	54.11	02/23/1998
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	BN	5,958,750	09/28/1999	Au-Young et al.	435	201	07/03/1996
	BO	5,985,263	11/16/1999	Lee et al.	424	85.2	12/19/1997
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Examiner Signature	Date Considered
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	Applicant Wei <i>et al.</i>			
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	CK	7,781,397	08/24/2010	Stern et al.	424	94.62	10/03/2006
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	CY	8,580,252	11/12/2013	Bookbinder et al.	424	85.2	07/06/2012
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	DA	8,772,246	07/08/2014	Bookbinder et al.	435	200	10/18/2012
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	DJ	2001/0046481	11/29/2001	Bentley et al.	424	78.18	04/21/2001
	DK	2002/0052430	05/02/2002	Harris et al.	523	406	11/05/2001
	DL	2002/0072573	06/13/2002	Bentley et al.	525	409	02/08/2002

Examiner Signature	Date Considered
EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

Substitute Form PTO-1449 (Modified) List of Patents and Publications for Applicant's Information Disclosure Statement (37 CFR §1.98(b))	U.S. Department of Commerce Patent and Trademark Office		Attorney Docket No. 33320.03087.US26/ 3087C	Application No. 16/824,572
	Applicant Wei <i>et al.</i>			
	Filing Date March 19, 2020		Group Art Unit 1656	

U.S. Patent Documents

Examiner Initial	Desig . ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
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	DN	2003/0017108	01/23/2003	Zamora et al.	424	001.490	04/30/2002
	DO	2003/0114647	06/19/2003	Harris et al.	530	402	04/10/2002
	DP	2003/0143596	07/31/2003	Bentley et al.	435	6	11/07/2002
	DQ	2003/0158333	08/21/2003	Roberts et al.	530	402	10/09/2002
	DR	2003/0220447	11/27/2003	Harris	528	322	12/12/2002
	DS	2004/0013637	01/22/2004	Bentley et al.	424	78.17	02/10/2003
	DT	2004/0235734	11/25/2004	Bossard et al.	514	12	02/26/2004
	DU	2004/0268425	12/30/2004	Bookbinder et al.	800	18	03/05/2004
	DV	2005/0054048	03/10/2005	Grasso et al.	424	133.100	07/29/2004
	DW	2005/0114037	05/26/2005	Desjarlais et al.	702	19	09/30/2004
	DX	2005/0171328	08/04/2005	Harris	528	322	02/04/2005
	DY	2005/0209416	09/22/2005	Harris	525	523	04/22/2005
	DZ	2005/0260186	11/24/2005	Bookbinder at al.	424	094.610	02/23/2005
	EA	2006/0104968	05/18/2006	Bookbinder at al.	424	094.610	09/27/2005
	EB	2007/0067855	03/22/2007	Jarvis et al.	800	13	10/28/2004
	EC	2007/0189962	08/16/2007	Pastan et al.	424	133.100	04/11/2007
	ED	2009/0042785	02/12/2009	Matschiner et al.	514	012	04/28/2008
	EE	2009/0123367	05/14/2009	Bookbinder et al.	424	001.490	10/09/2008
	EF	2009/0181032	07/16/2009	Bookbinder at al.	424	141.1	02/20/2009
	EG	2009/0214505	08/27/2009	Bookbinder at al.	424	94.1	04/16/2009
	EH	2009/0253175	10/08/2009	Bookbinder at al.	435	69.1	06/03/2009
	EI	2009/0304665	12/10/2009	Frost et al.	424	94.5	04/28/2009
	EJ	2009/0305982	12/10/2009	Jensen et al.	435	069.100	06/11/2009
	EK	2009/0311237	12/17/2009	Frost	424	094.620	04/14/2009
	EL	2010/0003238	01/07/2010	Frost et al.	424	94.62	04/14/2009
	EM	2010/0074885	03/28/2010	Schiff et al.	424	130.100	03/16/2009
	EN	2010/0143457	06/10/2010	Wei et al.	424	450	12/09/2009
	EO	2010/0172892	07/08/2010	Uvarkina et al.	424	94.62	06/19/2008
	EP	2011/0066111	03/17/2011	Teschner et al.	514	183	09/16/2010

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Substitute Form PTO-1449 (Modified) List of Patents and Publications for Applicant's Information Disclosure Statement (37 CFR §1.98(b))	U.S. Department of Commerce Patent and Trademark Office		Attorney Docket No. 33320.03087.US26/ 3087C	Application No. 16/824,572
	Applicant Wei <i>et al.</i>			
	Filing Date March 19, 2020		Group Art Unit 1656	

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Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
	EQ	2011/0152359	06/23/2011	Bookbinder et al.	435	200	12/21/2010
	ER	2012/0020951	01/26/2012	Shepard et al.	424	130.1	07/15/2011
	ES	2012/0148555	06/14/2012	Bookbinder et al.	435	200	12/28/2011
	ET	2012/0171153	07/05/2012	Frost et al.	424	94.62	02/22/2012
	EU	2012/0213767	08/23/2012	Wei et al.	424	450	02/21/2012
	EV	2012/0251517	10/04/2012	Frost et al.	424	94.62	05/18/2012
	EW	2012/0251620	10/04/2012	Bookbinder et al.	424	450	05/16/2012
	EX	2012/0294830	11/22/2012	Bookbinder et al.	424	85.2	07/06/2012
	EY	2013/0011378	01/10/2013	Yang et al.	424	094.300	06/15/2012
	EZ	2013/0022588	01/24/2013	Yang et al.	424	094.300	06/15/2012
	FA	2013/0022592	01/24/2013	Vaughn et al.	424	094.620	06/15/2012
	FB	2013/0058893	03/07/2013	Bookbinder et al.	435	200	10/18/2012
	FC	2013/0101577	04/25/2013	Wei et al.	424	130.1	02/21/2012
	FD	2013/0202583	08/08/2013	Jiang et al.	424	094.620	10/24/2012
	FE	2013/0251786	09/26/2013	Li et al.	424	094.620	02/19/2013
	FF	2013/0302275	11/14/2013	Wei et al.	424	094.620	12/28/2012
	FG	2013/0302400	11/14/2013	Maneval et al.	435	195	03/15/2013
	FH	2014/0037613	02/06/2014	Bookbinder et al.	424	094.620	09/25/2013
	FI	2014/0105824	04/17/2014	Shepard et al.	424	009.200	10/16/2013
	FJ	2014/0135682	05/15/2014	Frost et al.	424	094.500	09/24/2013
	FK	2014/0199282	07/17/2014	Bookbinder et al.	435	200	02/26/2014
	FL	2015/0010529	01/08/2015	Wei	424	94.62	07/03/2014
	FM	2016/0362670	12/15/2016	Wei et al.	424	094.620	08/02/2016
	FN	2017/0290796	10/12/2017	Maneval et al.	435	195	06/16/2017
	FO	2019/0336587	11/07/2019	Frost et al.	424	78.17	05/21/2019

Foreign Patent Documents or Published Foreign Patent Applications

Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Translation	
					Yes	No
	FP**	CN 102065886A	05/18/2011	CN		X* (Item GD)
	FQ**	EP 0400472	12/05/1990	EP		

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				Filing Date March 19, 2020		Group Art Unit 1656	
Foreign Patent Documents or Published Foreign Patent Applications							
Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Translation		
					Yes	No	
	FR **	EP 0822199	09/22/2004	EP			
	FS **	EP 1064951	08/22/2007	EP			
	FT	EP 3636752	04/15/2020	EP			
	FU **	JP 2007-153797	06/21/2007	JP		X** (Item HY)	
	FV **	KR 10-2020-0017538	02/18/2020	KR	X		
	FW **	WO 1992/16640	10/01/1992	WIPO			
	FX **	WO 1994/028024	12/08/1994	WIPO			
	FY **	WO 2000/002017	01/13/2000	WIPO			
	FZ **	WO 2001/087925	04/26/2001	WIPO			
	GA **	WO 2002/049673	06/27/2002	WIPO			
	GB **	WO 2004/056312	07/08/2004	WIPO			
	GC **	WO 2005/000360	01/06/2005	WIPO			
	GD **	WO 2009/128917	10/22/2009	WIPO			
	GE **	WO 2009/134380	11/05/2009	WIPO			
	GF **	WO 2010/077297	07/08/2010	WIPO			
	GG **	WO 2010/149772	12/29/2010	WIPO			
	GH **	WO 2012/136768	11/10/2012	WIPO			
	GI **	WO 2012/174478	12/20/2012	WIPO			
	GJ **	WO 2013/102144	07/04/2013	WIPO			
	GK **	WO 2015/003167	01/08/2015	WIPO			
** = Copies not provided herewith as they have been previously provided in connection with U.S. Serial No. 13/694,731 and/or 15/226,489 which are relied upon for an earlier filing date in accordance with 35 U.S.C. §120. X* = An English language equivalent has been previously provided in connection with U.S. Serial No. 13/694,731. X** = An English Derwent Abstract (Item HY) for Japanese Publication No. JP 2007-153797 has been previously provided in connection with U.S. Serial No. 13/694,731. X = A machine generated English translation was previously provided in connection with U.S. Serial No. 15/226,489.							

Other Documents (include Author, Title, Date, and Place of Publication)		
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	GL	Letter/Written Disclosure of the Information Disclosure Statement for the above-referenced application, filed herewith on May 15, 2020, 2 pages.
	GM **	Adams, G.E. and I.J. Stratford, "Bioreductive drugs for cancer therapy: the search for tumor specificity," Int. J. Radiat. Oncol. Biol. Phys. 29(2): 231-238 (1994).

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		Filing Date March 19, 2020	Group Art Unit 1656

Other Documents (include Author, Title, Date, and Place of Publication)

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	GN**	Alexander et al., "Expression of the c-myc oncogene under control of an immunoglobulin enhancer in E mu-myc transgenic mice," Mol. Cell Biol. 7:1436-1444 (1987).
	GO**	Ansel, H., <i>Introduction to Pharmaceutical Dosage Forms</i> , Fourth Edition, Lea & Febiger: Philadelphia, page 126 (1985).
	GP**	Anttila et al., "High levels of stromal hyaluronan predict poor disease outcome in epithelial ovarian cancer," Cancer Research 60:150-155 (2000).
	GQ**	Arming et al., "In vitro mutagenesis of PH-20 hyaluronidase from human sperm," Eur J Biochem 247(3):810-814 (1997).
	GR**	Atkinson, M. and E. Leiter, "The NOD mouse model of type 1 diabetes: as good as it gets?" Nature Med. 5:601-604 (1999).
	GS**	Auvinen, P. "Hyaluronan in peritumoral stroma and malignant cells associates with breast cancer spreading and predicts survival," American Journal of Pathology 156(2):529-536 (2000).
	GT**	Baumgartner et al., "Phase I study in chemoresistant loco-regional malignant disease with hyaluronidase," Reg. Cancer Treat. 1:55-58 (1988).
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	GW**	Bianchi et al., "Synthetic depsiptide substrates for the assay of human hepatitis C virus protease," Anal. Biochem. 237: 239-244 (1996).
	GX**	Bitter et al., "Expression and secretion vectors for yeast," Methods in Enzymol 153:516-544 (1987).
	GY**	Bonner, W. and E. Cantey, "Colorimetric method for determination of serum hyaluronidase activity," Clin. Chim. Acta 13:746-752 (1966).
	GZ**	Bookbinder et al., "A recombinant human enzyme for enhanced interstitial transport of therapeutics," J Control Release 114:230-241 (2006).
	HA**	Bordier C., "Phase separation of integral membrane proteins in Triton X-114 solution," J Biol Chem. 256(4):1604-1607 (1981).
	HB**	Bouffard et al., "An in vitro assay for hepatitis C virus NS3 serine proteinase," Virology 209:52-59 (1995).
	HC**	Brinster et al., "Regulation of metallothionein--thymidine kinase fusion plasmids injected into mouse eggs," Nature 296:39-42 (1982).
	HD**	Brown et al., "Codon utilisation in the pathogenic yeast, Candida albicans," Nucleic Acids Res. 19(15):4298 (1991).
	HE**	Brumeanu et al., "Derivatization with monomethoxypolyethylene glycol of Igs expressing viral epitopes obviates adjuvant requirements," J Immunol. 154:3088-3095 (1995).
	HF**	Caliceti, P. and F. Veronese, "Pharmacokinetic and biodistribution properties of poly(ethylene glycol)-protein conjugates," Adv. Drug Deliv. Rev. 55(10):1261-1277 (2003).
	HG**	Carrillo, H. and D. Lipman, "The multiple-sequence alignment problem in biology," SIAM J Applied Math 48:1073-1082 (1988).
	HH**	Cefalu, W., "Animal models of type 2 diabetes: clinical presentation and pathophysiological relevance to the human condition," ILAR Journal 47(3):186-198 (2006).
	HI**	Chapman et al., "Therapeutic antibody fragments with prolonged in vivo half-lives," Nature Biotech. 17:780-783 (1999).
	HJ**	Cheng et al., "PEGylated adenoviruses for gene delivery to the intestinal epithelium by the oral route," Pharm. Res. 20(9):1444-1451 (2003).

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	HK**	Cherr et al., "The dual functions of GPI-anchored PH-20: hyaluronidase and intracellular signaling," <i>Matrix Biol.</i> 20:515-525 (2001).			
	HL**	Cherr et al., "The PH-20 protein in cynomolgus macaque spermatozoa: identification of two different forms exhibiting hyaluronidase activity," <i>Dev. Biol.</i> 175:142-153 (1996).			
	HM**	Cho et al., "Construction of hepatitis C-SIN virus recombinants with replicative dependency on hepatitis C virus serine protease activity," <i>J. Virol. Meth.</i> (65):201-207 (1997).			
	HN**	Chowpongpan et al., "Cloning and characterization of the bovine testicular PH-20 hyaluronidase core domain," <i>Biotechnol Lett.</i> 26(15):1247-1252 (2004).			
	HO**	Colbere-Garapin et al., "A new dominant hybrid selective marker for higher eukaryotic cells," <i>J Mol Biol</i> 150:1-14 (1981).			
	HP**	Conserved domain search from US Application No. 10/795,095 of SEQ ID NO:6, Primakoff et al. US 5,721,348, performed on the NCBI website on August 5, 2008.			
	HQ**	Csoka et al., "Hyaluronidases in tissue invasion," <i>Invasion Metastasis</i> 17:297-311 (1997).			
	HR**	Csoka et al., "Purification and microsequencing of hyaluronidase isozymes from human urine," <i>FEBS Lett.</i> 417(3):307-310 (1997).			
	HS**	Csoka et al., "The six hyaluronidase-like genes in the human and mouse genomes," <i>Matrix Biol.</i> 20:499-508 (2001).			
	HT**	Czejka et al., "Influence of hyaluronidase on the blood plasma levels of 5-fluorouracil in patients," <i>Pharmazie</i> 45:H.9 (1990).			
	HU**	De Maeyer et al., "The growth rate of two transplantable murine tumors, 3LL lung carcinoma and B16F10 melanoma, is influenced by Hyal-1, a locus determining hyaluronidase levels and polymorphism," <i>Int. J. Cancer</i> 51:657-660 (1992).			
	HV**	De Salegui et al., "A comparison of serum and testicular hyaluronidase," <i>Arch. Biochem. Biophys.</i> 121:548-554 (1967).			
	HW**	DeBoer et al., "The tac promoter: a functional hybrid derived from the trp and lac promoters," <i>Proc. Natl. Acad. Sci. USA</i> 80:21-25 (1983).			
	HX**	Delpech et al., "Enzyme-linked hyaluronectin: a unique reagent for hyaluronan assay and tissue location and for hyaluronidase activity detection," <i>Anal. Biochem.</i> 229:35-41 (1995).			
	HY**	Derwent English abstract for Japanese Publication No. JP 2007-153797, published Jun. 21, 2007, entitled "Therapeutic Agent And Preventive Agent Of Autoimmune Disease, Inflammation, And Nervous Disease," 3 pages.			
	HZ**	Dorfman, A. and M. Ott, "A turbidimetric method for the assay of hyaluronidase," <i>J. Biol. Chem.</i> 172:367-375 (1948).			
	IA**	D'Souza et al., "In vitro cleavage of hepatitis C virus polyprotein substrates by purified recombinant NS3 protease," <i>J. Gen. Virol.</i> 76:1729-1736 (1995).			
	IB**	Duttaroy et al., "Development of a long-acting insulin analog using albumin fusion technology," <i>Diabetes</i> 54(1):251-258 (2005).			
	IC**	Elder et. al, "Intra-arterial hyaluronidase in severe peripheral arterial disease," <i>Lancet</i> 648-649 (1980).			
	ID**	Ernst et al., "Enzymatic degradation of glycosaminoglycans," <i>Critical Reviews in Biochemistry and Molecular Biology</i> 30(5):387-444 (1995).			
	IE**	Eskens et al., "Enzymatic glycocalyx treatment impairs insulin-mediated recruitment of microvascular blood volume and decreases insulin sensitivity in rats," <i>FASEB Journal</i> 25: 1023.13 (2011) (Abstract).			
	IF**	European Pharmacopoeia, Chapter 5.1.3, "Efficacy of antimicrobial preservation," pages 447-449 (2005).			

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				Filing Date March 19, 2020	Group Art Unit 1656
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	IG**	Fankhauser, N. and P.Mäser, "Identification of GPI anchor attachment signals by a Kohonen self-organizing map," <i>Bioinformatics</i> 21(9) 1846-1852 (2005).			
	IH**	Felix et al., "Pegylated peptides. IV. Enhanced biological activity of site-directed pegylated GRF analogs," <i>Int. J. Peptide Res.</i> 46:253-264 (1995).			
	II**	Few, B., "Hyaluronidase for treating intravenous extravasations," <i>MCN Amer. J. Matern. Child Nurs.</i> 12(1):23 (1987).			
	IJ**	Filocamo et al., "Chimeric Sindbis viruses dependent on the NS3 protease of hepatitis C virus," <i>J. Virology</i> 71:1417-1427 (1997).			
	IK**	Forsburg, S., "Codon usage table for <i>Schizosaccharomyces pombe</i> ," <i>Yeast</i> 10(8):1045-1047 (1994).			
	IL**	Fransson et al., "Solvent effects on the solubility and physical stability of human insulin-like growth factor I," <i>Pharm Res.</i> 14(5):606-612 (1997).			
	IM**	Frost, G. and R. Stern, "A microtiter-based assay for hyaluronidase activity not requiring specialized reagents," <i>Anal. Biochem.</i> 251:263-269 (1997).			
	IN**	Gardner et al., "The complete nucleotide sequence of an infectious clone of cauliflower mosaic virus by M13mp7 shotgun sequencing," <i>Nucleic Acids Res.</i> 9:2871-2888 (1981).			
	IO**	GenBank Accession No. AAC60607, PH-20 [<i>Homo sapiens</i>], published on Jun. 05, 2000 [online] [retrieved on Dec. 12, 2012][retrieved from URL:< ncbi.nlm.nih.gov/protein/AAC60607 >, 1 page.			
	IP**	Gilbert, W. and L. Villa-Komaroff, "Useful Proteins from Recombinant Bacteria," <i>Scientific American</i> 242(4):74-94 (1980).			
	IQ**	Girish et al., "Hyaluronidase inhibitors: a biological and therapeutic perspective," <i>Curr Med Chem</i> 16(18):2261-2288 (2009).			
	IR**	Gmachl et al., "The human sperm protein PH-20 has hyaluronidase activity," <i>FEBS</i> 336(3):545-548 (1993).			
	IS**	Good et al., "Hydrogen ion buffers for biological research," <i>Biochemistry</i> 5(2):467-477 (1966).			
	IT**	Gribskov et al., "Sigma factors from <i>E. coli</i> , <i>B. subtilis</i> , phage SP01, and phage T4 are homologous proteins," <i>Nucl. Acids Res.</i> 14(16):6745-6763 (1986).			
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	IV**	Guiotto et al., "An improved procedure for the synthesis of branched polyethylene glycols (PEGs) with the reporter dipeptide Met-betaAla for protein conjugation," <i>Bioorg. Med. Chem. Lett.</i> 12:177-180 (2002).			
	IW**	Guntenhoner et al., "A substrate-gel assay for hyaluronidase activity," <i>Matrix</i> 12:388-396 (1992).			
	IX**	Guo et al., "Protein tolerance to random amino acid change," <i>Proc. Nat'l. Acad. Sci. USA</i> 101:9205-9210 (2004).			
	IY**	Hahm et al., "Generation of a novel poliovirus with a requirement of hepatitis C virus protease NS3 activity," <i>Virology</i> 226:318-326 (1996).			
	IZ**	Haller et al., "Escaping the interstitial matrix with enzyme-mediated drug delivery," <i>Drug Delivery Technology</i> , 5(5):1-6 (2005).			
	JA**	Hamatake et al., "Establishment of an in vitro assay to characterize hepatitis C virus NS3-4A protease trans-processing activity," <i>Intervirology</i> 39:249-258 (1996).			
	JB**	Hammer et al., "Diversity of alpha-fetoprotein gene expression in mice is generated by a combination of separate enhancer elements," <i>Science</i> 235:53-58 (1987).			

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	JC**	Hanahan, D., "Heritable formation of pancreatic beta-cell tumours in transgenic mice expressing recombinant insulin/simian virus 40 oncogenes," <i>Nature</i> 315(6015):115-122 (1985).
	JD**	Harris, J. and R. Chess, "Effect of pegylation on pharmaceuticals," <i>Nat Rev Drug Discov</i> 2(3):214-221 (2003).
	JE**	Hartman S. and R. Mulligan, "Two dominant-acting selectable markers for gene transfer studies in mammalian cells," <i>Proc Natl Acad Sci</i> 85:8047-8051 (1988).
	JF**	Have et al., "Cloning and characterization of the cDNA encoding the PH20 protein in the European red fox <i>Vulpes vulpes</i> ," <i>Reproduct Fertil Dev</i> 10:165-172 (1998).
	JG**	Herrera-Estrella et al., "Expression of chimaeric genes transferred into plant cells using a ti-plasmid-derived vector," <i>Nature</i> 303:209-213 (1983).
	JH**	Herrera-Estrella et al., "Light-inducible and chloroplast-associated expression of a chimaeric gene introduced into <i>Nicotiana tabacum</i> using a Ti plasmid vector," <i>Nature</i> 310(5973):115-120 (1984).
	JI**	Hibi et al., "Chondroitinase C activity of <i>Streptococcus intermedius</i> ," <i>FEMS-Microbiol-Lett.</i> 48(2):121-124 (1989).
	JJ**	Hofinger et al., "Isoenzyme-specific differences in the degradation of hyaluronic acid by mammalian-type hyaluronidases," <i>Glycoconj J</i> 25:101-109 (2008).
	JK**	Holash et al., "VEGF-Trap: a VEGF blocker with potent antitumor effects," <i>Proc Natl Acad Sci USA</i> 99(17):11393-11398 (2002).
	JL**	Hooper et al., "Determination of glycosyl-phosphatidylinositol membrane protein anchorage" <i>Proteomics</i> 1:748-755 (2001)
	JM**	Horn et al., "Intravesical chemotherapy of superficial bladder tumors in a controlled trial with cis-platinum versus cis-platinum plus hyaluronidase," <i>J. Surg. Oncol.</i> 28:304-307 (1985).
	JN**	Huang et al., "Recombinant Human Hyaluronidase PH20 Does Not Stimulate an Acute Inflammatory Response and Inhibits Lipopolysaccharide-Induced Neutrophil Recruitment in the Air Pouch Model of Inflammation," <i>J Immunol.</i> 192(11):5285-5295 (2014).
	JO**	Huang, X. and M. Miller, "A time-efficient, linear-space local similarity algorithm," <i>Adv. Appl. Math.</i> 12:337-357 (1991).
	JP**	Hunnicut et al., "Structural relationship of sperm soluble hyaluronidase to the sperm membrane protein PH-20," <i>Biol Reprod.</i> 54(6):1343-1349 (1996).
	JQ**	Infante et al., "Phase I trials of PEGylated recombinant human hyaluronidase PH20 in patients with advanced solid tumours," <i>Br J Cancer</i> 118(2):153-161 (2018).
	JR**	Ito et al., "Cultivation of hepatitis C virus in primary hepatocyte culture from patients with chronic hepatitis C results in release of high titre infectious virus," <i>J. Gen. Virol.</i> 77:1043-1054 (1996).
	JS**	IUPAC-IUB Commission on Biochemical Nomenclature, "A One-Letter Notation for Amino Acid Sequences: Tentative Rules," <i>J. Biol. Chem.</i> 243:3557-3559 (1968).
	JT**	IUPAC-IUB, "Abbreviated nomenclature of synthetic polypeptides-polymerized amino acids-revised recommendations," <i>Commission on Biochemical Nomenclature, Biochemistry</i> 11:1726-1731 (1972).
	JU**	Jadin et al., "A comprehensive model of hyaluronan turnover in the mouse," <i>Matrix Biol</i> 31(2):81-89 (2012).
	JV**	Jay et al., "Construction of a general vector for efficient expression of mammalian proteins in bacteria: use of a synthetic ribosome binding site," <i>Proc. Natl. Acad. Sci. USA</i> 78:5543-5548 (1981).
	JW**	Karvinen et al., "Hyaluronan, CD44 and versican in epidermal keratinocyte tumors," <i>British Journal of Dermatology</i> 148:86-94 (2003).

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	JX**	Kelsey et al., "Species- and tissue-specific expression of human alpha 1-antitrypsin in transgenic mice," Genes And Devel. 1:161-171 (1987).			
	JY**	Kim et al., "Sperm penetration through cumulus mass and zona pellucida," Int J Dev Biol. 52(5-6):677-682 (2008).			
	JZ**	Kodukula et al., "Biosynthesis of phosphatidylinositol glycan-anchored membrane proteins" J. Biol. Chem. 266:4464-4470 (1991).			
	KA**	Kohno et al., "Effects of hyaluronidase on doxorubicin penetration into squamous carcinoma multicellular tumor spheroids and its cell lethality," J. Cancer Res. Oncol. 120:293-297 (1994).			
	KB**	Kollias et al., "Regulated expression of human A gamma-, beta-, and hybrid gamma beta-globin genes in transgenic mice: manipulation of the developmental expression patterns," Cell 46:89-94 (1986).			
	KC**	Krumlauf et al., "Developmental regulation of alpha-fetoprotein genes in transgenic mice, Mol. Cell. Biol. 5:1639-1648 (1985).			
	KD**	Krupers et al., "Complexation of poly(ethylene oxide) with poly(acrylic acid-co-hydroxyethyl methacrylate)s," Eur. Polym J. 32(6):785-790 (1996).			
	KE**	Kyte et al., "A Simple Method for Displaying the Hydropathic Character of a Protein" J. Mol. Biol. 157:105-132 (1982).			
	KF**	Lalancette et al., "Characterization of an 80-kilodalton bull sperm protein identified as PH-20," Biol Reprod. 65(2):628-636 (2001).			
	KG**	Lam et al., "The effect of benzyl alcohol on recombinant human interferon-gamma," Pharm Res. 14(6):725-729 (1997).			
	KH**	Lammerts van Bueren et al., "The antibody zalutumumab inhibits epidermal growth factor receptor signaling by limiting intra- and intermolecular flexibility," Proc Natl Acad Sci U S A. 105(16):6109-6114 (2008). Retraction also included, Proc Natl Acad Sci U S A. 109(14):5548 (2008).			
	KI**	Lathrop et al., "cDNA cloning reveals the molecular structure of a sperm surface protein, PH-20, involved in sperm-egg adhesion and the wide distribution of its gene among mammals," J Cell Biol. 111(6 Pt 2):2939-2949 (1990).			
	KJ**	Laurent, T. and J. Fraser, "Hyaluronan," FASEB J 6:2397-2404 (1992).			
	KK**	Leder et al., "Consequences of widespread deregulation of the c-myc gene in transgenic mice: multiple neoplasms and normal development," Cell 45:485-495 (1986).			
	KL**	Li et al., "Importance of glycosylation and disulfide bonds in hyaluronidase activity of macaque sperm surface PH-20," J. Androl. 23:211-219 (2002).			
	KM**	Li et al., "Structural basis for EGF receptor inhibition by the therapeutic antibody IMC-11F8," Structure. 16(2):216-227 (2008).			
	KN**	Liang et al., "Prediction of antigenic epitopes on protein surfaces by consensus scoring," BMC Bioinformatics. 10:302 (2009), 10 pages.			
	KO**	Lin et al., "A hyaluronidase activity of the sperm plasma membrane protein PH-20 enables sperm to penetrate the cumulus cell layer surrounding the egg," J Cell Biol. 125(5):1157-1163 (1994).			
	KP**	Lin et al., "Molecular cloning of the human and monkey sperm surface protein PH-20," Proc. Natl. Acad. Sci. USA 90:10071-10075 (1993).			
	KQ**	Lipponen et al "High stromal hyaluronan level is associated with poor differentiation and metastasis in prostate cancer," European Journal of Cancer 37:849-856 (2001).			
	KR**	Locke et al., "ENHANZE® drug delivery technology: a novel approach to subcutaneous administration using recombinant human hyaluronidase PH20," Drug Deliv 26(1):98-106 (2019).			
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	KS**	Louveau, I. and F. Gondret, "GH and insulin affect fatty acid synthase activity in isolated porcine adipocytes in culture without any modifications of sterol regulatory element binding protein-1 expression," J Endocrin. 181:271-280 (2004).		
	KT**	Lowy et al., "Isolation of transforming DNA: cloning the hamster aprt gene," Cell 22:817-823 (1980).		
	KU**	Lu, H. and E. Wimmer., "Poliovirus chimeras replicating under the translational control of genetic elements of hepatitis C virus reveal unusual properties of the internal ribosomal entry site of hepatitis C virus," Proc. Natl. Acad. Sci. USA 93:1412-1417 (1996).		
	KV**	Lu, Y. and A. Felix, "Pegylated peptides I: Solid-phase synthesis of N alpha-pegylated peptides using Fmoc strategy," Peptide Res 6:140-146 (1993).		
	KW**	Lu, Y. and A. Felix, "Pegylated peptides. II. Solid-phase synthesis of amino-, carboxy- and side-chain pegylated peptides," Int. J. Peptide Protein Res. 43:127-138 (1994).		
	KX**	M3WD76 Felca (2015, updated) Hyaluronidase/PH20 from Felis catus, 3 pages.		
	KY**	Ma et al., "Fucosylation in prokaryotes and eukaryotes" Glycobiology 16(12):158R-184R (2006)		
	KZ**	Maa and Hsu, "Aggregation of recombinant human growth hormone induced by phenolic compounds" Int. J. Pharm. 140(2):155-168 (1996).		
	LA**	MacDonald, R., "Expression of the pancreatic elastase I gene in transgenic mice," Hepatology 7:42S-51S(1987).		
	LB**	Magram et al., "Developmental regulation of a cloned adult beta-globin gene in transgenic mice," Nature 315:338-340 (1985).		
	LC**	Maksimenko et al. "Resistance of dextran-modified hyaluronidase to inhibition by heparin" Biochemistry (Mosc). 66(4):456-463 (2001).		
	LD**	Mammalian Gene Collection (MGC) Program Team, "Generation and initial analysis of more than 15,000 full-length human and mouse cDNA sequences," Proc. Natl. Acad. Sci. USA 99:16899-16903 (2002).		
	LE**	Marković-Housley et al., "Crystal Structure of Hyaluronidase, a Major Allergen of Bee Venom," Structure 8: 1025-1035 (2000).		
	LF**	McIlvaine, WB, "A buffer solution for colorimetric comparison," J. Biol. Chem. 49:183-186 (1921).		
	LG**	Mehvar et al., "Modulation of the pharmacokinetics and pharmacodynamics of proteins by polyethylene glycol conjugation," J. Pharm. Pharmaceut. Sci. 3(1):125-136 (2000).		
	LH**	Menzel, E. and C. Farr, "Hyaluronidase and its substrate hyaluronan: biochemistry, biological activities and therapeutic uses," Cancer Lett. 131:3-11 (2003).		
	LI**	Merrifield, J., "Solid phase peptide synthesis. I. The synthesis of a tetrapeptide," J Am Chem Soc 85:2149-2154 (1963).		
	LJ**	Meyer et al., "The soluble hyaluronidase from bull testes is a fragment of the membrane-bound PH-20 enzyme." FEBS Letters 413(2):385-388 (1997).		
	LK**	Michelacci et al., "Chondroitinase C from Flavobacterium heparinum," J. Biol. Chem. 251:1154-1158 (1976).		
	LL**	Miller et al., "Use of retroviral vectors for gene transfer and expression," Meth. Enzymol. 217:581-599 (1993).		
	LM**	Mizutani et al., "Characterization of hepatitis C virus replication in cloned cells obtained from a human T-cell leukemia virus type 1-infected cell line, MT-2," J.Virol. 70:7219-7223 (1996).		
	LN**	Mizutani et al., "Inhibition of hepatitis C virus replication by antisense oligonucleotide in culture cells," Biochem. Biophys. Res. Commun. 212:906-911 (1995).		

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	LO**	Molineux, G., "Pegylation: engineering improved biopharmaceuticals for oncology," <i>Pharmacotherapy</i> 23 (8 Pt 2):3S-8S (2003).			
	LP**	Monfardini et al., "A branched monomethoxypoly(ethylene glycol) for protein modification," <i>Bioconjugate Chem.</i> 6:62-69 (1995).			
	LQ**	Nadsombati et al., "Dose-range developmental toxicity of rHuPH20 in mice," <i>Matrix Biology</i> 27:23 (2008).			
	LR**	NCBI Reference Sequence XP_011728213.1, <i>Macaca nemestrina</i> (pig-tailed macaque) PH-20 hyaluronidase. Published on Apr. 24, 2018. Retrieved from URL: <ncbi.nlm.nih.gov/protein/795324051/ [retrieved on Apr. 20, 2020], 2 pages.			
	LS**	Nakayama et al., "CD15 expression in mature granulocytes is determined by alpha 1,3-fucosyltransferase IX, but in promyelocytes and monocytes by alpha 1,3-fucosyltransferase IV," <i>J. Biol. Chem.</i> , 276(19):16100-16106 (2001).			
	LT**	Needleman, S. and C. Wunsch "A general method applicable to the search for similarities in the amino acid sequence of two proteins," <i>J Mol Biol.</i> 48:443-453 (1970).			
	LU**	Nekoroski et al., "A recombinant human hyaluronidase sustained release gel for the treatment of post-surgical edema," <i>Int J Dermatol.</i> 53(6):777-785 (2014). Epub 2013 Oct 29.			
	LV**	Omaetxebarria et al., "Computational approach for identification and characterization of GPI-anchored peptides in proteomics experiments," <i>Proteomics</i> 7(12):1951-1960 (2007).			
	LW**	Ornitz et al., "Elastase I promoter directs expression of human growth hormone and SV40 T antigen genes to pancreatic acinar cells in transgenic mice," <i>Cold Spring Harbor Symp. Quant. Biol.</i> 50:399-409 (1986).			
	LX**	Ostresh et al., "Peptide libraries: determination of relative reduction rates of protected amino acids in competitive couplings," <i>Biopolymers</i> 34:1681-1689 (1994).			
	LY**	Padavattan, S. "Crystal structure determination of hyaluronidase : a major bee venom allergen, in complex with an IgG Fab fragment and purification and biophysical characterization of bovine testes hyaluronidase," 2006, PhD Thesis, University of Basel, Faculty of Science. DOI: 10.5451/unibas-004349798. 98 pages.			
	LZ**	Paul, A. and D. Sochart, "Improving the results of ganglion aspiration by the use of hyaluronidase," <i>J Hand Surg</i> 22(2):219-221 (1997).			
	MA**	Paulick, M. and C. Bertozzi, "The glycosylphosphatidylinositol anchor: A complex membrane-anchoring structure for proteins," <i>Biochemistry</i> 47:6991-7000 (2008).			
	MB**	Pawlowski et al., "The effects of hyaluronidase upon tumor formation in BALB/c mice painted with 7,12-dimethylbenz-(a)anthracene," <i>Int. J. Cancer</i> 23:105-109 (1979).			
	MC**	Pedersen et al., "Sym004: a novel synergistic anti-epidermal growth factor receptor antibody mixture with superior anticancer efficacy," <i>Cancer Res.</i> 70(2):588-597 (2010).			
	MD**	Pham et al., "Large-scale transient transfection of serum-free suspension-growing HEK293 EBNA1 cells: peptone additives improve cell growth and transfection efficiency," <i>Biotechnology and Bioengineering</i> 84:332-342 (2003).			
	ME**	Phelps et al., "Restricted lateral diffusion of PH-20, a PI-anchored sperm membrane protein," <i>Science</i> 240:1780-1782 (1988).			
	MF**	Pierleoni et al., "PredGPI: a GPI-anchor predictor," <i>BMC Bioinformatics</i> 9:392 (2008).			
	MG**	Pinkert et al., "An albumin enhancer located 10 kb upstream functions along with its promoter to direct efficient, liver-specific expression in transgenic mice," <i>Genes and Devel.</i> 1:268- 276 (1987).			
	MH**	Pirinen et al "Prognostic value of hyaluronan expression in non-small cell lung cancer: Increased stromal expression indicated unfavorable outcome in patients with adenocarcinoma," <i>Int. J. Cancer</i> 95:12-17 (2001).			
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	MI**	Primakoff et al., "Fully effective contraception in male and female guinea pigs immunized with the sperm protein PH-20," <i>Nature</i> 335:543-546 (1988).			
	MJ	Prothmann et al., "Sexual size dimorphism predicts rates of sequence evolution of Sperm Adhesion Molecule 1 (SPAM1, also PH-20) in monkeys, but not in hominoids (apes including humans)," <i>Mol Phy Ev</i> 63:52-63 (2012).			
	MK**	Readhead et al., "Expression of a myelin basic protein gene in transgenic shiverer mice: correction of the dysmyelinating phenotype," <i>Cell</i> 48:703-712 (1987).			
	ML**	Reitinger et al., ""Designed human serum hyaluronidase 1 variant, HYAL1DeltaL, exhibits activity up to pH 5.9,"" <i>J Biol Chem.</i> 284(29):19173-177 (2009).			
	MM**	Remmele et al., "Interleukin-1 receptor (IL-1R) liquid formulation development using differential scanning calorimetry," <i>Pharm Res.</i> 15(2):200-208 (1998).			
	MN**	Rhodes et al., "Transformation of maize by electroporation of embryos," <i>Methods Mol Biol</i> 55:121-131 (1995).			
	MO**	Richmond, T., "Precompiled codon-usage tables," <i>Genome Biology</i> 1(1):reports241 (2000), 2 pages.			
	MP**	Ripka et al., "Two Chinese hamster ovary glycosylation mutants affected in the conversion of GDP-mannose to GDP-fucose," <i>Arch. Biochem. Biophys.</i> 249(2):533-545 (1986).			
	MQ**	Roberts et al., "Chemistry for peptide and protein PEGylation," <i>Advanced Drug Delivery Review</i> 54:459-476 (2002).			
	MR**	Ropponen et al "Tumor Cell-associated Hyaluronan as an Unfavorable Prognostic Factor in Colorectal Cancer," <i>Cancer Research</i> 58:342-347 (1998).			
	MS**	Sato et al., "Cloning and expression in <i>Escherichia coli</i> of the gene encoding the <i>Proteus vulgaris</i> chondroitin ABC lyase," <i>Appl. Microbiol. Biotechnol.</i> 41(1):39-46 (1994).			
	MT**	Sato, H., "Enzymatic procedure for site-specific pegylation of proteins," <i>Adv. Drug Deliv. Rev.</i> 54:487-504 (2002).			
	MU**	Sawhney et al., "Bioerodible hydrogels based on photopolymerized poly(ethylene glycol)-co poly(hydroxyl acid) Diacrylate Macromers," <i>Macromolecules</i> 26:581-587 (1993).			
	MV**	Schanté et al., "Improvement of hyaluronic acid enzymatic stability by the grafting of amino-acids," <i>Carbohydrate Polymers</i> , 87(3):2211-2216 (2012).			
	MW**	Scharf et al., "Heat stress promoters and transcription factors," <i>Results Probl Cell Differ</i> 20:125-162 (1994).			
	MX**	Scheithauer et al., "In vitro evaluation of the anticancer drug modulatory effect of hyaluronidase in human gastrointestinal cell lines," <i>Anticancer Res.</i> 8:391-396 (1988).			
	MY**	Schuller et al., "Pharmacokinetics of intrahepatic 5-fluorouracil + preinjected hyaluronidase," <i>Proc. Amer. Assoc. Cancer Res.</i> 32:173, abstract no. 1034 (1991).			
	MZ**	Schwartz and Dayhoff, eds., <i>Atlas of Protein Science and Structure</i> , National Biomedical Research Foundation, pp. 353-358 (1979).			
	NA**	Schwartzman, J., "Hyaluronidase: A Review in Its Therapeutic Use in Pediatrics," <i>J. Pediat.</i> 39:491-502 (1951).			
	NB**	Seaton et al., "Rat sperm 2B1 glycoprotein (PH20) contains a C-terminal sequence motif for attachment of a glycosyl phosphatidylinositol anchor. Effects of endoproteolytic cleavage on hyaluronidase activity," <i>Biol Reprod.</i> 62(6):1667-1676 (2000).			
	NC**	Shani, M., "Tissue-specific expression of rat myosin light-chain," <i>Nature</i> 314:283-286 (1985).			
	ND**	Sharp et al., "Codon usage patterns in <i>Escherichia coli</i> , <i>Bacillus subtilis</i> , <i>Saccharomyces cerevisiae</i> , <i>Schizosaccharomyces pombe</i> , <i>Drosophila melanogaster</i> and <i>Homo sapiens</i> ; a review of the considerable within-species diversity," <i>Nucleic Acids Res.</i> 16(17):8207-8211 (1988).			

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	NE**	Sharp, P. and E. Cowe, "Synonymous codon usage in <i>Saccharomyces cerevisiae</i> ," <i>Yeast</i> . 7(7):657-678 (1991).
	NF**	Shekhar et al., "The matrix reloaded: halozyme's recombinant enzyme helps injected drugs spread faster," <i>Chem. Biol.</i> 14:603-604 (2007).
	NG**	Shimizu, Y. and H. Yoshikura, "Multicycle infection of hepatitis C virus in cell culture and inhibition by alpha and beta interferons," <i>J. Virol.</i> 68:8406-8408 (1994).
	NH**	Singh et al., "Mechanisms of m-cresol-induced protein aggregation studied using a model protein cytochrome c," <i>J Pharm Sci.</i> 100(5):1679-1689 (2011); Epub date Jan. 12, 2011.
	NI**	Smith, T. and M. Waterman, "Comparison of biosequences," <i>Advances in Applied Mathematics</i> 2:482-489 (1981).
	NJ**	St Croix et al., "Reversal of intrinsic and acquired forms of drug resistance by hyaluronidase treatment of solid tumors," <i>Cancer Lett</i> 131(1):35-44 (1998).
	NK**	Steinkuhler et al., "Product inhibition of the hepatitis C virus NS3 protease," <i>Biochem.</i> 37:8899-8905 (1998).
	NL**	Stern et al., "Hyaluronidases: their genomics, structures, and mechanisms of action," <i>Chem Rev</i> 106: 818-839 (2006).
	NM**	Stern, R., "Devising a pathway for hyaluronan catabolism: are we there yet?" <i>Glycobiology</i> 13:105R-115R (2003).
	NN**	Sturla et al., "Core fucosylation of N-linked glycans in leukocyte adhesion deficiency/congenital disorder of glycosylation IIc fibroblasts," <i>Glycobiology</i> 15(10):924-935 (2005).
	NO**	Sudo et al., "Establishment of an in vitro assay system for screening hepatitis C virus protease inhibitors using high performance liquid chromatography," <i>Antiviral Res.</i> 32:9-18 (1996).
	NP**	Sutton, S. and D. Porter, "Development of the antimicrobial effectiveness as USP chapter <51>," <i>PDA J. Pharm. Sci Technol.</i> , 56(6):300-311 (2002).
	NQ**	Swift et al., "Tissue-specific expression of the rat pancreatic elastase I gene in transgenic mice," <i>Cell</i> 38(3):639-646 (1984).
	NR**	Takahashi et al., "A fluorimetric Morgan-Elson assay method for hyaluronidase activity," <i>Anal. Biochem.</i> 322:257-263 (2003).
	NS**	Takeshita et al., "An enzyme-linked immunosorbent assay for detecting proteolytic activity of hepatitis C virus proteinase," (1997) <i>Anal. Biochem.</i> 247:242-246.
	NT**	Taliani et al., "A continuous assay of hepatitis C virus protease based on resonance energy transfer depsipeptide substrates," <i>Anal. Biochem.</i> 240:60-67 (1996).
	NU**	ten Have et al., "Cloning and characterization of the cDNA encoding the PH20 protein in the European red fox <i>Vulpes vulpes</i> ," <i>Reprod Fertil Dev.</i> 10(2):165-172 (1998).
	NV**	Tkalec et al., "Isolation and expression in <i>Escherichia coli</i> of cslA and cslB, genes coding for the chondroitin sulfate-degrading enzymes chondroitinase AC and chondroitinase B, respectively, from <i>Flavobacterium heparinum</i> ," <i>Applied and Environmental Microbiology</i> 66(1):29-35 (2000).
	NW**	Tsubery et al., "Prolonging the action of protein and peptide drugs by a novel approach of reversible polyethylene glycol modification," <i>J Biol. Chem</i> 279(37):38118-38124 (2004).
	NX**	Tsuda et al., "Substrate specificity studies of flavobacterium chondroitinase C and heparitinases towards the glycosaminoglycan protein linkage region. Use of a sensitive analytical method developed by chromophore-labeling of linkage glycoserines using dimethylaminoazobenzenesulfonyl chloride," <i>Eur. J. Biochem.</i> 262:127-133 (1999).
	NY**	Tung et al., "Mechanism of infertility in male guinea pigs immunized with sperm PH-20," <i>Biol. Reprod.</i> 56(5):1133-1141 (1997).

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	NZ**	Udenfriend, S. and K. Kodukula, "Prediction of omega site in nascent precursor of glycosylphosphatidylinositol protein," <i>Methods Enzymol.</i> 250:571-582 (1995).			
	OA**	UniProt Murine PH20 sequence, Retrieved from: <URL: uniprot.org/uniprot/P48794 [retrieved on Sept. 1, 2010] [5 pages].			
	OB**	United States Pharmacopeia. USP <51>. Antimicrobial effectiveness testing. United States Pharmacopeia Convention, Inc, Rockville, MD., 5 pages.			
	OC**	USP XXII-NF XVII, United States Pharmacopeia Convention, Inc, Rockville, MD., pages 644-645 (1990).			
	OD**	Varela et al., "Exome sequencing identifies frequent mutation of the SWI/SNF complex gene PBRM1 in renal carcinoma," <i>Nature</i> 469(7331):539-542 (2011).			
	OE**	Veronese et al., "Branched and Linear Poly(Ethylene Glycol): Influence of the Polymer Structure on Enzymological, Pharmacokinetic, and Immunological Properties of Protein Conjugates," <i>J. Bioactive Compatible Polymers</i> 12:197-207 (1997).			
	OF	Von Sivaraman Padavattan (2006) Thesis of University of Basel, "Crystal structure determination of hyaluronidase, a major bee venom allergen, in complex with an IgG Fab fragment and purification and biophysical characterization of bovine testes hyaluronidase," 100 pages.			
	OG**	Wagner et al., "Nucleotide sequence of the thymidine kinase gene of herpes simplex virus type 1," <i>Proc. Natl. Acad. Sci. USA</i> 78:1441-1445 (1981).			
	OH**	Wang et al., "The molecular physiology of hepatic nuclear factor 3 in the regulation of gluconeogenesis," <i>J. Biol. Chem.</i> 275(19):14717-14721 (2000).			
	OI**	Watson et al., <i>Molecular Biology of the Gene</i> , 4th Edition, The Benjamin/Cummings Pub. Co., p. 224 (1987).			
	OJ**	Weiss et al., "Activities of monomeric insulin analogs at position A8 are uncorrelated with their thermodynamic stabilities," <i>J. Biol. Chem.</i> 276(43):40018-40024 (2001).			
	OK**	Wells et al., "Additivity of Mutational Effects in Proteins," <i>Biochem</i> 29:8509-8517 (1990).			
	OL**	White et al., "Comparison of the glycosyl-phosphatidylinositol cleavage/attachment site between mammalian cells and parasitic protozoa," <i>J. Cell Sci.</i> 113(Pt.4):721-727 (2000).			
	OM**	Wigler et al., "Transfer of purified herpes virus thymidine kinase gene to cultured mouse cells," <i>Cell</i> 11:223-232 (1977).			
	ON**	Wigler et al., "Transformation of mammalian cells with an amplifiable dominant-acting gene," <i>Proc Natl Acad Sci. USA</i> 77:3567-3570 (1980).			
	OO**	Yamamoto et al., "Identification of a functional promoter in the long terminal repeat of Rous sarcoma virus," <i>Cell</i> 22:787-797 (1980).			
	OP**	Yamane-Ohnuki et al., "Establishment of FUT8 knockout Chinese hamster ovary cells: an ideal host cell line for producing completely defucosylated antibodies with enhanced antibody-dependent cellular cytotoxicity," <i>Biotech. Bioeng.</i> 87:614-622 (2004).			
	OQ**	Yang, X. and X. Yu, "An introduction to epitope prediction methods and software," <i>Rev Med Virol.</i> 19(2):77-96 (2009).			
	OR**	Yocum et al., "Assessment and implication of the allergic sensitivity to a single dose of recombinant human hyaluronidase injection: A double-blind placebo-controlled clinical trial," <i>J Infus Nursing</i> 30:293-299 (2007).			
	OS**	Yudin et al., "Characterization of the active site of monkey sperm hyaluronidase," <i>Reproduction.</i> 121(5):735-743 (2001).			
	OT**	Zalipsky, S., "Chemistry of polyethylene glycol conjugates with biologically active molecules," <i>Adv. Drug Del. Rev.</i> 16:157-182 (1995).			

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Substitute Form PTO-1449 (Modified)		U.S. Department of Commerce Patent and Trademark Office		Attorney Docket No. 33320.03087.US26/ 3087C	Application No. 16/824,572
List of Patents and Publications for Applicant's Information Disclosure Statement (37 CFR §1.98(b))				Applicant <i>Wei et al.</i>	
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	OU**	Zanker et al., "Induction of response in previous chemotherapy resistant patients by hyaluronidase," Proc. Amer. Assoc. Cancer Res. 27:390 Abstract 1550 (1986).			
	OV**	Zhang et al., "Hyaluronidase Activity of Hyman Hyal1 Requires Active Site Acidic and Tyrosine residues," J Biol Chem 284(14):9433-9442 (2009).			
	OW**	Zhao, X. and J. Harris, "Novel degradable poly(ethylene glycol) esters for delivery," in Poly(ethylene glycol), Chemistry and Biological Applications, ACS Symposium Series 680, Hams, J. and S. Zalipsky, (eds), 458-472 (1997).			
	OX**	Bee et al., "Recombinant human PH20 is well tolerated at higher intravenous and subcutaneous doses in cynomolgus monkeys," EUFEPS 2008, Munich, Germany. Abstract, 2 pages.			
	OY**	Bee et al., "Recombinant human PH20 is well tolerated at higher intravenous and subcutaneous doses in cynomolgus monkeys," EUFEPS 2008, Munich, Germany. Poster and individual panels, 9 pages.			
	OZ**	Bookbinder et al., "Biochemical characterization of recombinant human PH20 (SPAM1) hyaluronidase," Hyaluronan (ISHAS) 2007, Charleston, SC. Abstract, 1 page.			
	PA **	Bookbinder et al., "Biochemical characterization of recombinant human PH20 (SPAM1) hyaluronidase," Hyaluronan (ISHAS) 2007, Charleston, SC. Poster, 1 page.			
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	PD **	Bookbinder et al., "Evaluation of the compatibility and pharmacokinetics of co-formulated biologics with recombinant human hyaluronidase: Dose Response," American Association of Pharmaceutical Scientists Conference, November 2006. Abstract, 2 pages.			
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	PG **	Frost et al., "Punctuated equilibrium: The evolution of recombinant human hyaluronidase," Ophthalmic Anesthesia Society, 2006, Chicago, IL, abstract, 1 page.			
	PH **	Frost et al., "Punctuated equilibrium: The evolution of recombinant human hyaluronidase," Ophthalmic Anesthesia Society, 2006, Chicago, IL, presentation, 35 pages.			
	PI **	Haller et al., "Enhance technology – a revolution in drug dispersion," Biotechnology Industry Organization (BIO) Annual Meeting, June 19-22, 2005, Philadelphia, PA. Abstract, 3 pages.			
	PJ **	Haller et al., "Recombinant human hyaluronidase for the interstitial transport of therapeutics," American Association of Pharmaceutical Scientists Conference, June 2006, San Antonio, TX, Abstract, 2 pages.			
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	PL **	Haller et al., "Revolutionizing drug dispersion with enhance technology," American Association of Pharmaceutical Scientists Annual Meeting, Nov 6-10, 2005, Nashville, TN, Poster, 1 page.			
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	PN **	Haller et al., "The effects of recombinant human hyaluronidase on drug dispersion," American Association of Pharmaceutical Scientists Annual Meeting, Abstract in AAPS Journal 7(S2) May 5, 2005; 3 pages.			
	PO **	Haller, "Enhance technology – an enzymatic drug delivery system (DDS)," Japanese Export Trade Organization, November 2005, Santa Clara, CA. Abstract, 2 pages.			
	PP **	Haller, M., "Focus on enhanced and innovative recombinant human enzymes," Japanese Export Trade Organization, September 2004, Chicago, IL., Presentation, 16 pages.			
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	PU **	Jiang et al., "Effects of Recombinant Human PH20 (rHuPH20) on Interstitial Matrices: Creating a Favorable Environment for The Delivery of Cytostatic Agents," [abstract]. In: Proceedings of the 96th Annual Meeting of the American Association for Cancer Research; 2005 Apr 16-20; Anaheim, CA.:AACR; 2005. Vol. 46, page 1198, Abstract no. 5075, April 2005.			
	PV **	Keller et al., "Pharmacokinetic, pharmacodynamic and toxicologic effects of a recombinant human hyaluronidase (rHuPH20) in rodent and non-human primate models," Hyaluronan (ISHAS) 2007, Charleston, SC, Abstract, 1 page.			
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	PX **	Kodandapani et al., "Diverse structural and functional roles of N-glycosylations on rHuPH20," Glycan Abstract, 1 page (2009).			
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	PZ **	Nadsombati et al., "Evaluation of developmental and prenatal/postnatal reproduction toxicity of rHuPH20 in mice," American College of Toxicology 30th annual meeting, 2009, November 1-4, Palm Springs, CA, Abstract, 1 page.			
	QA **	Nagy et al., "Prospective, randomized study on bovine and recombinant human (Cumulase®) Hyaluronidases," American Society of Reproductive Medicine, 2006, New Orleans, LA, 06-A-886-ASRM, 2 pages.			
	QB **	Nagy, Z., "Prospective study on rHuPH20," European Society of Human Reproduction & Embryology Annual Meeting, June 19-22, 2005, Copenhagen, Denmark. Abstract O-213, 1 page.			
	QC **	"PEGPH20: The Science & The Strategy," presented at J. P. Morgan Healthcare Conference on Jan. 7, 2015. Presentation, 81 pages.			
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	QD **	Pinkstaff et al., "Recombinant human hyaluronidase for drug and fluid dispersion," American Association of Pharmaceutical Scientists Annual Meeting, November 2006, Boston, MA, Abstract, 2 pages.			
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	QG **	Torley, H., "Halozyne Therapeutics, Inc. The next chapter begins: creating value through growth," Presented at the 32nd Annual J.P. Morgan Healthcare Conference January 2014, 26 pages.			
	QH **	Wei et al., "Functions of N-linked glycans on human hyaluronidase PH20," presented at San Diego Glycobiology Symposium 2009. Poster 83 and individual panels, 5 pages.			
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	QL **	News Release, "Halozyne Announces Presentation Of Clinical Data At The American Diabetes Association 74th Scientific Sessions," Published on Jun. 15, 2014 [online][retrieved on Aug. 18, 2014] Retrieved from the internet: <URL: halozyne.com/Investors/News-Releases/News-Release-Details/2014/Halozyne-Announces-Presentation-Of-Clinical-Data-At-The-American-Diabetes-Association-74th-Scientific-Sessions/default.aspx [3 pages].			
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	QO **	News Release, "Bristol, Roche tap Halozyne for tech platform," Published Sept. 14, 2017 [online] Retrieved from:<URL: biopharmadive.com/news/bristol-roche-tap-halozyne-for-tech-platform/504958/ [retrieved on Sept. 18, 2017], 3 pages.			
	QP **	News Article, "Alteogen Inc. to Develop Herceptin Biosimilar for Subcutaneous Injection," Published on Aug. 23, 2018 [online] Retrieved from: <URL:thebell.co.kr/free/Content/ArticleView.asp?key=201808220100037100002360 [Original document retrieved from the internet and English translation], 4 pages.			
	QQ **	News Article, "[Promising biocompany] Alteogen Inc. tries to differentiate itself with specialized bio technology and strategy," Published on Sept. 17, 2018 [online] Retrieved from: <URL:edaily.co.kr/news/read?newsId=01105366619341104&mediaCodeNo=257&OutLnkChk=Y [Original document retrieved from the internet and English translation], 4 pages.			
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	QS **	News Article, "Alteogen, Inc. challenges to the ethical drug market by utilizing 'Human Hyaluronidase'," Published on Oct. 29 2018 [online] Retrieved from: <URL:fnnews.com/news/201810290941498520 [Original document retrieved from the internet and English translation], 6 pages.			
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	QV **	News Release, Halozyme Therapeutics, Inc., "Halozyme Announces Actions To Focus Strategy On ENHANZE® Drug Delivery Technology," Published Nov. 04, 2019 [online], Retrieved from: <URL: halozyme.com/investors/news-releases/news-release-details/2019/Halozyme-Announces-Actions-To-Focus-Strategy-On-ENHANZE-Drug-Delivery-Technology/default.aspx [retrieved on Nov. 11, 2019], 4 pages.			
	QW **	News Release, Halozyme Therapeutics, Inc., "Halozyme Announces HALO-301 Phase 3 Study Fails To Meet Primary Endpoint," Published Nov. 04, 2019 [online], Retrieved from: <URL: halozyme.com/investors/news-releases/news-release-details/2019/Halozyme-Announces-HALO-301-Phase-3-Study-Fails-To-Meet-Primary-Endpoint/default.aspx [retrieved on Nov. 11, 2019], 3 pages.			
	QX **	English translation of News Article, "Alteogen files a PCT application for subcutaneous pharmaceutical composition," Published on Mar. 24, 2020 [online], retrieved from <URL: medipana.com/news/news_viewer.asp?NewsNum=254556&MainKind=A&NewsKind=5&vCount=12&vKind [retrieved on Mar. 26, 2020], 2 pages.			
	QY **	Partial International Search Report, sent by facsimile Sept. 9, 2013, in connection with International Patent Application No. PCT/US2012/072182, 6 pages.			
	QZ **	International Search Report and Written Opinion, mailed Dec. 17, 2013, in connection with International Patent Application No. PCT/US2012/072182, 18 pages.			
	RA **	Response, dated March 17, 2014, to Written Opinion, mailed Dec. 17, 2013, in connection with International Patent Application No. PCT/US2012/072182, 94 pages.			
	RB **	Second Written Opinion, mailed May 21, 2014, in connection with International Patent Application No. PCT/US2012/072182, 8 pages.			
	RC **	Response, dated July 21, 2014, to second Written Opinion, mailed May 21, 2014, in connection with International Patent Application No. PCT/US2012/072182, 72 pages.			
	RD **	Second Written Opinion, mailed Jul. 30, 2014, in connection with International Patent Application No. PCT/US2012/072182, 9 pages.			
	RE **	Response, dated Sept. 1, 2014, to second Written Opinion, mailed Jul. 30, 2014, in connection with International Patent Application No. PCT/US2012/072182, 13 pages			
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	RF **	International Preliminary Report on Patentability, mailed Sept. 12, 2014, in connection with International Patent Application No. PCT/US2012/072182, 11 pages.			
	RG **	Office Action, mailed November 2, 2015, in connection with U.S. Patent Application Serial No. 13/694,731, 14 pages.			
	RH **	Response, filed Apr. 20, 2016, to Office Action, mailed Nov. 2, 2015, in connection with U.S. Patent Application Serial No. 13/694,731, 43 pages.			
	RI **	Notice of Allowance, mailed May 20, 2016, in connection with U.S. Patent Application Serial No. 13/694,731, 16 pages.			
	RJ	Office Action, issued May 15, 2019, in connection with U.S. Patent Application No. 15/226,489, 16 pages.			
	RK	Response, filed Oct. 15, 2019, to Office Action, issued May 15, 2019, in connection with U.S. Patent Application No. 15/226,489, 30 pages.			
	RL	Office Action, issued Jan. 23, 2020, in connection with U.S. Patent Application No. 15/226,489, 19 pages.			
	RM	Response, filed Apr. 24, 2020, to Office Action, issued Jan. 23, 2020, in connection with U.S. Patent Application No. 15/226,489, 25 pages.			
	RN **	Examination Report, issued Jan. 13, 2017, in connection with Australian Patent Application No. 2012362141, 3 pages.			
	RO **	Response, filed Aug. 14, 2017, to Examination Report, issued Jan. 13, 2017, in connection with Australian Patent Application No. 2012362141, 43 pages.			
	RP **	Notice of Acceptance, dated Sept. 11, 2017, issued in connection with Australian Patent Application No. 2012362141, 3 pages.			
	RQ **	Office Action (claimed deemed allowable), dated Oct. 19, 2018, issued in connection with Australian Patent Application No. 2017245352, 7 pages.			
	RR **	Notice of Acceptance, issued Jul. 17, 2019, in connection with Australian Patent Application No. 2017245352, 3 pages.			
	RS **	Examiner's Report, issued March 1, 2016, in connection with Canadian Patent Application No. 2861919, 7 pages.			
	RT **	Response, filed Jul. 14, 2016, to Examiner's Report, issued Mar. 1, 2016, in connection with Canadian Patent Application No. 2861919, 37 pages.			
	RU **	Examiner's Report, issued Jan. 24, 2017, in connection with Canadian Patent Application No. 2861919, 4 pages.			
	RV **	Response, filed Jul. 24, 2017, to Examiner's Report, issued Jan. 24, 2017, in connection with Canadian Patent Application No. 2861919, 26 pages.			
	RW **	Examiner's Report, issued Jan. 23, 2018, in connection with Canadian Patent Application No. 2861919, 4 pages.			
	RX **	Response, filed Jun. 21, 2018, to Examiner's Report, dated Jan. 23, 2018, issued in connection with Canadian Patent Application No. 2861919, 39 pages.			
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	RZ **	Office Action, issued May 25, 2015, in connection with Chinese Patent Application No. 201280070954.9 [English language translation and original document in Chinese], 7 pages.			
	SA **	Response, filed Oct. 9, 2015, to Office Action, issued May 25, 2015, in connection with Chinese Patent Application No. 201280070954.9 [English instructions and document as filed in Chinese], 37 pages.			
	SB **	Office Action, issued Feb. 3, 2016, in connection with Chinese Patent Application No. 201280070954.9 [English language translation and original document in Chinese], 6 pages.			
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	SC **	Response, filed Jun. 20, 2016, to Office Action, issued Feb. 3, 2016, in connection with Chinese Patent Application No. 201280070954.9 [English language instructions, document as filed in Chinese and claims, as filed, in English], 58 pages.			
	SD **	Office Action, issued Oct. 17, 2016, in connection with Chinese Patent Application No. 201280070954.9 [English language translation and original document in Chinese], 4 pages.			
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	SF **	Letter, dated Mar. 15, 2017, reporting Telephonic Interview with Examiner in connection with Chinese Patent Application No. 201280070954.9, 1 page.			
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	SH **	Notice of Granting Patent Right for Invention, issued April 28, 2017, in connection with Chinese Patent Application No. 201280070954.9 [English translation and original document in Chinese], 4 pages.			
	SI **	Notice of Allowance, dated Dec. 7, 2017, issued in connection with Eurasian Patent Application No. 201400772 [English letter and original document in Russian], 2 pages.			
	SJ **	Response, filed Mar. 3, 2015, to Communication Pursuant to Rules 161(1) and 162 EPC, issued Sept. 4, 2014, in connection with European Patent Application No. 12816624.6, 40 pages.			
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	SL **	Extended European Search Report, dated Jan. 12, 2017, issued in connection with European Patent Application No. 16189970.3, 11 pages.			
	SM **	Response, filed Aug. 15, 2017, to Extended European Search Report, dated Jan. 12, 2017, issued in connection with European Patent Application No. 16189970.3, 55 pages.			
	SN **	Examination Report, dated Sept. 14, 2017, issued in connection with European Patent Application No. 16189970.3, 3 pages.			
	SO **	Response, dated Oct. 13, 2017, to Examination Report, dated Sept. 14, 2017, issued in connection with European Patent Application No. 16189970.3, 19 pages.			
	SP **	Communication Pursuant to Article 94(3) EPC (claims deemed allowable), dated Feb. 26, 2018, issued in connection with European Patent Application No. 16189970.3, 3 pages.			
	SQ **	Response, filed Sept. 10, 2018, to Communication Pursuant to Article 94(3) EPC (claims deemed allowable), issued Feb. 26, 2018, issued in connection with European Patent Application No. 16189970.3, 821 pages.			
	SR **	Communication Pursuant to Article 71(3) EPC (Intention to Grant), dated Apr. 08, 2019, issued in connection with European Patent Application No. 16189970.3, 7 pages.			
	SS **	Decision to Grant, issued Aug. 22, 2019, in connection with European Patent Application No. 16189970.3, 2 pages.			
	ST **	Examination Report, issued Dec. 4, 2018, in connection with Indian Patent Application No. 6272/DELNP/2014, 6 pages.			
	SU **	Response, filed Sept. 4, 2019, to Examination Report, issued Dec. 4, 2018, in connection with Indian Patent Application No. 6272/DELNP/2014, 79 pages.			
	SV **	Office Action, dated Aug. 3, 2016, in connection with Israeli Patent Application No. 233192 [English language translation], 3 pages.			
	SW **	Response, filed Jan. 3, 2017, to Office Action, dated Aug. 3, 2016, in connection with Israeli Patent Application No. 233192 [English language translation], 32 pages.			

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	SX **	Office Action, dated Nov. 20, 2017, issued in connection with Israeli Patent Application No. 233192 [English language translation], 2 pages.			
	SY **	Response, filed May 21, 2018, to Office Action, dated Nov. 20, 2017, issued in connection with Israeli Patent Application No. 233192 [English language translation], 22 pages.			
	SZ **	Office Action (claims deemed allowable), dated Feb. 20, 2019, issued in connection with Israeli Patent Application No. 233192 [English letter reporting Office Action and original document in Hebrew], 5 pages.			
	TA **	Official Action, issued Jan. 19, 2016, in connection with Japanese Patent Application No. 2014-550526 [English translation and original document in Japanese], 8 pages.			
	TB **	Response, filed Jul. 15, 2016, to Official Action, issued Jan. 19, 2016, in connection with Japanese Patent Application No. 2014-550526 [English instructions and document as filed in Japanese], 138 pages.			
	TC **	Decision to Grant, issued Nov. 22, 2016, in connection with Japanese Patent Application No. 2014-550526 [Letter reporting decision to grant and original document in Japanese], 5 pages.			
	TD **	Office Action, issued Dec 12, 2017, in connection with Japanese Patent Application No. 2016-247708 [English translation and original document in Japanese], 6 pages.			
	TE **	Response, filed May 22, 2018, to Office Action, issued Dec. 12, 2017, in connection with Japanese Patent Application No. 2016-247708 [English instructions with amended claims, documents as-filed in Japanese and English translation of claims as-filed], 90 pages.			
	TF **	Decision to Grant, issued Sept. 18, 2018, in connection with Japanese Patent Application No. 2016-247708 [English reporting letter and original document in Japanese], 4 pages.			
	TG **	Office Action, dated May 25, 2018, in connection with Mexican Patent Application No. MX/a/2014/007966 [English translation and original document in Spanish], 6 pages.			
	TH **	Response, filed Oct. 10, 2018, to Office Action, dated May 25, 2018, in connection with Mexican Patent Application No. MX/a/2014/007966 [English instructions and document as-filed in Spanish], 13 pages.			
	TI **	Notice of Allowance, issued Oct. 18, 2018, in connection with Mexican Patent Application No. MX/a/2014/007966 [English reporting letter and original document in Spanish], 4 pages.			
	TJ **	Examination Report, dated Mar. 26, 2015, in connection with New Zealand Patent Application No. 626126, 32 pages.			
	TK **	Response, dated May 16, 2016, to Examination Report, dated Mar. 26, 2015, in connection with New Zealand Patent Application No. 626126, 70 pages.			
	TL **	Notice of Acceptance, dated Jun. 8, 2016, in connection with New Zealand Patent Application No. 626126, 1 page.			
	TM **	Letters Patent, issued Sept. 27, 2016, in connection with New Zealand Patent No. 626126, 1 page.			
	TN **	Examination Report, dated Jul. 27, 2017, issued in connection with New Zealand Patent Application No. 720075, 4 pages.			
	TO **	Response, filed Feb. 26, 2018, to Examination Report, dated Jul. 27, 2017, issued in connection with New Zealand Patent Application No. 720075, 88 pages.			
	TP **	Notice of Acceptance, dated Mar. 10, 2020, issued in connection with New Zealand Patent Application No. 720075, 1 page.			
	TQ **	Search Report and Written Opinion, dated Dec. 4, 2015, in connection with Singaporean Patent Application No. 11201403714T, 7 pages.			
	TR **	Response, filed May 23, 2016, to Search Report and Written Opinion, dated Dec. 4, 2015, in connection with Singaporean Patent Application No. 11201403714T, 21 pages.			

Examiner Signature	Date Considered
EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

Substitute Form PTO-1449 (Modified)		U.S. Department of Commerce Patent and Trademark Office		Attorney Docket No. 33320.03087.US26/ 3087C	Application No. 16/824,572
List of Patents and Publications for Applicant's Information Disclosure Statement (37 CFR §1.98(b))				Applicant <i>Wei et al.</i>	
				Filing Date March 19, 2020	Group Art Unit 1656
Other Documents (include Author, Title, Date, and Place of Publication)					
Examiner Initial	Desig. ID	Document			
	TS **	Written Opinion, dated Sept. 18, 2017, in connection with Singapore Patent Application No. 11201403714T, 9 pages.			
	TT **	Response, filed Oct. 27, 2017, to Written Opinion, dated Sept. 18, 2017, in connection with Singapore Patent Application No. 11201403714T, 6 pages.			
	TU **	Corrected Notice of Eligibility for Grant and Examination Report, dated Jul. 02, 2018, in connection with Singapore Patent Application No. 11201403714T, 8 pages.			
	TV **	Certificate of Grant, dated Oct. 3, 2018, in connection with Singapore Patent Application No. 11201403714T [Grant Certificate and Granted Claims], 6 pages.			
	TW **	Search Report and Written Opinion, issued Oct. 20, 2017, in connection with Singapore Patent Application No. 10201604470T, 14 pages.			
	TX **	Response, filed Mar. 20, 2018, to Search Report and Written Opinion, issued Oct. 20, 2017, in connection with Singapore Patent Application No. 10201604470T [Response, replacement specification pages, amended claims and cited document], 105 pages.			
	TY **	Examination Report, dated Aug. 6, 2018, and Notice of Eligibility for Grant, dated Aug. 7, 2018, issued in connection with Singapore Patent Application No. 10201604470T, 6 pages.			
	TZ **	English translation of Official Action, issued Mar. 20, 2020, in connection with Korean Application No. 10-2020-7002955.			
** = Copies not provided herewith as they have been previously provided in connection with U.S. Serial No. 13/694,731 and/or 15/226,489 which are relied upon for an earlier filing date in accordance with 35 U.S.C. §120.					

Examiner Signature	Date Considered
EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

Electronic Acknowledgement Receipt	
EFS ID:	39456670
Application Number:	16824572
International Application Number:	
Confirmation Number:	1431
Title of Invention:	PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF
First Named Inventor/Applicant Name:	Ge WEI
Customer Number:	13565
Filer:	Stephanie L. Seidman/Hyun Jeung Ji
Filer Authorized By:	Stephanie L. Seidman
Attorney Docket Number:	33320.03087.US26/3087C
Receipt Date:	15-MAY-2020
Filing Date:	19-MAR-2020
Time Stamp:	19:02:00
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment		no			
File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	3087Ctra.pdf	25575	no	1
			32b4e912c902f5eb406a67bdce0853888cbf845a		
Warnings:					

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	3087Cids.pdf	140913	no	2
			b1526a98d91482f30b0cf07022b6d9c2dfcd804a		
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Foreign Reference	FT.pdf	6241030	no	70
			f7ce4fc756bfc347d204ae64c984e39a22906bfe		
Warnings:					
Information:					
4	Non Patent Literature	MJ.pdf	1844035	no	12
			6479df7e4b23d5d69ebc1c2a0632cf0686fa407e		
Warnings:					
Information:					
5	Non Patent Literature	RJ.pdf	1316147	no	16
			75e51cc4b4917ae0fc03748a33f79b2abfb7d937		
Warnings:					
Information:					
6	Non Patent Literature	RK.pdf	2674718	no	30
			ddbcb6963c6c553e28ee3f62fe34453db0d8120c2		
Warnings:					
Information:					
7	Non Patent Literature	RL.pdf	1599589	no	19
			d5295cd1c5dca6e8e0a307444c5628145edd9ada2		
Warnings:					
Information:					
8	Non Patent Literature	RM.pdf	359508	no	25
			42ff32779903556e956e679ecce88bf8ffcbab387		
Warnings:					
Information:					

9	Non Patent Literature	GL.pdf	55621	no	2
			4893e8631ec65f403530a736e112b91ff74fc80b		
Warnings:					
Information:					
10	Information Disclosure Statement (IDS) Form (SB08)	3087Cp49.pdf	535546	no	24
			b77c7d65dfa112f6faa6fa7db798cf9dd6da0b59		
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
11	Non Patent Literature	OF.pdf	7937785	no	100
			ee930dddbc47a6c5b1932fa2f20ca8457f6e7e738		
Warnings:					
Information:					
Total Files Size (in bytes):			22730467		
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>					

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Wei <i>et al.</i>	Art Unit	: 1656
Serial No.	: 16/824,572	Examiner	: Not Yet Assigned
Filed	: March 19, 2020	Conf. No.	: 1431
		Cust. No.	: 13565
Title	: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF		

Mail Stop Amendment

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT TRANSMITTAL LETTER

Dear Sir:

Transmitted herewith are an Information Disclosure Statement (2 pages), Forms PTO-1449 (24 pages), and cited non-U.S. patent documents for filing in connection with the above-identified application. Because this Information Disclosure Statement is filed before the receipt of a First Office Action on the Merits for the above-captioned application, a fee is not required. However, should it be determined that a fee for filing these papers is required, the Commissioner is authorized to charge Deposit Account No. 50-0911.

☒ The Commissioner is hereby authorized to charge any fees that may be due in connection with this paper or with this application during its entire pendency to Deposit Account No. 50-0911.

Respectfully submitted,

/Stephanie Seidman/

Stephanie Seidman
Reg. No. 33,779

Attorney Docket No.: 33320.03087.US26/3087C

Address all correspondence to: 13565

Stephanie Seidman
Dentons US LLP
4655 Executive Drive, Ste. 700
San Diego, California 92121
Telephone: (619) 595-8010
Facsimile: (619) 595-8135
email: stephanie.seidman@dentons.com

CERTIFICATE OF TRANSMISSION VIA EFS-WEB

I hereby certify that this paper is being transmitted via the Electronic Filing System (EFS-WEB) to the United States Patent and Trademark Office on May 15, 2020.

/Hyun Jeung Ji/
Hyun Jeung Ji



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/824,572	03/19/2020	Ge WEI	33320.03087.US26/3087C	1431
13565	7590	05/21/2020	EXAMINER	
Dentons US LLP 4655 Executive Drive Suite 700 San Diego, CA 92121			ART UNIT	PAPER NUMBER
			1656	
			NOTIFICATION DATE	DELIVERY MODE
			05/21/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

MLAIPSD@Dentons.com
lucy.begalla@dentons.com
rosalind.smith@dentons.com

<i>Decision Granting Request for Prioritized Examination (Track I)</i>	Application No. 16/824,572	Applicant(s) WEI et al.	
	Examiner APRIL M WISE	Art Unit OPET	AIA (FITF) Status No
<p>1. THE REQUEST FILED <u>19 March 2020</u> IS GRANTED .</p> <p>The above-identified application has met the requirements for prioritized examination</p> <p>A. ☒ for an original nonprovisional application (Track I).</p> <p>B. ☐ for an application undergoing continued examination (RCE).</p> <p>2. The above-identified application will undergo prioritized examination. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:</p> <p>A. filing a <u>petition for extension of time</u> to extend the time period for filing a reply;</p> <p>B. filing an <u>amendment to amend the application to contain more than four independent claims, more than thirty total claims</u>, or a multiple dependent claim;</p> <p>C. filing a <u>request for continued examination</u> ;</p> <p>D. filing a notice of appeal;</p> <p>E. filing a request for suspension of action;</p> <p>F. mailing of a notice of allowance;</p> <p>G. mailing of a final Office action;</p> <p>H. completion of examination as defined in 37 CFR 41.102; or</p> <p>I. abandonment of the application.</p> <p>Telephone inquiries with regard to this decision should be directed to undersigned at (571)272-1642. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.</p>			
/APRIL M WISE/ Paralegal Specialist, Office of Petitions			



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/824,572	03/19/2020	Ge WEI	33320.03087.US26/3087C	1431
13565	7590	06/26/2020	EXAMINER	
Dentons US LLP 4655 Executive Drive Suite 700 San Diego, CA 92121			LIU, SAMUEL W	
			ART UNIT	PAPER NUMBER
			1656	
			NOTIFICATION DATE	DELIVERY MODE
			06/26/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

MLAIPSD@Dentons.com
lucy.begalla@dentons.com
rosalind.smith@dentons.com

<i>Office Action Summary</i>	Application No. 16/824,572	Applicant(s) WEI et al.	
	Examiner SAMUEL W LIU	Art Unit 1656	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 3/19/2020.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.

4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☒ Claim(s) 1-20 is/are pending in the application.
 5a) Of the above claim(s) none is/are withdrawn from consideration.

6) ☐ Claim(s) ____ is/are allowed.

7) ☐ Claim(s) ____ is/are rejected.

8) ☐ Claim(s) ____ is/are objected to.

9) ☒ Claim(s) 1-20 are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10) ☐ The specification is objected to by the Examiner.

11) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some** c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
 Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413)
 Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Election/Restrictions

Restriction is required under 35 U.S.C. 121.

Group I, claims 1-20, drawn to a modified PG20 polypeptide comprises one or more amino acid replacement (substitution) and pharmaceutical composition comprising said polypeptide, classified in CPC C07K 14/00, C12N 15/00, A61K 41/00..

Group II, claim 21, drawn to a method of treating condition or a disease state including an excess of glycosaminoglycans; a tumor; glycosaminoglycan accumulation in the brain; a cardiovascular disorder; an ophthalmic disorder and pulmonary disease or edema; and a method of increasing delivery of therapeutic agents; the method comprising administering to a subject a pharmaceutical composition comprising classified in CPC A61K 38/16, A61K48/0008, A61K 41/00.

Species election

This application contains claims directed to the following patentably distinct species:

(i) Claim 1 and 6-8 (Group I) is directed to the different species, i.e., different peptide sequences of SEQ ID NOs: 3, 7 and 32-66; they differ from one another in amino acid sequence and biological or pharmaceutical functionalities.

(ii) Claim 13 (Group I) is directed to the different species, i.e., different peptide sequences of SEQ ID NOs: 576-581 and 591-598; they differ from one another in amino acid sequence and biological or pharmaceutical functionalities.

(iii) Claim **21** (Group II) is directed to the different species, i.e., different conditions or disease states (for the treatment): an excess of glycosaminoglycans; a tumor; glycosaminoglycan accumulation in the brain; a cardiovascular disorder; an ophthalmic disorder and pulmonary disease or edema; they differ from one another in patient populations, pathological mechanisms and treatment outcomes.

Also, claim 21 as written is drawn to a method of *increasing* delivery of therapeutic agents. an isolated polypeptide which differ from the above-mentioned treatment of different conditions or disease states.

These species are not obvious variants of one other based on the current record in protein chemistry, molecular biology, pharmacology and relative medicine.

Applicant is required under 35 U.S.C. 121 to elect a disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. It is noted that, since claim 21 as written is directed to method of *treatment* of a condition or a disease, and also directed to a method of *increasing* delivery of therapeutic agents, if applicant elect a species from the “condition or a disease” for the treatment, the method of *increasing* delivery of therapeutic agents of claim 21 is drawn to non-elected species; or, vice versa.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species. Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

The inventions are distinct, each from the other because of the following reasons:

Invention I and Invention II are related as product and process of use (wherein the nucleic acid (Group I) encoding enzyme can be used in the process of Group II). The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the “polypeptide” of Group I can be utilized in a materially different processes such as raising an antibody against said polypeptide, for example.

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search burden and/or examination if restriction were not required because at least following reasons(s) apply:

- the inventions have acquired a separate status in the art in view of their different classification
- the inventions have acquired a separated status in the art due to their recognized divergent subject matter
- the inventions require a different field of search (e.g., searching different classes/subclasses or electronic resource, or employing different search strategies or search queries).

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product/apparatus, and all product/apparatus claims are subsequently found allowable, withdrawn process claims that include all the limitations of the allowable product/apparatus claims should be considered for rejoinder. All claims directed to a nonelected process invention must include all the limitations of an allowable product/apparatus claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product/apparatus claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product/apparatus are found allowable, an otherwise proper restriction requirement between product/apparatus claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product/apparatus claim will not be rejoined. See MPEP § 821.04. Additionally, in order for rejoinder to occur, applicant is advised that the process claims should be amended during

prosecution to require the limitations of the product/apparatus claims. Failure to do so may result in no rejoinder. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Liu whose telephone number is (571)272-0949. The examiner can normally be reached on M-F, from 9 am to 5:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Samuel Wei Liu/

Patent Examiner, Art Unit 1656
June 9, 2020

/PAUL J HOLLAND/
Primary Examiner, Art Unit 1656

Application/Control Number: 16/824,572
Art Unit: 1656

Page 6



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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/824,572	03/19/2020	Ge WEI	33320.03087.US26/3087C

CONFIRMATION NO. 1431

PUBLICATION NOTICE



OC000000119228415

13565
Dentons US LLP
4655 Executive Drive
Suite 700
San Diego, CA 92121

Title:PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF

Publication No.US-2020-0255814-A1

Publication Date:08/13/2020

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently <http://www.uspto.gov/patft/>.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently <https://portal.uspto.gov/pair/PublicPair>. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875				Application or Docket Number 16/824,572		Filing Date 03/19/2020		☐ To be Mailed					
ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO													
APPLICATION AS FILED - PART I													
		(Column 1)		(Column 2)									
FOR		NUMBER FILED		NUMBER EXTRA		RATE (\$)		FEE (\$)					
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))		N/A		N/A		N/A							
☐ SEARCH FEE (37 CFR 1.16(k), (l), or (m))		N/A		N/A		N/A							
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))		N/A		N/A		N/A							
TOTAL CLAIMS (37 CFR 1.16(i))		minus 20 = *				x \$100 =							
INDEPENDENT CLAIMS (37 CFR 1.16(h))		minus 3 = *				x \$460 =							
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))		If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).											
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))													
* If the difference in column 1 is less than zero, enter "0" in column 2.						TOTAL							
APPLICATION AS AMENDED - PART II													
		(Column 1)		(Column 2)		(Column 3)							
AMENDMENT	08/24/2020		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR		PRESENT EXTRA		RATE (\$)		ADDITIONAL FEE (\$)		
	Total (37 CFR 1.16(i))		* 18		Minus ** 20		= 0		x \$100 =		0		
	Independent (37 CFR 1.16(h))		* 2		Minus *** 3		= 0		x \$460 =		0		
	☐ Application Size Fee (37 CFR 1.16(s))												
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))												
										TOTAL ADD'L FEE		0	
AMENDMENT			CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR		PRESENT EXTRA		RATE (\$)		ADDITIONAL FEE (\$)		
	Total (37 CFR 1.16(i))		*		Minus **		=		x \$0 =				
	Independent (37 CFR 1.16(h))		*		Minus ***		=		x \$0 =				
	☐ Application Size Fee (37 CFR 1.16(s))												
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))												
										TOTAL ADD'L FEE			
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.										LIE			
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".										/MARSHA R RICHARDS/			
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".													
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.													

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s) : Wei <i>et al.</i>	Art Unit : 1656
Serial No. : 16/824,572	Examiner : Liu, Samuel W.
Filed : March 19, 2020	Conf. No. : 1431
	Cust. No. : 13565
Title : PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF	

Mail Stop Amendment

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

ELECTION AND PRELIMINARY AMENDMENT

Dear Sir:

Responsive to the Office Action dated June 26, 2020, setting forth a Restriction Requirement, Applicant elects, without traverse, Group I, Claims 1-20, drawn to a modified PH20 polypeptide having increased hyaluronidase activity compared to a corresponding unmodified polypeptide, and to pharmaceutical compositions comprising the modified PH20 polypeptide. Applicant further elects, **with traverse**, species as follows:

Species I: an unmodified polypeptide that has the sequence of amino acids set forth as **SEQ ID NO:35**.

Species II: a modified PH20 polypeptide with a replacement at the position corresponding to 313; if necessary where the replacement at 313 is K (Lys); if necessary wherein the polypeptides comprises the sequence set forth as **SEQ ID NO:594** or a sequence of amino acids that has at least 91% sequence identity to SEQ ID NO:594 and comprises the replacement at residue 313.

Claims 1, 3, 5, 6 and 8-20 of elected Group I read on the elected species.

Amendments to the Claims begin on page 2 of this paper

Remarks/Arguments begin on page 5 of this paper.

CERTIFICATE OF TRANSMISSION VIA EFS-WEB

I hereby certify that this paper is being transmitted via the Electronic Filing System (EFS-WEB) to the United States Patent and Trademark Office on **August 24, 2020**.

/FevianMiano/
Fevian Miano

Electronic Acknowledgement Receipt	
EFS ID:	40354468
Application Number:	16824572
International Application Number:	
Confirmation Number:	1431
Title of Invention:	PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF
First Named Inventor/Applicant Name:	Ge WEI
Customer Number:	13565
Filer:	Stephanie L. Seidman/Fevian Miano
Filer Authorized By:	Stephanie L. Seidman
Attorney Docket Number:	33320.03087.US26/3087C
Receipt Date:	24-AUG-2020
Filing Date:	19-MAR-2020
Time Stamp:	12:54:42
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment		no			
File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	3087Ctra.pdf	140601	no	1
			512f1bcc1ca38ebd07eab2969e1180497a3ad402		
Warnings:					

Information:					
2		3087Crrr.pdf	175795	yes	8
			298d253a3a16d749800205397e00017339a32af9		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Applicant Arguments/Remarks Made in an Amendment		5	8	
	Claims		2	4	
	Response to Election / Restriction Filed		1	1	
Warnings:					
Information:					
Total Files Size (in bytes):			316396		
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>					

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s) : Wei <i>et al.</i>	Art Unit : 1656
Serial No. : 16/824,572	Examiner : Liu, Samuel W.
Filed : March 19, 2020	Conf. No. : 1431
	Cust. No. : 13565
Title : PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF	

Mail Stop Amendment

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

Dear Sir:

Responsive to the *Office Action*, mailed June 26, 2020, transmitted herewith is an *Election and Preliminary Amendment* (8 pages) for filing in connection with the above-identified application.

☒ The Commissioner is hereby authorized to charge any fees that may be due in connection with this paper or with this application during its entire pendency to Deposit Account No. 50-0911.

Respectfully submitted,

/Stephanie Seidman/
Stephanie Seidman
Reg. No. 33,779

Attorney Docket No.: 33320.03087.US26/3087C

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CERTIFICATE OF TRANSMISSION VIA EFS-WEB

I hereby certify that this paper is being transmitted via the Electronic Filing System (EFS-WEB) to the United States Patent and Trademark Office on **August 24, 2020**.

/Fevian Miano/
Fevian Miano

Inventor(s) : Wei *et al.*
Serial No. : 16/824,572
Filed : March 19, 2020

Attorney Docket No.: 33320.03087.US26/ 3087C
Election and Preliminary Amendment

REMARKS

Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 50-0911. If a Petition for Extension of Time is needed, this paper is to be considered such Petition.

A Supplemental Information Disclosure Statement is filed under separate cover.

Applicant draws the Examiner's attention to an error on page 1 of the Office Action, the Office Action Summary, which recites that "claims 1-20 are pending in the application," and "Claims 1-20 are subject to restriction and/or election requirement." This is incorrect, Claim 21 also is pending.

Claims 1, 3, 5, 6 and 8-21 are pending. Claims 1, 3, 5, 6 and 8-20 of elected Group I read on the elected species. Claims 2, 4 and 7, which are directed to non-elected subject matter, are cancelled without prejudice or disclaimer. Claims 1, 9-11 and 13 are amended to conform to the elected subject matter and for clarity. Claim 21, which is withdrawn from consideration as drawn to non-elected subject matter, is retained for possible joinder.

TRAVERSAL OF THE REQUIREMENT FOR ELECTION OF SPECIES

Applicant respectfully traverses the requirement for Election of Species because, at least with respect to **Species I**, the Examiner requires elections among species that are not independent or distinct.

Traversal of requirement to elect a species of unmodified polypeptide sequence selected from among SEQ ID NOs: 3, 7 and 32-66 (Species I)

The Examiner states, on page 2 of the Office Action, that Claims 1 and 6-8 are "directed to the different species, i.e., different peptide sequences of SEQ ID NOs: 3, 7, and 32-66; they differ from one another in amino acid sequences and biological or pharmaceutical functionalities." The Examiner states that the species of unmodified polypeptides differ in their amino acid sequence and their enzymatic activities. Applicant respectfully disagrees.

The instant claims are directed to *modified* polypeptides that contain one or more modifications in any of the unmodified polypeptides whose sequences are set forth as SEQ ID NOs: 3, 7 and 32-66. As discussed in more detail below, the unmodified polypeptides share a common enzymatic activity; they all are neutral active hyaluronidases, and they share 100% sequence identity along their length, differing only in the residue at which polypeptide terminates. Because each of the recited unmodified polypeptides in the claims differ *only* in the extent to which they are C-terminally truncated relative to full-length mature PH20 (SEQ ID NO:7), modified polypeptides containing a modification at one or more particular positions in one of the unmodified polypeptides have the *same* corresponding modification(s) in any of the

Inventor(s) : Wei *et al.*
Serial No. : 16/824,572
Filed : March 19, 2020

Attorney Docket No.: 33320.03087.US26/ 3087C
Election and Preliminary Amendment

other recited unmodified polypeptides; the only difference is the C-terminal residues. The recited positions for the amino acid replacements, *e.g.*, in Claim 1, are the *same* for all the unmodified PH20 polypeptides, regardless of whether it is SEQ ID NO:3, SEQ ID NO: 7, or any of SEQ ID NOS: 32-66.

Claims 1 and 6-8 are not “directed to” polypeptides having the peptide sequences set forth in SEQ ID NOS: 3, 7, and 32-66. They are directed to *modified* polypeptides having one or more amino acid modifications in *unmodified* polypeptides whose sequences are set forth as SEQ ID NOS: 3, 7, and 32-66. Modification is with respect to unmodified PH20 polypeptides that have the sequences set forth in SEQ ID NOS: 3, 7, and 32-66, that differ only in their C-termini; all share the same neutral hyaluronidase activity. SEQ ID NO:7 sets forth the sequence of full-length mature PH20, and SEQ ID NOS: 3, and 32-66, set forth soluble forms of mature PH20 that each terminate at a different C-terminal residue. The unmodified PH20 polypeptides are *known* PH20 polypeptides selected from among: full-length mature PH20 set forth in SEQ ID NO:7, the mature C-terminally truncated PH20 polypeptide set forth in SEQ ID NO:3, which corresponds to residues 36-482 of the full-length mature PH20 set forth in SEQ ID NO:7, and other known active soluble PH20 polypeptides set forth in any of SEQ ID NOS: 32-66 all of which are known to be soluble and to have neutral active hyaluronidase activity. These truncated, secreted and soluble active polypeptides have been identified and are the subject of patents/patent applications (*e.g.*, U.S. Patent Nos. 8,431,380, 8,927,249 and other related family members, which describe soluble forms of human PH20) and, thus, are *known*.

The language of the instant claims parallels the language in the claims of U.S. Application Serial No. 13/694,731, now issued as U.S. Patent No. 9,447,401, and U.S. Application Serial No. 15/226,489, now allowed. Similar election of species were set forth in these parent applications. In each of the parent applications, petitions traversing the same election of species requirements were filed, and were granted, and the species elections were withdrawn. The Office, thus, has held that this requirement for election of species among a series of polypeptides that differ only in their C-terminus is not sustainable.

The unmodified soluble PH20 polypeptides, thus, are *known* PH20 polypeptides selected from among: full-length mature PH20 set forth in SEQ ID NO:7, which corresponds to residues 36-509 of full length precursor PH20 of SEQ ID NO:6, a mature C-terminally truncated PH20 polypeptide set forth in SEQ ID NO:3, which corresponds to residues 36-482 of the full-length precursor PH20 set forth in SEQ ID NO:6, and other known active soluble PH20 polypeptides set forth in any of SEQ ID NOS: 32-66 (corresponding to polypeptides

Inventor(s) : Wei *et al.*
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Election and Preliminary Amendment

with C-terminal amino acid residues corresponding to 36-465 to 36-500 with reference to the full length precursor PH20 of SEQ ID NO:6). The hyaluronidase domain is known and encompasses residues 36-464 (see, *e.g.*, any of U.S. Patent Nos. 9,562,223, 8,765,685, 8,431,380, 8,202,517, and 7,767,429); each recited unmodified polypeptide includes a single additional amino acid at the C-terminus from residues from 465 up to 500 (the full length PH20 is 509 amino acids).

All of the unmodified PH20 polypeptides have neutral active hyaluronidase activity; and all of the truncated forms, SEQ ID NOs:3 and 32-66, are neutral active and soluble. These truncated, secreted and soluble active polypeptides have been identified and are the subject of patents (*e.g.*, U.S. Patent Nos. 9,562,223; 8,765,685; 8,431,380; 8,202,517; 7,767,429; 8,927,249; and 9,284,543), which describe forms of human PH20, including those from residues 36-474 to 36-494 (SEQ ID NO:6), that are soluble and neutral active, and describe that the hyaluronidase protease domain is 36-464. See also U.S. Patent Nos. 9,284,543 and 8,927,249, which are based on the application or claim priority to the same application as published application Publication No. US-2012-0213767, which show that polypeptides from 36-466 to 36-500 are soluble and neutral active. The USPTO has granted patents to soluble neutral active PH20 polypeptides that have C-termini that terminate at 464 up to 500. The unmodified PH20 polypeptides, thus, are *known* and share properties in common. They share the same properties of neutral hyaluronidase activity, and along each of their lengths, share 100% sequence identity with full length PH20. Thus, the reasons set forth by the Examiner are incorrect.

Any of the replacements recited in the claims, if novel, in one of the unmodified PH20 polypeptides, is novel in all of the unmodified PH20 polypeptides. If a modified PH20 polypeptide containing an amino acid replacement in SEQ ID NO:7 (full length mature PH20) is novel, then the corresponding replacement in SEQ ID NOS: 3 and 32-66 also *must* be novel. The unmodified polypeptide sequences set forth in SEQ ID NOs: 3, 7 and 32-66 are **not independent**. Because each of the recited unmodified polypeptides in the claims differs *only* in the extent to which they are C-terminally truncated (*i.e.*, the differences are in their C-termini), modified polypeptides containing a modification at one or more particular positions in one of the unmodified polypeptides have the *same* corresponding modification(s) in any of the other recited unmodified polypeptides. The recited positions for the amino acid substitutions, *e.g.*, in Claim 1, are the *same* for all the unmodified PH20 polypeptides, regardless of whether the

Inventor(s) : Wei *et al.*
Serial No. : 16/824,572
Filed : March 19, 2020

Attorney Docket No.: 33320.03087.US26/ 3087C
Election and Preliminary Amendment

unmodified PH20 has the sequence set forth in SEQ ID NO:3, SEQ ID NO: 7, or any of SEQ ID NOS: 32-66.

For example, the **Species II** election made by Applicant of a modified polypeptide sequence containing the amino acid replacement M313K at position 313, where residues are numbered with reference to SEQ ID NO:3, of the unmodified polypeptide. If the M313K replacement in SEQ ID NO:3 is novel, then the M313K modification in SEQ ID NOS: 7 and 32-66 also *must* be novel. Thus, the unmodified polypeptide sequences set forth in SEQ ID NOS: 3, 7 and 32-66 are **not independent**. Selection of a particular mutation fixes the sequence of all of the modified polypeptides. Thus, the species of unmodified PH20 polypeptides as set forth are not independent or distinct as the species are known and share the same activities (neutral hyaluronidase activity), and 100% sequence identity up to the C-terminus.

The Office is reminded that having set forth a requirement to elect a species of unmodified polypeptide, the Office is precluded from finding obviousness-type double patenting in applications filed in reliance on this requirement. For example, obviousness-type double patenting cannot be held as between a claim to a modified PH20 polypeptide that corresponds to amino acids 36-**480** of full-length precursor PH20, and a later issued patent to a modified PH20 polypeptide that corresponds to amino acids 36-**481** of full-length precursor PH20. Each modified PH20 polypeptide would only differ by a single amino acid at the C-terminus, and would have the same or substantially the same enzymatic activity and physical properties. The Office could not reject the claims for obviousness-type double patenting. Therefore, withdrawal of the requirement for election of species respectfully is requested.

In view of the election and remarks herein, examination on the merits and allowance of the application respectfully are requested.

Respectfully submitted,
/Stephanie Seidman/
Stephanie Seidman
Reg. No. 33,779

Attorney Docket No. 33320.03087.US26/ 3087C
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Inventor(s) : Wei *et al.*
Serial No. : 16/824,572
Filed : March 19, 2020

Attorney Docket No.: 33320.03087.US26/ 3087C
Election and Preliminary Amendment

AMENDMENTS TO THE CLAIMS:

Please amend claims 1, 9-11 and 13, and cancel claims 2, 4 and 7, without prejudice or disclaimer as follows:

LISTING OF CLAIMS:

1. (Currently Amended) A modified PH20 polypeptide, comprising one or more amino acid replacements in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the sequence of amino acids set forth in SEQ ID NO: 3, 7 or 32-66;

the modified PH20 polypeptide exhibits increased hyaluronidase activity compared to the unmodified PH20 polypeptide not containing the amino acid replacement(s);

the amino acid replacement(s) confer(s) the increased hyaluronidase activity;

the amino acid replacement(s) is at a position corresponding to ~~309 or~~ 313 with reference to amino acid positions set forth in SEQ ID NO:3, which confers increased hyaluronidase activity;

corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the sequence of amino acids set forth in SEQ ID NO:3; and

the modified PH20 polypeptide has at least 91% sequence identity to the sequence of amino acids set forth as SEQ ID NO: 3, 7 or 32-66.

2. (Cancelled)

3. (Original) The modified PH20 polypeptide of claim 1, wherein the replacement is selected from among A at a position corresponding to position 313; G at a position corresponding to position 313; H at a position corresponding to position 313; K at a position corresponding to position 313; P at a position corresponding to position 313; R at a position corresponding to position 313; T at a position corresponding to position 313; and Y at a position corresponding to position 313.

4. (Cancelled)

5. (Original) The modified PH20 polypeptide of claim 3, wherein the replacement at the position corresponding to 313 is K.

6. (Original) The modified PH20 polypeptide of claim 1, wherein the unmodified PH20 polypeptide consists of the sequence of amino acids set forth in SEQ ID NO: 3, 7 or 32-66.

7. (Cancelled)

Inventor(s) : Wei *et al.*
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Filed : March 19, 2020

Attorney Docket No.: 33320.03087.US26/ 3087C
Election and Preliminary Amendment

8. (Original) The modified PH20 polypeptide of claim 3, wherein the unmodified PH20 polypeptide consists of the sequence of amino acids set forth in SEQ ID NO: 3, 7 or 32-66.

9. (Currently Amended) The modified PH20 polypeptide of claim 1, wherein the ~~modified unmodified~~ PH20 polypeptide ~~consists of the sequence of amino acids set forth in SEQ ID NO:35 or a sequence that has at least 95% sequence identity to SEQ ID NO:35~~ the sequence of amino acids set forth as SEQ ID NO: 3, 7 or 32-66.

10. (Currently Amended) The modified PH20 polypeptide of claim 14, wherein the ~~modified unmodified~~ PH20 polypeptide ~~consists of the sequence of amino acids set forth in SEQ ID NO:35 or a sequence that has at least 95% sequence identity to SEQ ID NO:35.~~

11. (Currently Amended) The modified PH20 polypeptide of claim 5, wherein the unmodified PH20 polypeptide consists of the sequence of amino acids set forth in SEQ ID NO:35 ~~or a sequence that has at least 95% sequence identity to SEQ ID NO:35.~~

12. (Original) The modified PH20 polypeptide of claim 1, wherein the modified PH20 polypeptide exhibits increased hyaluronidase activity that is at least 120% of the hyaluronidase activity compared to the unmodified PH20 polypeptide not containing the amino acid replacement or replacements.

13. (Currently Amended) A modified PH20 polypeptide, comprising a sequence of amino acids set forth in any of SEQ ID NOS: ~~576-581 and 591-598~~, or a sequence of amino acids that exhibits at least 91% sequence identity to a sequence of amino acids set forth in any of SEQ ID NOS: ~~591-598~~ 576-581 and that contains the amino acid replacement at residue ~~309 and/or~~ 313 compared to corresponding positions in a polypeptide of any of SEQ ID NOS: 3 and 32-66.

14. (Original) The modified PH20 polypeptide of claim 1 that comprises one or more of a modification selected from among glycosylation, sialation, albumination, farnesylation, carboxylation, hydroxylation, and phosphorylation.

15. (Original) The modified PH20 polypeptide of claim 1 that comprises an N-acetylglucosamine moiety linked to each of at least three asparagine (N) residues.

16. (Original) The modified PH20 polypeptide of claim 1 that is conjugated to a polymer.

17. (Original) The modified PH20 polypeptide of claim 16, wherein the polymer is dextran or polyethylene glycol (PEG).

Inventor(s) : Wei *et al.*
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18. (Original) The modified PH20 polypeptide of claim 1, further comprising a heterologous signal sequence.
19. (Original) A chimeric polypeptide comprising the modified PH20 polypeptide of claim 1.
20. (Original) A pharmaceutical composition, comprising a modified PH20 polypeptide of claim 1.
21. (Withdrawn) A method of treatment, comprising administering a pharmaceutical composition of claim 20, wherein the method is selected from a method that treats an excess of glycosaminoglycans; a tumor; glycosaminoglycan accumulation in the brain; a cardiovascular disorder; an ophthalmic disorder; pulmonary disease or edema; and a method of increasing delivery of therapeutic agents.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s)	: Wei <i>et al.</i>	Art Unit	: 1656
Serial No.	: 16/824,572	Examiner	: Liu, Samuel W.
Filed	: March 19, 2020	Conf. No.	: 1431
		Cust. No.	: 13565
Title	: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF		

Mail Stop Amendment

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT IN
ACCORDANCE WITH 37 C.F.R. §§ 1.97-1.98**

Dear Sir:

Because this Supplemental Information Disclosure Statement is filed before the receipt of a First Office Action on the Merits for the above-captioned application, a fee is not required. If a fee for filing these papers is required, the Commissioner is authorized to charge Deposit Account No. 50-0911.

In accordance with the duty of disclosure imposed by 37 C.F.R. § 1.56 to inform the Patent Office of all information known by Applicant or Applicant's representative that may be material to the examination of the subject application, Applicant's representative hereby provides this Supplemental Information Disclosure Statement that is prepared in accordance with 37 C.F.R. §§ 1.97-1.98. A Form PTO-1449 (1 page) and copies of the cited non-U.S. patent documents are provided herewith in connection with the above-captioned application.

The documents cited on the Form PTO-1449 are in the English language. Hence, in accordance with the requirements of 37 C.F.R. § 1.98, no further explanation of the listed items is necessary.

Although these documents and applications are made known to the Patent and Trademark Office in compliance with Applicant's duty of disclosure, such disclosure is not to be construed as an admission by Applicant or Applicant's representative that any of the documents, singly or in any combination thereof, is effective as prior art against the subject application. In accordance with 37 C.F.R. § 1.97(g) and (h), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 C.F.R. § 1.56(b) exists.

CERTIFICATE OF TRANSMISSION VIA EFS-WEB

I hereby certify that this paper is being transmitted via the Electronic Filing System (EFS-WEB) to the United States Patent and Trademark Office on August 24, 2020.

/Hyun Jeung Ji/
Hyun Jeung Ji

Inventor(s) : Wei *et al.*
Serial No. : 16/824,572
Filed : March 19, 2020

Attorney Docket No.: 33320.03087.US26/3087C
Supplemental Information Disclosure Statement

Applicant respectfully requests that the Examiner review the foregoing documents and they be made of record in the file history of the above-captioned application.

Respectfully submitted,

/Stephanie Seidman/

Stephanie Seidman

Reg. No. 33,779

Attorney Docket No.: 33320.03087.US26/3087C

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Substitute Form PTO-1449 (Modified)		U.S. Department of Commerce Patent and Trademark Office		Attorney Docket No. 33320.03087.US26/ 3087C		Application No. 16/824,572	
List of Patents and Publications for Applicant's Information Disclosure Statement (37 CFR §1.98(b))				Inventor(s) <i>Wei et al.</i>			
				Filing Date March 19, 2020		Group Art Unit 1656	
U.S. Patent Documents							
Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
None							

Foreign Patent Documents or Published Foreign Patent Applications						
Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Translation	
					Yes	No
None						

Other Documents (include Author, Title, Date, and Place of Publication)		
Examiner Initial	Desig. ID	Document
	AA	Letter/Written Disclosure of the Information Disclosure Statement for the above-referenced application, filed herewith on August 24, 2020, 2 pages.
	AB	Notice of Allowance, issued Jul. 16, 2020, in connection with U.S. Patent Application No. 15/226,489, 13 pages.
	AC	Hearing Notice, issued Jun. 17, 2020, in connection with Indian Patent Application No. 6272/DELNP/2014, 2 pages.

Examiner Signature	Date Considered
EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

Electronic Acknowledgement Receipt	
EFS ID:	40364579
Application Number:	16824572
International Application Number:	
Confirmation Number:	1431
Title of Invention:	PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF
First Named Inventor/Applicant Name:	Ge WEI
Customer Number:	13565
Filer:	Stephanie L. Seidman/Hyun Jeung Ji
Filer Authorized By:	Stephanie L. Seidman
Attorney Docket Number:	33320.03087.US26/3087C
Receipt Date:	24-AUG-2020
Filing Date:	19-MAR-2020
Time Stamp:	15:29:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment		no			
File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	3087Ctra.pdf	25565	no	1
			fa155ff0b4a3250692b761fe847e5717712e6aa7		
Warnings:					

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	3087Cids.pdf	29485	no	2
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Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Information Disclosure Statement (IDS) Form (SB08)	3087Cp49.pdf	30149	no	1
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Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
4	Non Patent Literature	AA.pdf	101246	no	2
			9d4d89716462d0107233ac85976cbc48539519a5		
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
5	Non Patent Literature	AB.pdf	750051	no	13
			fc9f0ff6931826858cd2fb2d2d406f6a78606028		
Warnings:					
Information:					
6	Non Patent Literature	AC.pdf	1147658	no	2
			3969e047e36b88c893cfa59ac78f7f32a7dd2b6f		
Warnings:					
Information:					
Total Files Size (in bytes):			2084154		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s) : Wei *et al.* Art Unit : 1656
Serial No. : 16/824,572 Examiner : Liu, Samuel W.
Filed : March 19, 2020 Conf. No. : 1431
Cust. No. : 13565
Title : **PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES
THEREOF**

Mail Stop Amendment

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT TRANSMITTAL
LETTER**

Dear Sir:

Transmitted herewith are a Supplemental Information Disclosure Statement (2 pages), Form PTO-1449 (1 page), and cited non-U.S. patent documents for filing in connection with the above-identified application. Because this Information Disclosure Statement is filed before the receipt of a First Office Action on the Merits for the above-captioned application, a fee is not required. However, should it be determined that a fee for filing these papers is required, the Commissioner is authorized to charge Deposit Account No. 50-0911.

☒ The Commissioner is hereby authorized to charge any fees that may be due in connection with this paper or with this application during its entire pendency to Deposit Account No. 50-0911.

Respectfully submitted,

/Stephanie Seidman/

Stephanie Seidman
Reg. No. 33,779

Attorney Docket No.: 33320.03087.US26/3087C

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CERTIFICATE OF TRANSMISSION VIA EFS-WEB

I hereby certify that this paper is being transmitted via the Electronic Filing System (EFS-WEB) to the United States Patent and Trademark Office on August 24, 2020.

/Hyun Jeung Ji/
Hyun Jeung Ji



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/824,572	03/19/2020	Ge WEI	33320.03087.US26/3087C	1431
13565	7590	10/27/2020	EXAMINER	
Dentons US LLP 4655 Executive Drive Suite 700 San Diego, CA 92121			LIU, SAMUEL W	
			ART UNIT	PAPER NUMBER
			1656	
			NOTIFICATION DATE	DELIVERY MODE
			10/27/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

MLAIPSD@Dentons.com
lucy.begalla@dentons.com
rosalind.smith@dentons.com

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Status of the claims: Claims 1, 3, 5-6 and 8-21 are pending.

The amendment filed 8/24/2020 which amends claims 1, 9-11 and 13, and cancels claims 2, 4 and 7 has been entered.

CONTINUING DATA

This application is a CON of 1522,489 8/2/2016 which is a DIV of 13694731 filed 12/28/2012 (now US Pat. No. 9447401) which claims benefit of 61796208 filed 11/01/2012, and claims benefit of 61631313 filed 12/30/2011; wherein provisional application 61631313 has support for the elected invention (see below).

IDS

The references cited in the information disclosure statement (IDS) filed 8/24/2020, and the IDS filed 5/15/2020 some which can be found in the parent application 15226489 have been considered by Examiner.

Election/Restriction

Applicants' election (filed 8/24/2020) of Group I, claims 1, 3, 5-6 and 8-20 and election of the species: SEQ ID NOs: 35 and 594 with traverse is acknowledged. However, applicants elected the species with traverse. The elected species are the following: (1) the unmodified polypeptide of SEQ ID NO:3 (claims 1, 3); (2) the modified polypeptide of SEQ ID NO:196 (claim 4) or SEQ ID NO:209 (claim 5); (3) glycosylation (claim 7); PEG (claim 12); amino acid modification is "replacement" (substitution) (claims 13, 14).

The applicants' traversal with regard to the election of species from SEQ ID NOs: 3, 7 or 32-66" (claims 1, 6, 8 and 9) is under due consideration. The applicants' arguments as to this species election set forth at pages 5-7 in the response filed 8/24/2020 is persuasive; and thus, said species election requirement is withdrawn.

Claim 21 is withdrawn from further consideration, there being no allowable generic or linking claim. Claims 1, 3, 5-6 and 8-20 and elected SEQ ID NO: 594 are under examination.

Objection to specification

The disclosure is objected to because of the following informalities:

The use of the trademark (HydaseTM, VitraseTM and WydaseTM, see p.2, line 1) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the

proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

At page 3, line 20, “SEQ ID NOS” should be changed to “SEQ ID NOs”; similar changes should be made throughout the specification.

Objection to claims

In claim 1, “...unmodified PH20 polypeptide consists of the sequence of amino acid set forth in SEQ ID NO:3, 7 or 32-66” should be changed to “...modified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NO:3, 7 and 32-66”.

Also, in claim 1, “...amino acid positions set forth in SEQ ID NO:3” should be changed to “... amino acid positions of SEQ ID NO:3”.

Further, in claim 1, “...91% sequence identity to the sequence of amino acids set forth as SEQ ID NO: 3, 7 or 32-66” should be changed to “...91% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NO: 3, 7 and 32-66”.

In claims 6 and 8, “...the unmodified PH20 polypeptide consists of the sequence of amino acid set forth in SEQ ID NO:3, 7 or 32-66” should be changed to “...the modified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NO:3, 7 and 32-66”.

In claim 9, “...identity to the sequence of amino acid set forth in SEQ ID NO:3, 7 or 32-66” should be changed to “...identity to the amino acid sequence selected from the group consisting of SEQ ID NO:3, 7 and 32-66”.

In claim 11, “...PH20 polypeptide consists of the sequence of amino acid set forth in SEQ ID NO:35” should be changed to “...PH20 polypeptide consists of the amino acid sequence of SEQ ID NO:35”.

In claim 13, “...comprising a sequence of amino acid set forth in any of SEQ ID NOS: 591-598” should be changed to “...comprising the amino acid sequence selected from the group consisting of SEQ ID NOS: 591-598”.

Also, in claim 13, “...in a polypeptide of any of SEQ ID NOS: 3 and 32-66” should be changed to “...in the amino acid sequence selected from the group consisting of SEQ ID NOS: 3 and 32-66”.

In claim 13, “SEQ ID NOS” should be changed to “SEQ ID NOs”.

In claim 20, “...a modified PH20 polypeptide of claim 1” should be changed to “...the modified PH20 polypeptide of claim 1”.

Claim Rejections - 35 USC § 112(b)

The following is a quotation of 35 U.S.C. 112(b):

(B) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 5-6 and 8-20 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claim 1 sets forth “...unmodified PH20 polypeptide” is selected from SEQ ID NO: 3, 7 or 32-66” (lines 4 and 12-13, claim 1) which has broader scope than the scope of the unmodified PH20 polypeptide of “SEQ ID NO:3” (lines 9 and 11-12, claim 1). A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite; and thus, claim 1 as written is indefinite.

Also, claim 1 recites “...modified PH20 polypeptide consists of the sequence of amino acid set forth in SEQ ID NO:3, 7 or 32-66 ...”; the recitation is unclear because all of the sequences of SEQ ID NOs:3 and 32-66 are truncated forms of the full-length amino acid sequence of SEQ ID NO:7 (unmodified) wherein said “truncated” is considered to be a type of “modified” polypeptide. Thus, the claim 1 simultaneously setting forth the truncated SEQ ID NOs:3 and 32-66 along with the unmodified (non-truncated) SEQ ID NO:7 renders the claim 1 indefinite. It is noted that the specification does not define the terms “modified” and “unmodified”.

Claims 3, 5-6 and 8-20 which depend from claim 1 are also rejected.

Claim Rejection –Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of

Claims 1, 3, 5-6, 8-17 and 20 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 6-14 and 19 of Application No. 15226489 (**‘489**). This is a provisional double patenting rejection because the conflicting claims have not in fact been patented.

Although the conflicting claims are not identical, they are not patentable distinct from each other because of the reasons set forth below.

Claims 10-12 of '489 disclose that the modified PH20 polypeptide is conjugated to a polymer such as dextran or PEG, which is the common subject matters of instant claims 16-17.

Claim 19 of '489 discloses a pharmaceutical composition comprising the modified PH20 polypeptide, which is the common subject matters of instant claim 20.

SEQ ID NO **594**

Qy 1 LNFRAAPPVVPINVPFLWAWNAPSEFCLGKFDEPLDMSLFSFIGSPRINATGQGVTIFYVDR 60
 |||
 Db 1 LNFRAAPPVVPINVPFLWAWNAPSEFCLGKFDEPLDMSLFSFIGSPRINATGQGVTIFYVDR 60

Qy 61 LGYYPYIDSITGVTVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVIDWEEWRPTWA
 120 |||
 Db 61 LGYYPYIDSITGVTVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVIDWEEWRPTWA
 120

Conclusion

During examination, US 20110053247 was also reviewed.

/Samuel Wei Liu/
Patent Examiner, Art Unit 1656
October 21, 2020

Application/Control Number: 16/824,572
Art Unit: 1656

Page 7

/PAUL J HOLLAND/
Primary Examiner, Art Unit 1656

Notice of References Cited	Application/Control No. 16/824,572		Applicant(s)/Patent Under Reexamination WEI et al.	
	Examiner SAMUEL W LIU		Art Unit 1656	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-20110053247-A1	03-2011	Baker; David	C12Y302/01036	435/201
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

U.S. Patent and Trademark Office
PTO-892 (Rev. 01-2001)

Notice of References Cited

Part of Paper No. 20201021

<i>Search Notes</i> 	Application/Control No. 16/824,572	Applicant(s)/Patent Under Reexamination WEI et al.
	Examiner SAMUEL W LIU	Art Unit 1656

CPC - Searched*		
Symbol	Date	Examiner
C12N 9/2474	10/20/2020	SWL

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
STIC sequence search for SEQ ID NOs:3, 7, 32-39 and 591-598.	10/21/2020	SWL
WEST search ad google prior art search for (PH20 protein or hyaluronidase or EC 3.2.1.35) and PH20 polypeptide variant or mutant/replacement or substitution at residue 313/ substitution M313K/ PH20 polypeptide with signal sequence or signal peptide) and PH20 fusion or chimeric polypeptide/N-glycosylation/ conjugated or linked to a polymer such as polyethylene glycol or dextran.	10/22/2020	SWL
PALM inventor name search, and reviewed application 16912590 and US Pat. No.9447401.	10/21/2020	SWL

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/SAMUEL W LIU/ Examiner, Art Unit 1656	
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<i>Search Notes</i> 	Application/Control No. 16/824,572	Applicant(s)/Patent Under Reexamination WEI et al.
	Examiner SAMUEL W LIU	Art Unit 1656

/SAMUEL W LIU/ Examiner, Art Unit 1656	
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Web Search History

date, time	web site	search string
10/22/2020 5:44:35 PM	Google	(PH20 (protein or polypeptide) or hyaluronidase or EC 3.2.1.35) (varinat or mutant) and substitution
10/22/2020 5:44:43 PM	Google	PH20 (protein or polypeptide) or hyaluronidase or EC 3.2.1.35) (varinat or mutant) and substitution
10/22/2020 5:45:03 PM	Google	PH20 (protein or polypeptide) and substitution 313
10/22/2020 5:45:34 PM	Google	PH20 (protein or polypeptide) and substitution 313 and (fusion or chimerc polypeptide)
10/22/2020 5:45:43 PM	Google	PH20 (protein or polypeptide) and (fusion or chimerc polypeptide)
10/22/2020 5:46:11 PM	Google	PH20 (protein or polypeptide) and signal (peptide or sequence)
10/22/2020 5:46:23 PM	Google	PH20 (protein or polypeptide) and glycosylation
10/22/2020 5:46:30 PM	Google	PH20 (protein or polypeptide) and N-glycosylation
10/22/2020 5:47:06 PM	Google	PH20 (protein or polypeptide) and conjugate with (polymer or PEG or dextran)
10/22/2020 5:47:20 PM	Google	PH20 (protein or polypeptide) and (linked or conjugated) with (polymer or PEG or dextran)

Substitute Form PTO-1449 (Modified)		U.S. Department of Commerce Patent and Trademark Office		Attorney Docket No. 33320.03087.US26/ 3087C		Application No. 16/824,572	
List of Patents and Publications for Applicant's Information Disclosure Statement (37 CFR §1.98(b))				Applicant <i>Wei et al.</i>			
				Filing Date March 19, 2020		Group Art Unit 1656	
U.S. Patent Documents							
Examiner Initial	Desig ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
	AA	3,536,809	10/27/1970	Applezweig	424	28	02/17/1969
	AB	3,598,123	08/10/1971	Zaffaroni	424	435	04/01/1969
	AC	3,630,200	12/28/1971	Higuchi	424	427	06/09/1969
	AD	3,710,795	01/16/1973	Higuchi et al.	424	424	09/29/1970
	AE	3,845,770	11/05/1974	Theeuwes et al.	424	427	06/05/1972
	AF	3,916,899	11/04/1975	Theeuwes et al.	424	424	02/07/1974
	AG	4,002,531	01/11/1977	Royer	435	188	01/22/1976
	AH	4,008,719	02/22/1977	Theeuwes et al.	424	427	02/02/1976
	AI	4,044,126	08/23/1977	Cook et al.	514	180	07/09/1976
	AJ	4,179,337	12/18/1979	Davis et al.	435	181	07/28/1977
	AK	4,364,923	12/21/1982	Cook et al.	424	46	04/30/1981
	AL	4,414,209	11/08/1983	Cook et al.	514	180	06/13/1977
	AM	4,769,027	09/06/1988	Baker et al.	424	493	02/24/1987
	AN	4,952,496	08/28/1990	Studier et al.	435	91.41	12/29/1986
	AO	4,980,286	12/25/1990	Morgan et al.	435	371	01/03/1989
	AP	5,033,252	07/23/1991	Carter	53	425	07/30/1990
	AQ	5,052,558	10/01/1991	Carter	206	439	07/27/1990
	AR	5,059,595	10/22/1991	Le Grazie	424	468	03/20/1990
	AS	5,073,543	12/17/1991	Marshall et al.	514	21	07/21/1988
	AT	5,120,548	06/09/1992	McClelland et al.	424	473	11/07/1989
	AU	5,122,614	06/16/1992	Zalipsky	548	520	04/19/1990
	AV	5,323,907	06/28/1994	Kalvelage	206	531	03/15/1993
	AW	5,324,844	06/28/1994	Zalipsky	548	520	01/08/1992
	AX	5,446,090	08/29/1995	Harris	525	54.1	11/12/1993
	AY	5,591,767	01/07/1997	Mohr et al.	514	413	06/06/1995
	AZ	5,612,460	03/18/1997	Zalipsky	530	391.9	02/17/1994
	BA	5,639,476	06/17/1997	Oshlack et al.	424	468	06/02/1995
	BB	5,643,575	07/01/1997	Martinez et al.	424	194.1	10/27/1993
	BC	5,672,662	09/30/1997	Harris et al.	525	408	10/02/1995
	BD	5,674,533	10/07/1997	Santus et al.	424	493	05/26/1995
Examiner Signature <i>/SAMUEL W LIU/</i>				Date Considered 06/03/2020			
EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.							

Substitute Form PTO-1449 (Modified)		U.S. Department of Commerce Patent and Trademark Office		Attorney Docket No. 33320.03087.US26/ 3087C		Application No. 16/824,572	
List of Patents and Publications for Applicant's Information Disclosure Statement (37 CFR §1.98(b))				Applicant <i>Wei et al.</i>			
				Filing Date March 19, 2020		Group Art Unit 1656	
U.S. Patent Documents							
Examiner Initial	Desig . ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
	BE	5,721,348	02/24/1998	Primakoff et al.	536	22.1	10/21/1991
	BF	5,733,566	03/31/1998	Lewis	424	426	10/30/1995
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	BH	5,795,569	08/18/1998	Bartley et al.	424	85.1	10/12/1994
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	DJ	2001/0046481	11/29/2001	Bentley et al.	424	78.18	04/21/2001
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	IE**	Eskens et al., "Enzymatic glyocalyx treatment impairs insulin-mediated recruitment of microvascular blood volume and decreases insulin sensitivity in rats," <i>FASEB Journal</i> 25: 1023.13 (2011) (Abstract).
	IF**	European Pharmacopoeia, Chapter 5.1.3, "Efficacy of antimicrobial preservation," pages 447-449 (2005).

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	IG**	Fankhauser, N. and P.Mäser, "Identification of GPI anchor attachment signals by a Kohonen self-organizing map," <i>Bioinformatics</i> 21(9) 1846-1852 (2005).
	IH**	Felix et al., "Pegylated peptides. IV. Enhanced biological activity of site-directed pegylated GRF analogs," <i>Int. J. Peptide Res.</i> 46:253-264 (1995).
	II**	Few, B., "Hyaluronidase for treating intravenous extravasations," <i>MCN Amer. J. Matern. Child Nurs.</i> 12(1):23 (1987).
	IJ**	Filocamo et al., "Chimeric Sindbis viruses dependent on the NS3 protease of hepatitis C virus," <i>J.Virology</i> 71:1417-1427 (1997).
	IK**	Forsburg, S., "Codon usage table for <i>Schizosaccharomyces pombe</i> ," <i>Yeast</i> 10(8):1045-1047 (1994).
	IL**	Fransson et al., "Solvent effects on the solubility and physical stability of human insulin-like growth factor I," <i>Pharm Res.</i> 14(5):606-612 (1997).
	IM**	Frost, G. and R. Stern, "A microtiter-based assay for hyaluronidase activity not requiring specialized reagents," <i>Anal. Biochem.</i> 251:263-269 (1997).
	IN**	Gardner et al., "The complete nucleotide sequence of an infectious clone of cauliflower mosaic virus by M13mp7 shotgun sequencing," <i>Nucleic Acids Res.</i> 9:2871-2888 (1981).
	IO**	GenBank Accession No. AAC60607, PH-20 [<i>Homo sapiens</i>], published on Jun. 05, 2000 [online] [retrieved on Dec. 12, 2012][retrieved from URL:<ncbi.nlm.nih.gov/protein/AAC60607>], 1 page.
	IP**	Gilbert, W. and L. Villa-Komaroff, "Useful Proteins from Recombinant Bacteria," <i>Scientific American</i> 242(4):74-94 (1980).
	IQ**	Girish et al., "Hyaluronidase inhibitors: a biological and therapeutic perspective," <i>Curr Med Chem</i> 16(18):2261-2288 (2009).
	IR**	Gmachl et al., "The human sperm protein PH-20 has hyaluronidase activity," <i>FEBS</i> 336(3):545-548 (1993).
	IS**	Good et al., "Hydrogen ion buffers for biological research," <i>Biochemistry</i> 5(2):467-477 (1966).
	IT**	Gribskov et al., "Sigma factors from <i>E. coli</i> , <i>B. subtilis</i> , phage SP01, and phage T4 are homologous proteins," <i>Nucl. Acids Res.</i> 14(16):6745-6763 (1986).
	IU**	Grosschedl et al., "Introduction of a mu immunoglobulin gene into the mouse germ line: specific expression in lymphoid cells and synthesis of functional antibody," <i>Cell</i> 38:647-658 (1984).
	IV**	Guiotto et al., "An improved procedure for the synthesis of branched polyethylene glycols (PEGs) with the reporter dipeptide Met-betaAla for protein conjugation," <i>Bioorg. Med. Chem. Lett.</i> 12:177-180 (2002).
	IW**	Guntenhoner et al., "A substrate-gel assay for hyaluronidase activity," <i>Matrix</i> 12:388-396 (1992).
	IX**	Guo et al., "Protein tolerance to random amino acid change," <i>Proc. Nat'l. Acad. Sci. USA</i> 101:9205-9210 (2004).
	IY**	Hahm et al., "Generation of a novel poliovirus with a requirement of hepatitis C virus protease NS3 activity," <i>Virology</i> 226:318-326 (1996).
	IZ**	Haller et al., "Escaping the interstitial matrix with enzyme-mediated drug delivery," <i>Drug Delivery Technology</i> , 5(5):1-6 (2005).
	JA**	Hamatake et al., "Establishment of an in vitro assay to characterize hepatitis C virus NS3-4A protease trans-processing activity," <i>Intervirology</i> 39:249-258 (1996).
	JB**	Hammer et al., "Diversity of alpha-fetoprotein gene expression in mice is generated by a combination of separate enhancer elements," <i>Science</i> 235:53-58 (1987).

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	JC**	Hanahan, D., "Heritable formation of pancreatic beta-cell tumours in transgenic mice expressing recombinant insulin/simian virus 40 oncogenes," <i>Nature</i> 315(6015):115-122 (1985).					
	JD**	Harris, J. and R. Chess, "Effect of pegylation on pharmaceuticals," <i>Nat Rev Drug Discov</i> 2(3):214-221 (2003).					
	JE**	Hartman S. and R. Mulligan, "Two dominant-acting selectable markers for gene transfer studies in mammalian cells," <i>Proc Natl Acad Sci</i> 85:8047-8051 (1988).					
	JF**	Have et al., "Cloning and characterization of the cDNA encoding the PH20 protein in the European red fox <i>Vulpes vulpes</i> ," <i>Reproduct Fertil Dev</i> 10:165-172 (1998).					
	JG**	Herrera-Estrella et al., "Expression of chimaeric genes transferred into plant cells using a ti-plasmid-derived vector," <i>Nature</i> 303:209-213 (1983).					
	JH**	Herrera-Estrella et al., "Light-inducible and chloroplast-associated expression of a chimaeric gene introduced into <i>Nicotiana tabacum</i> using a Ti plasmid vector," <i>Nature</i> 310(5973):115-120 (1984).					
	JI**	Hibi et al., "Chondroitinase C activity of <i>Streptococcus intermedius</i> ," <i>FEMS-Microbiol-Lett.</i> 48(2):121-124 (1989).					
	JJ**	Hofinger et al., "Isoenzyme-specific differences in the degradation of hyaluronic acid by mammalian-type hyaluronidases," <i>Glycoconj J</i> 25:101-109 (2008).					
	JK**	Holash et al., "VEGF-Trap: a VEGF blocker with potent antitumor effects," <i>Proc Natl Acad Sci USA</i> 99(17):11393-11398 (2002).					
	JL**	Hooper et al., "Determination of glycosyl-phosphatidylinositol membrane protein anchorage" <i>Proteomics</i> 1:748-755 (2001)					
	JM**	Horn et al., "Intravesical chemotherapy of superficial bladder tumors in a controlled trial with cis-platinum versus cis-platinum plus hyaluronidase," <i>J. Surg. Oncol.</i> 28:304-307 (1985).					
	JN**	Huang et al., "Recombinant Human Hyaluronidase PH20 Does Not Stimulate an Acute Inflammatory Response and Inhibits Lipopolysaccharide-Induced Neutrophil Recruitment in the Air Pouch Model of Inflammation," <i>J Immunol.</i> 192(11):5285-5295 (2014).					
	JO**	Huang, X. and M. Miller. "A time-efficient, linear-space local similarity algorithm." <i>Adv. Appl. Math.</i> 12:337-357 (1991).					
	JP**	Hunnicut et al., "Structural relationship of sperm soluble hyaluronidase to the sperm membrane protein PH-20," <i>Biol Reprod.</i> 54(6):1343-1349 (1996).					
	JQ**	Infante et al., "Phase I trials of PEGylated recombinant human hyaluronidase PH20 in patients with advanced solid tumours," <i>Br J Cancer</i> 118(2):153-161 (2018).					
	JR**	Ito et al., "Cultivation of hepatitis C virus in primary hepatocyte culture from patients with chronic hepatitis C results in release of high titre infectious virus," <i>J. Gen. Virol.</i> 77:1043-1054 (1996).					
	JS**	IUPAC-IUB Commission on Biochemical Nomenclature, "A One-Letter Notation for Amino Acid Sequences: Tentative Rules," <i>J. Biol. Chem.</i> 243:3557-3559 (1968).					
	JT**	IUPAC-IUB, "Abbreviated nomenclature of synthetic polypeptides-polymerized amino acids-revised recommendations," Commission on Biochemical Nomenclature, <i>Biochemistry</i> 11:1726-1731 (1972).					
	JU**	Jadin et al., "A comprehensive model of hyaluronan turnover in the mouse," <i>Matrix Biol</i> 31(2):81-89 (2012).					
	JV**	Jay et al., "Construction of a general vector for efficient expression of mammalian proteins in bacteria: use of a synthetic ribosome binding site," <i>Proc. Natl. Acad. Sci. USA</i> 78:5543-5548 (1981).					
	JW**	Karvinen et al., "Hyaluronan, CD44 and versican in epidermal keratinocyte tumors," <i>British Journal of Dermatology</i> 148:86-94 (2003).					
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	JX**	Kelsey et al., "Species- and tissue-specific expression of human alpha 1-antitrypsin in transgenic mice," <i>Genes And Devel.</i> 1:161-171 (1987).					
	JY**	Kim et al., "Sperm penetration through cumulus mass and zona pellucida," <i>Int J Dev Biol.</i> 52(5-6):677-682 (2008).					
	JZ**	Kodukula et al., "Biosynthesis of phosphatidylinositol glycan-anchored membrane proteins" <i>J. Biol. Chem.</i> 266:4464-4470 (1991).					
	KA**	Kohno et al., "Effects of hyaluronidase on doxorubicin penetration into squamous carcinoma multicellular tumor spheroids and its cell lethality," <i>J. Cancer Res. Oncol.</i> 120:293-297 (1994).					
	KB**	Kollias et al., "Regulated expression of human A gamma-, beta-, and hybrid gamma beta-globin genes in transgenic mice: manipulation of the developmental expression patterns," <i>Cell</i> 46:89-94 (1986).					
	KC**	Krumlauf et al., "Developmental regulation of alpha-fetoprotein genes in transgenic mice," <i>Mol. Cell. Biol.</i> 5:1639-1648 (1985).					
	KD**	Krupers et al., "Complexation of poly(ethylene oxide) with poly(acrylic acid-co-hydroxyethyl methacrylate)s," <i>Eur. Polym J.</i> 32(6):785-790 (1996).					
	KE**	Kyte et al., "A Simple Method for Displaying the Hydropathic Character of a Protein" <i>J. Mol. Biol.</i> 157:105-132 (1982).					
	KF**	Lalancette et al., "Characterization of an 80-kilodalton bull sperm protein identified as PH-20," <i>Biol Reprod.</i> 65(2):628-636 (2001).					
	KG**	Lam et al., "The effect of benzyl alcohol on recombinant human interferon-gamma," <i>Pharm Res.</i> 14(6):725-729 (1997).					
	KH**	Lammerts van Bueren et al., "The antibody zalutumumab inhibits epidermal growth factor receptor signaling by limiting intra- and intermolecular flexibility," <i>Proc Natl Acad Sci U S A.</i> 105(16):6109-6114 (2008). Retraction also included, <i>Proc Natl Acad Sci U S A.</i> 109(14):5548 (2008).					
	KI**	Lathrop et al., "cDNA cloning reveals the molecular structure of a sperm surface protein, PH-20, involved in sperm-egg adhesion and the wide distribution of its gene among mammals," <i>J Cell Biol.</i> 111(6 Pt 2):2939-2949 (1990).					
	KJ**	Laurent, T. and J. Fraser, "Hyaluronan," <i>FASEB J</i> 6:2397-2404 (1992).					
	KK**	Leder et al., "Consequences of widespread deregulation of the c-myc gene in transgenic mice: multiple neoplasms and normal development," <i>Cell</i> 45:485-495 (1986).					
	KL**	Li et al., "Importance of glycosylation and disulfide bonds in hyaluronidase activity of macaque sperm surface PH-20," <i>J. Androl.</i> 23:211-219 (2002).					
	KM**	Li et al., "Structural basis for EGF receptor inhibition by the therapeutic antibody IMC-11F8," <i>Structure.</i> 16(2):216-227 (2008).					
	KN**	Liang et al., "Prediction of antigenic epitopes on protein surfaces by consensus scoring," <i>BMC Bioinformatics.</i> 10:302 (2009), 10 pages.					
	KO**	Lin et al., "A hyaluronidase activity of the sperm plasma membrane protein PH-20 enables sperm to penetrate the cumulus cell layer surrounding the egg," <i>J Cell Biol.</i> 125(5):1157-1163 (1994).					
	KP**	Lin et al., "Molecular cloning of the human and monkey sperm surface protein PH-20," <i>Proc. Natl. Acad. Sci. USA</i> 90:10071-10075 (1993).					
	KQ**	Lipponen et al "High stromal hyaluronan level is associated with poor differentiation and metastasis in prostate cancer," <i>European Journal of Cancer</i> 37:849-856 (2001).					
	KR**	Locke et al., "ENHANZE® drug delivery technology: a novel approach to subcutaneous administration using recombinant human hyaluronidase PH20," <i>Drug Deliv</i> 26(1):98-106 (2019).					
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	KS**	Louveau, I. and F. Gondret, "GH and insulin affect fatty acid synthase activity in isolated porcine adipocytes in culture without any modifications of sterol regulatory element binding protein-1 expression," J Endocrin. 181:271-280 (2004).
	KT**	Lowy et al., "Isolation of transforming DNA: cloning the hamster aprt gene," Cell 22:817-823 (1980).
	KU**	Lu, H. and E. Wimmer., "Poliovirus chimeras replicating under the translational control of genetic elements of hepatitis C virus reveal unusual properties of the internal ribosomal entry site of hepatitis C virus," Proc. Natl. Acad. Sci. USA 93:1412-1417 (1996).
	KV**	Lu, Y. and A. Felix, "Pegylated peptides I: Solid-phase synthesis of N alpha-pegylated peptides using Fmoc strategy," Peptide Res 6:140-146 (1993).
	KW**	Lu, Y. and A. Felix, "Pegylated peptides. II. Solid-phase synthesis of amino-, carboxy- and side-chain pegylated peptides," Int. J. Peptide Protein Res. 43:127-138 (1994).
	KX**	M3WD76 Felca (2015, updated) Hyaluronidase/PH20 from Felis catus, 3 pages.
	KY**	Ma et al., "Fucosylation in prokaryotes and eukaryotes" Glycobiology 16(12):158R-184R (2006)
	KZ**	Maa and Hsu, "Aggregation of recombinant human growth hormone induced by phenolic compounds" Int. J. Pharm. 140(2):155-168 (1996).
	LA**	MacDonald, R., "Expression of the pancreatic elastase I gene in transgenic mice," Hepatology 7:42S-51S(1987).
	LB**	Magram et al., "Developmental regulation of a cloned adult beta-globin gene in transgenic mice," Nature 315:338-340 (1985).
	LC**	Maksimenko et al. "Resistance of dextran-modified hyaluronidase to inhibition by heparin" Biochemistry (Mosc). 66(4):456-463 (2001).
	LD**	Mammalian Gene Collection (MGC) Program Team, "Generation and initial analysis of more than 15,000 full-length human and mouse cDNA sequences," Proc. Natl. Acad. Sci. USA 99:16899-16903 (2002).
	LE**	Marković-Housley et al., "Crystal Structure of Hyaluronidase, a Major Allergen of Bee Venom," Structure 8: 1025-1035 (2000).
	LF**	McIlvaine, WB, "A buffer solution for colorimetric comparison," J. Biol. Chem. 49:183-186 (1921).
	LG**	Mehvar et al., "Modulation of the pharmacokinetics and pharmacodynamics of proteins by polyethylene glycol conjugation," J. Pharm. Pharmaceut. Sci. 3(1):125-136 (2000).
	LH**	Menzel, E. and C. Farr, "Hyaluronidase and its substrate hyaluronan: biochemistry, biological activities and therapeutic uses," Cancer Lett. 131:3-11 (2003).
	LI**	Merrifield, J., "Solid phase peptide synthesis. I. The synthesis of a tetrapeptide," J Am Chem Soc 85:2149-2154 (1963).
	LJ**	Meyer et al., "The soluble hyaluronidase from bull testes is a fragment of the membrane-bound PH-20 enzyme." FEBS Letters 413(2):385-388 (1997).
	LK**	Michelacci et al., "Chondroitinase C from Flavobacterium heparinum," J. Biol. Chem. 251:1154-1158 (1976).
	LL**	Miller et al., "Use of retroviral vectors for gene transfer and expression," Meth. Enzymol. 217:581-599 (1993).
	LM**	Mizutani et al., "Characterization of hepatitis C virus replication in cloned cells obtained from a human T-cell leukemia virus type 1-infected cell line, MT-2," J.Virol. 70:7219-7223 (1996).
	LN**	Mizutani et al., "Inhibition of hepatitis C virus replication by antisense oligonucleotide in culture cells," Biochem. Biophys. Res. Commun. 212:906-911 (1995).

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	LO**	Molineux, G., "Pegylation: engineering improved biopharmaceuticals for oncology," <i>Pharmacotherapy</i> 23 (8 Pt 2):3S-8S (2003).					
	LP**	Monfardini et al., "A branched monomethoxypoly(ethylene glycol) for protein modification," <i>Bioconjugate Chem.</i> 6:62-69 (1995).					
	LQ**	Nadsombati et al., "Dose-range developmental toxicity of rHuPH20 in mice," <i>Matrix Biology</i> 27:23 (2008).					
	LR**	NCBI Reference Sequence XP_011728213.1, <i>Macaca nemestrina</i> (pig-tailed macaque) PH-20 hyaluronidase. Published on Apr. 24, 2018. Retrieved from URL: <ncbi.nlm.nih.gov/protein/795324051/ [retrieved on Apr. 20, 2020], 2 pages.					
	LS**	Nakayama et al., "CD15 expression in mature granulocytes is determined by alpha 1,3-fucosyltransferase IX, but in promyelocytes and monocytes by alpha 1,3-fucosyltransferase IV," <i>J. Biol. Chem.</i> , 276(19):16100-16106 (2001).					
	LT**	Needleman, S. and C. Wunsch "A general method applicable to the search for similarities in the amino acid sequence of two proteins," <i>J Mol Biol.</i> 48:443-453 (1970).					
	LU**	Nekoroski et al., "A recombinant human hyaluronidase sustained release gel for the treatment of post-surgical edema," <i>Int J Dermatol.</i> 53(6):777-785 (2014). Epub 2013 Oct 29.					
	LV**	Omaetxebarria et al., "Computational approach for identification and characterization of GPI-anchored peptides in proteomics experiments," <i>Proteomics</i> 7(12):1951-1960 (2007).					
	LW**	Ornitz et al., "Elastase I promoter directs expression of human growth hormone and SV40 T antigen genes to pancreatic acinar cells in transgenic mice," <i>Cold Spring Harbor Symp. Quant. Biol.</i> 50:399-409 (1986).					
	LX**	Ostresh et al., "Peptide libraries: determination of relative reduction rates of protected amino acids in competitive couplings," <i>Biopolymers</i> 34:1681-1689 (1994).					
	LY**	Padavattan, S. "Crystal structure determination of hyaluronidase : a major bee venom allergen, in complex with an IgG Fab fragment and purification and biophysical characterization of bovine testes hyaluronidase," 2006, PhD Thesis, University of Basel, Faculty of Science. DOI: 10.5451/unibas-004349798. 98 pages.					
	LZ**	Paul, A. and D. Sochart, "Improving the results of ganglion aspiration by the use of hyaluronidase," <i>J Hand Surg</i> 22(2):219-221 (1997).					
	MA**	Paulick, M. and C. Bertozzi, "The glycosylphosphatidylinositol anchor: A complex membrane-anchoring structure for proteins," <i>Biochemistry</i> 47:6991-7000 (2008).					
	MB**	Pawlowski et al., "The effects of hyaluronidase upon tumor formation in BALB/c mice painted with 7,12-dimethylbenz-(a)anthracene," <i>Int. J. Cancer</i> 23:105-109 (1979).					
	MC**	Pedersen et al., "Sym004: a novel synergistic anti-epidermal growth factor receptor antibody mixture with superior anticancer efficacy," <i>Cancer Res.</i> 70(2):588-597 (2010).					
	MD**	Pham et al., "Large-scale transient transfection of serum-free suspension-growing HEK293 EBNA1 cells: peptone additives improve cell growth and transfection efficiency," <i>Biotechnology and Bioengineering</i> 84:332-342 (2003).					
	ME**	Phelps et al., "Restricted lateral diffusion of PH-20, a PI-anchored sperm membrane protein," <i>Science</i> 240:1780-1782 (1988).					
	MF**	Pierleoni et al., "PredGPI: a GPI-anchor predictor, <i>BMC Bioinformatics</i> 9:392 (2008).					
	MG**	Pinkert et al., "An albumin enhancer located 10 kb upstream functions along with its promoter to direct efficient, liver-specific expression in transgenic mice," <i>Genes and Devel.</i> 1:268- 276 (1987).					
	MH**	Pirinen et al "Prognostic value of hyaluronan expression in non-small cell lung cancer: Increased stromal expression indicated unfavorable outcome in patients with adenocarcinoma," <i>Int. J. Cancer</i> 95:12-17 (2001).					
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	MI**	Primakoff et al., "Fully effective contraception in male and female guinea pigs immunized with the sperm protein PH-20," Nature 335:543-546 (1988).
	MJ	Prothmann et al., "Sexual size dimorphism predicts rates of sequence evolution of Sperm Adhesion Molecule 1 (SPAM1, also PH-20) in monkeys, but not in hominoids (apes including humans)," Mol Phy Ev 63:52-63 (2012).
	MK**	Readhead et al., "Expression of a myelin basic protein gene in transgenic shiverer mice: correction of the dysmyelinating phenotype," Cell 48:703-712 (1987).
	ML**	Reitinger et al., "Designed human serum hyaluronidase 1 variant, HYALIDeltaL, exhibits activity up to pH 5.9," J Biol Chem. 284(29):19173-177 (2009).
	MM**	Remmele et al., "Interleukin-1 receptor (IL-1R) liquid formulation development using differential scanning calorimetry," Pharm Res. 15(2):200-208 (1998).
	MN**	Rhodes et al., "Transformation of maize by electroporation of embryos," Methods Mol Biol 55:121-131 (1995).
	MO**	Richmond, T., "Precompiled codon-usage tables," Genome Biology 1(1):reports241 (2000), 2 pages.
	MP**	Ripka et al., "Two Chinese hamster ovary glycosylation mutants affected in the conversion of GDP-mannose to GDP-fucose," Arch. Biochem. Biophys. 249(2):533-545 (1986).
	MQ**	Roberts et al., "Chemistry for peptide and protein PEGylation," Advanced Drug Delivery Review 54:459-476 (2002).
	MR**	Ropponen et al "Tumor Cell-associated Hyaluronan as an Unfavorable Prognostic Factor in Colorectal Cancer," Cancer Research 58:342-347 (1998).
	MS**	Sato et al., "Cloning and expression in Escherichia coli of the gene encoding the Proteus vulgaris chondroitin ABC lyase," Appl. Microbiol. Biotechnol. 41(1):39-46 (1994).
	MT**	Sato, H., "Enzymatic procedure for site-specific pegylation of proteins," Adv. Drug Deliv. Rev. 54:487-504 (2002).
	MU**	Sawhney et al., "Bioerodible hydrogels based on photopolymerized poly(ethylene glycol)-co poly(hydroxyl acid) Diacrylate Macromers," Macromolecules 26:581-587 (1993).
	MV**	Schanté et al., "Improvement of hyaluronic acid enzymatic stability by the grafting of amino-acids," Carbohydrate Polymers, 87(3):2211-2216 (2012).
	MW**	Scharf et al., "Heat stress promoters and transcription factors," Results Probl Cell Differ 20:125-162 (1994).
	MX**	Scheithauer et al., "In vitro evaluation of the anticancer drug modulatory effect of hyaluronidase in human gastrointestinal cell lines," Anticancer Res. 8:391-396 (1988).
	MY**	Schuller et al., "Pharmacokinetics of intrahepatic 5-fluorouracil + preinjected hyaluronidase," Proc. Amer. Assoc. Cancer Res. 32:173, abstract no. 1034 (1991).
	MZ**	Schwartz and Dayhoff, eds., Atlas of Protein Science and Structure, National Biomedical Research Foundation, pp. 353-358 (1979).
	NA**	Schwartzman, J., "Hyaluronidase: A Review in Its Therapeutic Use in Pediatrics," J. Pediat. 39:491-502 (1951).
	NB**	Seaton et al., "Rat sperm 2B1 glycoprotein (PH20) contains a C-terminal sequence motif for attachment of a glycosyl phosphatidylinositol anchor. Effects of endoproteolytic cleavage on hyaluronidase activity," Biol Reprod. 62(6):1667-1676 (2000).
	NC**	Shani, M., "Tissue-specific expression of rat myosin light-chain," Nature 314:283-286 (1985).
	ND**	Sharp et al., "Codon usage patterns in Escherichia coli, Bacillus subtilis, Saccharomyces cerevisiae, Schizosaccharomyces pombe, Drosophila melanogaster and Homo sapiens; a review of the considerable within-species diversity," Nucleic Acids Res. 16(17):8207-8211 (1988).

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	NE**	Sharp, P. and E. Cowe, "Synonymous codon usage in <i>Saccharomyces cerevisiae</i> ," <i>Yeast</i> 7(7):657-678 (1991).					
	NF**	Shekhar et al., "The matrix reloaded: halozyme's recombinant enzyme helps injected drugs spread faster," <i>Chem. Biol.</i> 14:603-604 (2007).					
	NG**	Shimizu, Y. and H. Yoshikura, "Multicycle infection of hepatitis C virus in cell culture and inhibition by alpha and beta interferons," <i>J. Virol.</i> 68:8406-8408 (1994).					
	NH**	Singh et al., "Mechanisms of m-cresol-induced protein aggregation studied using a model protein cytochrome c," <i>J Pharm Sci.</i> 100(5):1679-1689 (2011); Epub date Jan. 12, 2011.					
	NI**	Smith, T. and M. Waterman, "Comparison of biosequences," <i>Advances in Applied Mathematics</i> 2:482-489 (1981).					
	NJ**	St Croix et al., "Reversal of intrinsic and acquired forms of drug resistance by hyaluronidase treatment of solid tumors," <i>Cancer Lett</i> 131(1):35-44 (1998).					
	NK**	Steinkuhler et al., "Product inhibition of the hepatitis C virus NS3 protease," <i>Biochem.</i> 37:8899-8905 (1998).					
	NL**	Stern et al., "Hyaluronidases: their genomics, structures, and mechanisms of action," <i>Chem Rev</i> 106: 818-839 (2006).					
	NM**	Stern, R., "Devising a pathway for hyaluronan catabolism: are we there yet?" <i>Glycobiology</i> 13:105R-115R (2003).					
	NN**	Sturla et al., "Core fucosylation of N-linked glycans in leukocyte adhesion deficiency/congenital disorder of glycosylation IIc fibroblasts," <i>Glycobiology</i> 15(10):924-935 (2005).					
	NO**	Sudo et al., "Establishment of an in vitro assay system for screening hepatitis C virus protease inhibitors using high performance liquid chromatography," <i>Antiviral Res.</i> 32:9-18 (1996).					
	NP**	Sutton, S. and D. Porter, "Development of the antimicrobial effectiveness as USP chapter <51>," <i>PDA J. Pharm. Sci Technol.</i> , 56(6):300-311 (2002).					
	NQ**	Swift et al., "Tissue-specific expression of the rat pancreatic elastase I gene in transgenic mice," <i>Cell</i> 38(3):639-646 (1984).					
	NR**	Takahashi et al., "A fluorimetric Morgan-Elson assay method for hyaluronidase activity," <i>Anal. Biochem.</i> 322:257-263 (2003).					
	NS**	Takeshita et al., "An enzyme-linked immunosorbent assay for detecting proteolytic activity of hepatitis C virus proteinase," (1997) <i>Anal. Biochem.</i> 247:242-246.					
	NT**	Taliani et al., "A continuous assay of hepatitis C virus protease based on resonance energy transfer decapeptide substrates," <i>Anal. Biochem.</i> 240:60-67 (1996).					
	NU**	ten Have et al., "Cloning and characterization of the cDNA encoding the PH20 protein in the European red fox <i>Vulpes vulpes</i> ," <i>Reprod Fertil Dev.</i> 10(2):165-172 (1998).					
	NV**	Tkalec et al., "Isolation and expression in <i>Escherichia coli</i> of <i>csIA</i> and <i>csIB</i> , genes coding for the chondroitin sulfate-degrading enzymes chondroitinase AC and chondroitinase B, respectively, from <i>Flavobacterium heparinum</i> ," <i>Applied and Environmental Microbiology</i> 66(1):29-35 (2000).					
	NW**	Tsubery et al., "Prolonging the action of protein and peptide drugs by a novel approach of reversible polyethylene glycol modification," <i>J Biol. Chem</i> 279(37):38118-38124 (2004).					
	NX**	Tsuda et al., "Substrate specificity studies of flavobacterium chondroitinase C and heparitinases towards the glycosaminoglycan protein linkage region. Use of a sensitive analytical method developed by chromophore-labeling of linkage glycoserines using dimethylaminoazobenzenesulfonyl chloride," <i>Eur. J. Biochem.</i> 262:127-133 (1999).					
	NY**	Tung et al., "Mechanism of infertility in male guinea pigs immunized with sperm PH-20," <i>Biol. Reprod.</i> 56(5):1133-1141 (1997).					
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	OA**	UniProt Murine PH20 sequence, Retrieved from: <URL: uniprot.org/uniprot/P48794 [retrieved on Sept. 1, 2010] [5 pages].					
	OB**	United States Pharmacopeia. USP <51>. Antimicrobial effectiveness testing. United States Pharmacopeia Convention, Inc, Rockville, MD., 5 pages.					
	OC**	USP XXII-NF XVII, United States Pharmacopeia Convention, Inc, Rockville, MD., pages 644-645 (1990).					
	OD**	Varela et al., "Exome sequencing identifies frequent mutation of the SWI/SNF complex gene PBRM1 in renal carcinoma," Nature 469(7331):539-542 (2011).					
	OE**	Veronese et al., "Branched and Linear Poly(Ethylene Glycol): Influence of the Polymer Structure on Enzymological, Pharmacokinetic, and Immunological Properties of Protein Conjugates," J. Bioactive Compatible Polymers 12:197-207 (1997).					
	OF	Von Sivaraman Padavattan (2006) Thesis of University of Basel, "Crystal structure determination of hyaluronidase, a major bee venom allergen, in complex with an IgG Fab fragment and purification and biophysical characterization of bovine testes hyaluronidase," 100 pages.					
	OG**	Wagner et al., "Nucleotide sequence of the thymidine kinase gene of herpes simplex virus type 1," Proc. Natl. Acad. Sci. USA 78:1441-1445 (1981).					
	OH**	Wang et al., "The molecular physiology of hepatic nuclear factor 3 in the regulation of gluconeogenesis," J. Biol. Chem. 275(19):14717-14721 (2000).					
	OI**	Watson et al., Molecular Biology of the Gene, 4th Edition, The Benjamin/Cummings Pub. Co., p. 224 (1987).					
	OJ**	Weiss et al., "Activities of monomeric insulin analogs at position A8 are uncorrelated with their thermodynamic stabilities," J. Biol. Chem. 276(43):40018-40024 (2001).					
	OK**	Wells et al., "Additivity of Mutational Effects in Proteins," Biochem 29:8509-8517 (1990).					
	OL**	White et al., "Comparison of the glycosyl-phosphatidylinositol cleavage/attachment site between mammalian cells and parasitic protozoa," J. Cell Sci. 113(Pt.4):721-727 (2000).					
	OM**	Wigler et al., "Transfer of purified herpes virus thymidine kinase gene to cultured mouse cells," Cell 11:223-232 (1977).					
	ON**	Wigler et al., "Transformation of mammalian cells with an amplifiable dominant-acting gene," Proc Natl Acad Sci. USA 77:3567-3570 (1980).					
	OO**	Yamamoto et al., "Identification of a functional promoter in the long terminal repeat of Rous sarcoma virus," Cell 22:787-797 (1980).					
	OP**	Yamane-Ohnuki et al., "Establishment of FUT8 knockout Chinese hamster ovary cells: an ideal host cell line for producing completely defucosylated antibodies with enhanced antibody-dependent cellular cytotoxicity," Biotech. Bioeng. 87:614-622 (2004).					
	OQ**	Yang, X. and X. Yu, "An introduction to epitope prediction methods and software," Rev Med Virol. 19(2):77-96 (2009).					
	OR**	Yocum et al., "Assessment and implication of the allergic sensitivity to a single dose of recombinant human hyaluronidase injection: A double-blind placebo-controlled clinical trial," J Infus Nursing 30:293-299 (2007).					
	OS**	Yudin et al., "Characterization of the active site of monkey sperm hyaluronidase," Reproduction. 121(5):735-743 (2001).					
	OT**	Zalipsky, S., "Chemistry of polyethylene glycol conjugates with biologically active molecules," Adv. Drug Del. Rev. 16:157-182 (1995).					
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	OW**	Zhao, X. and J. Harris, "Novel degradable poly(ethylene glycol) esters for delivery," in Poly(ethylene glycol), Chemistry and Biological Applications, ACS Symposium Series 680, Hams, J. and S. Zalipsky, (eds), 458-472 (1997).
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	OZ**	Bookbinder et al., "Biochemical characterization of recombinant human PH20 (SPAM1) hyaluronidase," Hyaluronan (ISHAS) 2007, Charleston, SC. Abstract, 1 page.
	PA **	Bookbinder et al., "Biochemical characterization of recombinant human PH20 (SPAM1) hyaluronidase," Hyaluronan (ISHAS) 2007, Charleston, SC. Poster, 1 page.
	PB **	Bookbinder et al., "Enhancing drug transport through temporary matrix depolymerization," Keystone Symposia 2005. (poster and abstract- 13 pages).
	PC **	Bookbinder et al., "Enhancing drug transport through temporary matrix depolymerization," Keystone Symposia 2005, Abstract, 1 page.
	PD **	Bookbinder et al., "Evaluation of the compatibility and pharmacokinetics of co-formulated biologics with recombinant human hyaluronidase: Dose Response," American Association of Pharmaceutical Scientists Conference, November 2006. Abstract, 2 pages.
	PE **	Pinkstaff et al., "Evaluation of the compatibility and pharmacokinetics of co-formulated biologics with recombinant human hyaluronidase: Dose Response," American Association of Pharmaceutical Scientists Conference, November 2006. Poster, 1 page.
	PF **	Byerley et al., "'Cutting out the bull'. Recombinant human hyaluronidase: Moving to an animal-free system," Association of Clinical Embryologists, 2006, Dublin, Ireland. Abstract published in Human Fertility, 9(2):110 (2006).
	PG **	Frost et al., "Punctuated equilibrium: The evolution of recombinant human hyaluronidase," Ophthalmic Anesthesia Society, 2006, Chicago, IL, abstract, 1 page.
	PH **	Frost et al., "Punctuated equilibrium: The evolution of recombinant human hyaluronidase," Ophthalmic Anesthesia Society, 2006, Chicago, IL, presentation, 35 pages.
	PI **	Haller et al., "Enhance technology – a revolution in drug dispersion," Biotechnology Industry Organization (BIO) Annual Meeting, June 19-22, 2005, Philadelphia, PA. Abstract, 3 pages.
	PJ **	Haller et al., "Recombinant human hyaluronidase for the interstitial transport of therapeutics," American Association of Pharmaceutical Scientists Conference, June 2006, San Antonio, TX, Abstract, 2 pages.
	PK **	Haller et al., "Recombinant human hyaluronidase for the interstitial transport of therapeutics," Controlled Release Society Conference, Vienna, Austria, 2006, Abstract, 2 pages.
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	PS **	Hofer et al., "Human recombinant hyaluronidase increases the convection of molecules up to 0.2 µm in athymic nude mice," American Association for Laboratory Animal Science, 2006, Salt Lake City, UT. Abstract published in J. Am. Assoc. Lab. Animal Sci., 45:120, Abstract P97 (2006), 1 page.					
	PT **	Hofer, "Human Recombinant Hyaluronidase Increases the Convection of Molecules up to 0.2 µm in Athymic Nude Mice," American Association for Laboratory Animal Science, 2006, Salt Lake City, UT. Abstract published in J. Am. Assoc. Lab. Animal Sci., 45:120, 2006. Poster P97, 1 page.					
	PU **	Jiang et al., "Effects of Recombinant Human PH20 (rHuPH20) on Interstitial Matrices: Creating a Favorable Environment for The Delivery of Cytostatic Agents," [abstract]. In: Proceedings of the 96th Annual Meeting of the American Association for Cancer Research, 2005 Apr 16-20; Anaheim, CA.:AACR; 2005. Vol. 46, page 1198, Abstract no. 5075, April 2005.					
	PV **	Keller et al., "Pharmacokinetic, pharmacodynamic and toxicologic effects of a recombinant human hyaluronidase (rHuPH20) in rodent and non-human primate models," Hyaluronan (ISHAS) 2007, Charleston, SC, Abstract, 1 page.					
	PW **	Keller et al., "Pharmacokinetic, pharmacodynamic and toxicologic effects of a recombinant human hyaluronidase (rHuPH20) in rodent and non-human primate models," Hyaluronan (ISHAS) 2007, Charleston, SC, Poster and individual panels, 14 pages.					
	PX **	Kodandapani et al., "Diverse structural and functional roles of N-glycosylations on rHuPH20," Glycan Abstract, 1 page (2009).					
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	PZ **	Nadjsombati et al., "Evaluation of developmental and prenatal/postnatal reproduction toxicity of rHuPH20 in mice," American College of Toxicology 30th annual meeting, 2009, November 1-4, Palm Springs, CA, Abstract, 1 page.					
	QA **	Nagy et al., "Prospective, randomized study on bovine and recombinant human (Cumulase®) Hyaluronidases," American Society of Reproductive Medicine, 2006, New Orleans, LA, 06-A-886-ASRM, 2 pages.					
	QB **	Nagy, Z., "Prospective study on rHuPH20," European Society of Human Reproduction & Embryology Annual Meeting, June 19-22, 2005, Copenhagen, Denmark. Abstract O-213, 1 page.					
	QC **	"PEGPH20: The Science & The Strategy," presented at J. P. Morgan Healthcare Conference on Jan. 7, 2015. Presentation. 81 pages.					
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	QD **	Pinkstaff et al., "Recombinant human hyaluronidase for drug and fluid dispersion," American Association of Pharmaceutical Scientists Annual Meeting, November 2006, Boston, MA, Abstract, 2 pages.					
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	QG **	Torley, H., "Halozyne Therapeutics, Inc. The next chapter begins: creating value through growth," Presented at the 32nd Annual J.P. Morgan Healthcare Conference January 2014, 26 pages.					
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	QI **	Wei et al., "Structure function analysis of the human hyaluronidase enzymes," Matrix Biology 27 (Supplement 1):S41, December 2008, American Society for Matrix Biology (ASMB) Biennial Meeting, San Diego, CA, (available on-line November 17, 2008), ABSTRACT 132 (corresponding to poster B4), 2 pages.					
	QJ **	Wei et al., "Structure function analysis of the human hyaluronidase enzymes," Presented at American Society for Matrix Biology Biennial Meeting, San Diego, CA, December 9, 2008, Poster B4 and individual panels, 5 pages.					
	QK **	Wilson, M., "Enhance technology – an enzymatic drug delivery system (DDS)," Japanese Export Trade Organization, November 2005, Santa Clara, CA. Oral presentation, 22 pages.					
	QL **	News Release, "Halozyne Announces Presentation Of Clinical Data At The American Diabetes Association 74th Scientific Sessions," Published on Jun. 15, 2014 [online][retrieved on Aug. 18, 2014] Retrieved from the internet: <URL: .halozyne.com/Investors/News-Releases/News-Release-Details/2014/Halozyne-Announces-Presentation-Of-Clinical-Data-At-The-American-Diabetes-Association-74th-Scientific-Sessions/default.aspx [3 pages].					
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	QO **	News Release, "Bristol, Roche tap Halozyne for tech platform," Published Sept. 14, 2017 [online] Retrieved from:<URL: biopharmadive.com/news/bristol-roche-tap-halozyne-for-tech-platform/504958/ [retrieved on Sept. 18, 2017], 3 pages.					
	QP **	News Article, "Alteogen Inc. to Develop Herceptin Biosimilar for Subcutaneous Injection," Published on Aug. 23, 2018 [online] Retrieved from: <URL:thebell.co.kr/free/Content/ArticleView.asp?key=201808220100037100002360 [Original document retrieved from the internet and English translation], 4 pages.					
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	QR **	News Release, Halozyme Therapeutics, Inc., "Halozyme Publication In The Journal Clinical Cancer Research Highlights New Nonclinical Data Supporting Multiple Effects Of PEGPH20 On The Tumor Microenvironment," Published Oct. 04, 2018 [online] Retrieved from: <URL: halozyme.com/investors/news-releases/news-release-details/2018/Halozyme-Publication-In-The-Journal-Clinical-Cancer-Research-Highlights-New-Nonclinical-Data-Supporting-Multiple-Effects-Of-PEGPH20-On-The-Tumor-Microenvironment/default.aspx [retrieved on Oct. 5, 2018], 4 pages.					
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	QY **	Partial International Search Report, sent by facsimile Sept. 9, 2013, in connection with International Patent Application No. PCT/US2012/072182, 6 pages.					
	QZ **	International Search Report and Written Opinion, mailed Dec. 17, 2013, in connection with International Patent Application No. PCT/US2012/072182, 18 pages.					
	RA **	Response, dated March 17, 2014, to Written Opinion, mailed Dec. 17, 2013, in connection with International Patent Application No. PCT/US2012/072182, 94 pages.					
	RB **	Second Written Opinion, mailed May 21, 2014, in connection with International Patent Application No. PCT/US2012/072182, 8 pages.					
	RC **	Response, dated July 21, 2014, to second Written Opinion, mailed May 21, 2014, in connection with International Patent Application No. PCT/US2012/072182, 72 pages.					
	RD **	Second Written Opinion, mailed Jul. 30, 2014, in connection with International Patent Application No. PCT/US2012/072182, 9 pages.					
	RE **	Response, dated Sept. 1, 2014, to second Written Opinion, mailed Jul. 30, 2014, in connection with International Patent Application No. PCT/US2012/072182, 13 pages					
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	RF **	International Preliminary Report on Patentability, mailed Sept. 12, 2014, in connection with International Patent Application No. PCT/US2012/072182, 11 pages.					
	RG **	Office Action, mailed November 2, 2015, in connection with U.S. Patent Application Serial No. 13/694,731, 14 pages.					
	RH **	Response, filed Apr. 20, 2016, to Office Action, mailed Nov. 2, 2015, in connection with U.S. Patent Application Serial No. 13/694,731, 43 pages.					
	RI **	Notice of Allowance, mailed May 20, 2016, in connection with U.S. Patent Application Serial No. 13/694,731, 16 pages.					
	RJ	Office Action, issued May 15, 2019, in connection with U.S. Patent Application No. 15/226,489, 16 pages.					
	RK	Response, filed Oct. 15, 2019, to Office Action, issued May 15, 2019, in connection with U.S. Patent Application No. 15/226,489, 30 pages.					
	RL	Office Action, issued Jan. 23, 2020, in connection with U.S. Patent Application No. 15/226,489, 19 pages.					
	RM	Response, filed Apr. 24, 2020, to Office Action, issued Jan. 23, 2020, in connection with U.S. Patent Application No. 15/226,489, 25 pages.					
	RN **	Examination Report, issued Jan. 13, 2017, in connection with Australian Patent Application No. 2012362141, 3 pages.					
	RO **	Response, filed Aug. 14, 2017, to Examination Report, issued Jan. 13, 2017, in connection with Australian Patent Application No. 2012362141, 43 pages.					
	RP **	Notice of Acceptance, dated Sept. 11, 2017, issued in connection with Australian Patent Application No. 2012362141, 3 pages.					
	RQ **	Office Action (claimed deemed allowable), dated Oct. 19, 2018, issued in connection with Australian Patent Application No. 2017245352, 7 pages.					
	RR **	Notice of Acceptance, issued Jul. 17, 2019, in connection with Australian Patent Application No. 2017245352, 3 pages.					
	RS **	Examiner's Report, issued March 1, 2016, in connection with Canadian Patent Application No. 2861919, 7 pages.					
	RT **	Response, filed Jul. 14, 2016, to Examiner's Report, issued Mar. 1, 2016, in connection with Canadian Patent Application No. 2861919, 37 pages.					
	RU **	Examiner's Report, issued Jan. 24, 2017, in connection with Canadian Patent Application No. 2861919, 4 pages.					
	RV **	Response, filed Jul. 24, 2017, to Examiner's Report, issued Jan. 24, 2017, in connection with Canadian Patent Application No. 2861919, 26 pages.					
	RW **	Examiner's Report, issued Jan. 23, 2018, in connection with Canadian Patent Application No. 2861919, 4 pages.					
	RX **	Response, filed Jun. 21, 2018, to Examiner's Report, dated Jan. 23, 2018, issued in connection with Canadian Patent Application No. 2861919, 39 pages.					
	RY **	Notice of Allowance, dated Dec. 12, 2018, issued in connection with Canadian Patent Application No. 2861919, 1 page.					
	RZ **	Office Action, issued May 25, 2015, in connection with Chinese Patent Application No. 201280070954.9 [English language translation and original document in Chinese], 7 pages.					
	SA **	Response, filed Oct. 9, 2015, to Office Action, issued May 25, 2015, in connection with Chinese Patent Application No. 201280070954.9 [English instructions and document as filed in Chinese], 37 pages.					
	SB **	Office Action, issued Feb. 3, 2016, in connection with Chinese Patent Application No. 201280070954.9 [English language translation and original document in Chinese], 6 pages.					
Examiner Signature /SAMUEL W LIU/				Date Considered 06/03/2020			
EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.							

Substitute Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No. 33320.03087.US26/ 3087C	Application No. 16/824,572
List of Patents and Publications for Applicant's Information Disclosure Statement (37 CFR §1.98(b))		Applicant <i>Wei et al.</i>	
		Filing Date March 19, 2020	Group Art Unit 1656

Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig. ID	Document
	SC **	Response, filed Jun. 20, 2016, to Office Action, issued Feb. 3, 2016, in connection with Chinese Patent Application No. 201280070954.9 [English language instructions, document as filed in Chinese and claims, as filed, in English], 58 pages.
	SD **	Office Action, issued Oct. 17, 2016, in connection with Chinese Patent Application No. 201280070954.9 [English language translation and original document in Chinese], 4 pages.
	SE **	Response, filed Dec. 27, 2016, to Office Action, issued Oct. 17, 2016, in connection with Chinese Patent Application No. 201280070954.9 [English language instructions and document as-filed in Chinese], 18 pages.
	SF **	Letter, dated Mar. 15, 2017, reporting Telephonic Interview with Examiner in connection with Chinese Patent Application No. 201280070954.9, 1 page.
	SG **	Response, filed Mar. 23, 2017 to Telephonic Interview with Examiner in connection with Chinese Patent Application No. 201280070954.9, 10 pages.
	SH **	Notice of Granting Patent Right for Invention, issued April 28, 2017, in connection with Chinese Patent Application No. 201280070954.9 [English translation and original document in Chinese], 4 pages.
	SI **	Notice of Allowance, dated Dec. 7, 2017, issued in connection with Eurasian Patent Application No. 201400772 [English letter and original document in Russian], 2 pages.
	SJ **	Response, filed Mar. 3, 2015, to Communication Pursuant to Rules 161(1) and 162 EPC, issued Sept. 4, 2014, in connection with European Patent Application No. 12816624.6, 40 pages.
	SK **	Communication Pursuant to Rule 71(3) (Intention to Grant), issued Apr. 22, 2016, in connection with European Patent Application No. 12816624.6, 5 pages.
	SL **	Extended European Search Report, dated Jan. 12, 2017, issued in connection with European Patent Application No. 16189970.3, 11 pages.
	SM **	Response, filed Aug. 15, 2017, to Extended European Search Report, dated Jan. 12, 2017, issued in connection with European Patent Application No. 16189970.3, 55 pages.
	SN **	Examination Report, dated Sept. 14, 2017, issued in connection with European Patent Application No. 16189970.3, 3 pages.
	SO **	Response, dated Oct. 13, 2017, to Examination Report, dated Sept. 14, 2017, issued in connection with European Patent Application No. 16189970.3, 19 pages.
	SP **	Communication Pursuant to Article 94(3) EPC (claims deemed allowable), dated Feb. 26, 2018, issued in connection with European Patent Application No. 16189970.3, 3 pages.
	SQ **	Response, filed Sept. 10, 2018, to Communication Pursuant to Article 94(3) EPC (claims deemed allowable), issued Feb. 26, 2018, issued in connection with European Patent Application No. 16189970.3, 821 pages.
	SR **	Communication Pursuant to Article 71(3) EPC (Intention to Grant), dated Apr. 08, 2019, issued in connection with European Patent Application No. 16189970.3, 7 pages.
	SS **	Decision to Grant, issued Aug. 22, 2019, in connection with European Patent Application No. 16189970.3, 2 pages.
	ST **	Examination Report, issued Dec. 4, 2018, in connection with Indian Patent Application No. 6272/DELNP/2014, 6 pages.
	SU **	Response, filed Sept. 4, 2019, to Examination Report, issued Dec. 4, 2018, in connection with Indian Patent Application No. 6272/DELNP/2014, 79 pages.
	SV **	Office Action, dated Aug. 3, 2016, in connection with Israeli Patent Application No. 233192 [English language translation], 3 pages.
	SW **	Response, filed Jan. 3, 2017, to Office Action, dated Aug. 3, 2016, in connection with Israeli Patent Application No. 233192 [English language translation], 32 pages.

Examiner Signature /SAMUEL W LIU/	Date Considered 06/03/2020
EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

Substitute Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No. 33320.03087.US26/ 3087C	Application No. 16/824,572
List of Patents and Publications for Applicant's Information Disclosure Statement (37 CFR §1.98(b))		Applicant <i>Wei et al.</i>	
		Filing Date March 19, 2020	Group Art Unit 1656

Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig. ID	Document
	SX **	Office Action, dated Nov. 20, 2017, issued in connection with Israeli Patent Application No. 233192 [English language translation], 2 pages.
	SY **	Response, filed May 21, 2018, to Office Action, dated Nov. 20, 2017, issued in connection with Israeli Patent Application No. 233192 [English language translation], 22 pages.
	SZ **	Office Action (claims deemed allowable), dated Feb. 20, 2019, issued in connection with Israeli Patent Application No. 233192 [English letter reporting Office Action and original document in Hebrew], 5 pages.
	TA **	Official Action, issued Jan. 19, 2016, in connection with Japanese Patent Application No. 2014-550526 [English translation and original document in Japanese], 8 pages.
	TB **	Response, filed Jul. 15, 2016, to Official Action, issued Jan. 19, 2016, in connection with Japanese Patent Application No. 2014-550526 [English instructions and document as filed in Japanese], 138 pages.
	TC **	Decision to Grant, issued Nov. 22, 2016, in connection with Japanese Patent Application No. 2014-550526 [Letter reporting decision to grant and original document in Japanese], 5 pages.
	TD **	Office Action, issued Dec 12, 2017, in connection with Japanese Patent Application No. 2016-247708 [English translation and original document in Japanese], 6 pages.
	TE **	Response, filed May 22, 2018, to Office Action, issued Dec. 12, 2017, in connection with Japanese Patent Application No. 2016-247708 [English instructions with amended claims, documents as-filed in Japanese and English translation of claims as-filed], 90 pages.
	TF **	Decision to Grant, issued Sept. 18, 2018, in connection with Japanese Patent Application No. 2016-247708 [English reporting letter and original document in Japanese], 4 pages.
	TG **	Office Action, dated May 25, 2018, in connection with Mexican Patent Application No. MX/a/2014/007966 [English translation and original document in Spanish], 6 pages.
	TH **	Response, filed Oct. 10, 2018, to Office Action, dated May 25, 2018, in connection with Mexican Patent Application No. MX/a/2014/007966 [English instructions and document as-filed in Spanish], 13 pages.
	TI **	Notice of Allowance, issued Oct. 18, 2018, in connection with Mexican Patent Application No. MX/a/2014/007966 [English reporting letter and original document in Spanish], 4 pages.
	TJ **	Examination Report, dated Mar. 26, 2015, in connection with New Zealand Patent Application No. 626126, 32 pages.
	TK **	Response, dated May 16, 2016, to Examination Report, dated Mar. 26, 2015, in connection with New Zealand Patent Application No. 626126, 70 pages.
	TL **	Notice of Acceptance, dated Jun. 8, 2016, in connection with New Zealand Patent Application No. 626126, 1 page.
	TM **	Letters Patent, issued Sept. 27, 2016, in connection with New Zealand Patent No. 626126, 1 page.
	TN **	Examination Report, dated Jul. 27, 2017, issued in connection with New Zealand Patent Application No. 720075, 4 pages.
	TO **	Response, filed Feb. 26, 2018, to Examination Report, dated Jul. 27, 2017, issued in connection with New Zealand Patent Application No. 720075, 88 pages.
	TP **	Notice of Acceptance, dated Mar. 10, 2020, issued in connection with New Zealand Patent Application No. 720075, 1 page.
	TQ **	Search Report and Written Opinion, dated Dec. 4, 2015, in connection with Singaporean Patent Application No. 11201403714T, 7 pages.
	TR **	Response, filed May 23, 2016, to Search Report and Written Opinion, dated Dec. 4, 2015, in connection with Singaporean Patent Application No. 11201403714T, 21 pages.

Examiner Signature /SAMUEL W LIU/	Date Considered 06/03/2020
EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

Substitute Form PTO-1449 (Modified)		U.S. Department of Commerce Patent and Trademark Office		Attorney Docket No. 33320.03087.US26/ 3087C		Application No. 16/824,572	
List of Patents and Publications for Applicant's Information Disclosure Statement (37 CFR §1.98(b))				Applicant <i>Wei et al.</i>			
				Filing Date March 19, 2020		Group Art Unit 1656	
Other Documents (include Author, Title, Date, and Place of Publication)							
Examiner Initial	Desig. ID	Document					
	TS **	Written Opinion, dated Sept. 18, 2017, in connection with Singapore Patent Application No. 11201403714T, 9 pages.					
	TT **	Response, filed Oct. 27, 2017, to Written Opinion, dated Sept. 18, 2017, in connection with Singapore Patent Application No. 11201403714T, 6 pages.					
	TU **	Corrected Notice of Eligibility for Grant and Examination Report, dated Jul. 02, 2018, in connection with Singapore Patent Application No. 11201403714T, 8 pages.					
	TV **	Certificate of Grant, dated Oct. 3, 2018, in connection with Singapore Patent Application No. 11201403714T [Grant Certificate and Granted Claims], 6 pages.					
	TW **	Search Report and Written Opinion, issued Oct. 20, 2017, in connection with Singapore Patent Application No. 10201604470T, 14 pages.					
	TX **	Response, filed Mar. 20, 2018, to Search Report and Written Opinion, issued Oct. 20, 2017, in connection with Singapore Patent Application No. 10201604470T [Response, replacement specification pages, amended claims and cited document], 105 pages.					
	TY **	Examination Report, dated Aug. 6, 2018, and Notice of Eligibility for Grant, dated Aug. 7, 2018, issued in connection with Singapore Patent Application No. 10201604470T, 6 pages.					
	TZ **	English translation of Official Action, issued Mar. 20, 2020, in connection with Korean Application No. 10-2020-7002955.					
** = Copies not provided herewith as they have been previously provided in connection with U.S. Serial No. 13/694,731 and/or 15/226,489 which are relied upon for an earlier filing date in accordance with 35 U.S.C. §120.							

Examiner Signature /SAMUEL W LIU/	Date Considered 06/03/2020
EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

WEST Search History for Application 16824572

Creation Date: 2020102217:02

Prior Art Searches

Query	DB	Hits	Op.	Plur.	Thes.	Date
Ge-wei.in. or shepard-H-Michael.in. or Zhao-qiping.in. or James-Robert.in. and PH20 polypeptide	PGPB, USPT, USOC	109	ADJ	YES		10-22-2020
(PH20 (protein or polypeptide) or hyaluronidase or Ec 3.2.1.35) and (replacement or substitute\$3)	PGPB, USPT, USOC	14677	ADJ	YES		10-22-2020
((PH20 (protein or polypeptide) or hyaluronidase or Ec 3.2.1.35) and (replacement or substitute\$3)) and (amino acid or residue or position) with (replacement or substitute\$3) with 313	PGPB, USPT, USOC	n/a	ADJ	YES		10-22-2020
((PH20 (protein or polypeptide) or hyaluronidase or Ec 3.2.1.35) and (replacement or substitute\$3)) and (amino acid or residue or position) with (replacement or substitute\$3) with 313	PGPB, USPT, USOC	10	ADJ	YES		10-22-2020
((PH20 (protein or polypeptide) or hyaluronidase or Ec 3.2.1.35) and (replacement or substitute\$3) and (amino acid or residue or position) with (replacement or substitute\$3) with 313) and signal near1 (sequence or peptide)	PGPB, USPT, USOC	10	ADJ	YES		10-22-2020
((PH20 (protein or polypeptide) or hyaluronidase or Ec 3.2.1.35) and (replacement or substitute\$3) and (amino acid or residue or position) with (replacement or substitute\$3) with 313 and signal near1 (sequence or peptide)) an (fusion or chimeric)	PGPB, USPT, USOC	10	ADJ	YES		10-22-2020
((PH20 (protein or polypeptide) or hyaluronidase or Ec 3.2.1.35) and (replacement or substitute\$3) and (amino acid or residue or position) with (replacement or substitute\$3) with 313 and signal near1 (sequence or peptide)) and (fusion or chimer\$3)	PGPB, USPT, USOC	10	ADJ	YES		10-22-2020
((PH20 (protein or polypeptide) or hyaluronidase or Ec 3.2.1.35) and (replacement	PGPB, USPT,	7	ADJ	YES		10-22-2020

or substitute\$3) and (amino acid or residue or position) with (replacement or substitute\$3) with 313 and signal near1 (sequence or peptide) and (fusion or chimer\$3)) and (fusion or chimer\$3) with PH20	USOC					
and (recombinant or engineered or modified) with PH20	PGPB, USPT, USOC	7	ADJ	YES		10-22-2020
((PH20 (protein or polypeptide) or hyaluronidase or Ec 3.2.1.35) and (replacement or substitute\$3) and (amino acid or residue or position) with (replacement or substitute\$3) with 313 and signal near1 (sequence or peptide) and (fusion or chimer\$3)) and (recombinant or engineered or modified) with PH20	PGPB, USPT, USOC	9	ADJ	YES		10-22-2020



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
 Address: COMMISSIONER FOR PATENTS
 P.O. Box 1450
 Alexandria, Virginia 22313-1450
 www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 1431

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.		
16/824,572	03/19/2020	435	1656	33320.03087.US26/3087C		
APPLICANTS HALOZYME, INC., San Diego, CA; INVENTORS Ge WEI, San Diego, CA; H. Michael Shepard, San Diego, CA; Qiping Zhao, San Diego, CA; Robert James Connor, Oceanside, CA; ** CONTINUING DATA ***** This application is a CON of 15/226,489 08/02/2016 which is a DIV of 13/694,731 12/28/2012 PAT 9447401 which claims benefit of 61/796,208 11/01/2012 and claims benefit of 61/631,313 12/30/2011 This application 16/824,572 03/19/2020 is a DIV of 13/694,731 12/28/2012 PAT 9447401 which claims benefit of 61/796,208 11/01/2012 and claims benefit of 61/631,313 12/30/2011 ** FOREIGN APPLICATIONS ***** ** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** 05/01/2020						
Foreign Priority claimed ☐ Yes ☒ No 35 USC 119(a-d) conditions met ☐ Yes ☒ No Verified and /SAMUEL W LIU/ Acknowledged Examiner's Signature		☐ Met after Allowance Initials	STATE OR COUNTRY CA	SHEETS DRAWINGS 13	TOTAL CLAIMS 21	INDEPENDENT CLAIMS 2
ADDRESS Dentons US LLP 4655 Executive Drive Suite 700 San Diego, CA 92121 UNITED STATES						
TITLE PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF						
FILING FEE RECEIVED 3420	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:			☐ All Fees		
				☐ 1.16 Fees (Filing)		
				☐ 1.17 Fees (Processing Ext. of time)		
				☐ 1.18 Fees (Issue)		
				☐ Other _____		
				☐ Credit		

Substitute Form PTO-1449 (Modified)		U.S. Department of Commerce Patent and Trademark Office		Attorney Docket No. 33320.03087.US26/ 3087C		Application No. 16/824,572	
List of Patents and Publications for Applicant's Information Disclosure Statement (37 CFR §1.98(b))				Inventor(s) Wei <i>et al.</i>			
				Filing Date March 19, 2020		Group Art Unit 1656	
U.S. Patent Documents							
Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
None							

Foreign Patent Documents or Published Foreign Patent Applications						
Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Translation	
					Yes	No
None						

Other Documents (include Author, Title, Date, and Place of Publication)		
Examiner Initial	Desig. ID	Document
	AA	Letter/Written Disclosure of the Information Disclosure Statement for the above-referenced application, filed herewith on August 24, 2020, 2 pages.
	AB	Notice of Allowance, issued Jul. 16, 2020, in connection with U.S. Patent Application No. 15/226,489, 13 pages.
	AC	Hearing Notice, issued Jun. 17, 2020, in connection with Indian Patent Application No. 6272/DELNP/2014, 2 pages.

Examiner Signature	/SAMUEL W LIU/	Date Considered	10/21/2020
EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.			

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Wei *et al.* Art Unit : 1656
Serial No. : 16/824,572 Examiner : Not Yet Assigned
Filed : March 19, 2020 Conf. No. : 1431
Cust. No. : 13565
Title : **PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES
THEREOF**

Mail Stop Amendment

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**INFORMATION DISCLOSURE STATEMENT IN
ACCORDANCE WITH 37 C.F.R. §§ 1.97-1.98**

Dear Sir:

Because this Information Disclosure Statement is filed before the receipt of a First Office Action on the Merits for the above-captioned application, a fee is not required.

However, should it be determined that a fee for filing these papers is required, the Commissioner is authorized to charge Deposit Account No. 50-0911.

In accordance with the duty of disclosure imposed by 37 C.F.R. § 1.56 to inform the Patent Office of all information known by Applicant or Applicant's representative that may be material to the examination of the subject application, Applicant's representative hereby provides this Information Disclosure Statement that is prepared in accordance with 37 C.F.R. §§ 1.97-1.98. Forms PTO-1449 (24 pages) and copies of the cited non-U.S. patent documents are provided herewith in connection with the above-captioned application. In accordance with 37 C.F.R. § 1.98(d), copies of the references listed on the Forms PTO-1449 that are marked with a double asterisk (**) are not provided herewith as they have been previously provided in connection with U.S. Application Serial No. 13/694,731 and/or 15/226,489, which are relied upon for an earlier filing date in accordance with 35 U.S.C. § 120.

The documents cited on the Forms PTO-1449 are in the English language, with the exception of the items noted below. Item FP (CN 102065886A) is in the Chinese language and an English language equivalent (Item GD, WO 2009/128917) was previously provided in connection with U.S. Application Serial No. 13/694,731. Item FU (JP 2007-153797) is in the Japanese language and an English Derwent Abstract (Item HY) for Japanese Publication No. JP 2007-153797 was previously provided in connection with U.S. Application Serial No.

CERTIFICATE OF TRANSMISSION VIA EFS-WEB

I hereby certify that this paper is being transmitted via the Electronic Filing System (EFS-WEB) to the United States Patent and Trademark Office on May 15, 2020.

/Hyun Jeung Ji/
Hyun Jeung Ji

/SAMUEL W LIU/

10/21/2020

Applicant : Wei *et al.*
Serial No. : 16/824,572
Filed : March 19, 2020

Attorney Docket No.: 33320.03087.US26/3087C
Information Disclosure Statement

13/694,731. Item FV (KR 10-2020-0017538) is in the Korean language and a machine generated English translation was previously provided in connection with U.S. Application Serial No. 15/226,489. Hence, in accordance with the requirements of 37 C.F.R. § 1.98, no further explanation of the listed items is necessary.

Applicant also makes known to the Examiner the following pending U.S. Applications that have one or more common inventors and/or an owner in common:

	U.S.S.N.	Filing Date	Publ. No.	Publ. Date	Docket No.	
/S.W.L/	16/373,562	04/02/2019	2019-0224286	7/25/2019	3051L	10/21/2020
/S.W.L/	15/444,151	02/27/2017	2017/0218069 2018/0044419	08/03/2017 02/15/2018	3087B	10/21/2020

Although these documents and applications are made known to the Patent and Trademark Office in compliance with Applicant's duty of disclosure, such disclosure is not to be construed as an admission by Applicant or Applicant's representative that any of the documents, singly or in any combination thereof, is effective as prior art against the subject application. In accordance with 37 C.F.R. § 1.97(g) and (h), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 C.F.R. § 1.56(b) exists.

Applicant respectfully requests that the Examiner review the foregoing documents and they be made of record in the file history of the above-captioned application.

Respectfully submitted,

/Stephanie Seidman/
Stephanie Seidman
Reg. No. 33,779

Attorney Docket No.: 33320.03087.US26/3087C
Address all correspondence to: 13565
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email: stephanie.seidman@dentons.com

/SAMUEL W LIU/

10/21/2020

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875				Application or Docket Number 16/824,572		Filing Date 03/19/2020		☐ To be Mailed		
ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO										
APPLICATION AS FILED - PART I										
		(Column 1)		(Column 2)						
FOR		NUMBER FILED		NUMBER EXTRA		RATE (\$)		FEE (\$)		
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))		N/A		N/A		N/A				
☐ SEARCH FEE (37 CFR 1.16(k), (l), or (m))		N/A		N/A		N/A				
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))		N/A		N/A		N/A				
TOTAL CLAIMS (37 CFR 1.16(i))		minus 20 = *				x \$100 =				
INDEPENDENT CLAIMS (37 CFR 1.16(h))		minus 3 = *				x \$460 =				
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))		If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).								
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))										
* If the difference in column 1 is less than zero, enter "0" in column 2.						TOTAL				
APPLICATION AS AMENDED - PART II										
		(Column 1)		(Column 2)		(Column 3)				
AMENDMENT	01/27/2021		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR		PRESENT EXTRA		RATE (\$)	ADDITIONAL FEE (\$)
	Total (37 CFR 1.16(i))		* 18	Minus	** 20	= 0			x \$100 =	0
	Independent (37 CFR 1.16(h))		* 2	Minus	*** 3	= 0			x \$480 =	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))									
								TOTAL ADD'L FEE		0
AMENDMENT			CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR		PRESENT EXTRA		RATE (\$)	ADDITIONAL FEE (\$)
	Total (37 CFR 1.16(i))		*	Minus	**	=			x \$0 =	
	Independent (37 CFR 1.16(h))		*	Minus	***	=			x \$0 =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))									
								TOTAL ADD'L FEE		
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.								SLIE		
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".								/DEIDRE C KING-WOODWARD/		
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".										
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Doc Code: DIST.E.FILE Document Description: Electronic Terminal Disclaimer - Filed		PTO/SB/26 U.S. Patent and Trademark Office Department of Commerce
Electronic Petition Request	TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	
Application Number	16824572	
Filing Date	19-Mar-2020	
First Named Inventor	Ge WEI	
Attorney Docket Number	33320.03087.US26/3087C	
Title of Invention	PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF	
☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action ☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.		
Owner	Percent Interest	
HALOZYME, INC.	100%	
<p>The owner(s) with percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent number(s)</p> <p>10865400</p> <p>as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.</p> <p>In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:</p> <ul style="list-style-type: none"> - expires for failure to pay a maintenance fee; - is held unenforceable; - is found invalid by a court of competent jurisdiction; - is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321; - has all claims canceled by a reexamination certificate; - is reissued; or - is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer. <p>☒ Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.</p>		

☐ I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.	
Applicant claims the following fee status:	
☐ Small Entity ☐ Micro Entity ☒ Regular Undiscounted	
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 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.	
THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES I certify, in accordance with 37 CFR 1.4(d)(4) that I am:	
☒ An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application Registration Number <u>33779</u>	
☐ A sole inventor ☐ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application ☐ A joint inventor; all of whom are signing this request	
Signature	/Stephanie Seidman/
Name	Stephanie Seidman

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
 Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal				
Application Number:		16824572		
Filing Date:		19-Mar-2020		
Title of Invention:		PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF		
First Named Inventor/Applicant Name:		Ge WEI		
Filer:		Stephanie L. Seidman/Rosalind Smith		
Attorney Docket Number:		33320.03087.US26/3087C		
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	170	170
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				170

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 16824572

Filing Date: 19-Mar-2020

Applicant/Patent under Reexamination: WEI

Electronic Terminal Disclaimer filed on January 27, 2021

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This patent is subject to a terminal disclaimer

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Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt	
EFS ID:	41739384
Application Number:	16824572
International Application Number:	
Confirmation Number:	1431
Title of Invention:	PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF
First Named Inventor/Applicant Name:	Ge WEI
Customer Number:	13565
Filer:	Stephanie L. Seidman/Rosalind Smith
Filer Authorized By:	Stephanie L. Seidman
Attorney Docket Number:	33320.03087.US26/3087C
Receipt Date:	27-JAN-2021
Filing Date:	19-MAR-2020
Time Stamp:	18:09:12
Application Type:	Utility under 35 USC 111(a)

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Payment Type	DA
Payment was successfully received in RAM	\$170
RAM confirmation Number	E20211QI09098116
Deposit Account	500911
Authorized User	Rosalind Smith
<p>The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:</p> <p>37 CFR 1.16 (National application filing, search, and examination fees)</p> <p>37 CFR 1.17 (Patent application and reexamination processing fees)</p>	

37 CFR 1.19 (Document supply fees)
 37 CFR 1.20 (Post Issuance fees)
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Terminal Disclaimer-Filed (Electronic)	eTerminal-Disclaimer.pdf	33571	no	2
			1aa194832c13e9c81794f8c932e3c5952d0069d7		

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30486	no	2
			8f398aabe1d9dbab87fd71f3200ed2eae91059eb		

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If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s)	: Wei <i>et al.</i>	Art Unit	: 1656
Serial No.	: 16/824,572	Examiner	: Liu, Samuel W.
Filed	: March 19, 2020	Conf. No.	: 1431
		Cust. No.	: 13565
Title	: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF		

Mail Stop Amendment

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE

Dear Sir:

Responsive to the Office Action, mailed October 27, 2020, entry of the following amendments, and consideration of the following remarks, respectfully are requested

Amendments to the Specification begin on page **2** of this paper.

Amendments to the Claims begin on page **9** of this paper.

Remarks/Arguments begin on page **12** of this paper.

CERTIFICATE OF TRANSMISSION VIA EFS-WEB

I hereby certify that this paper is being transmitted via the Electronic Filing System (EFS-WEB) to the United States Patent and Trademark Office on **January 27, 2021**.

/Jimmy Schaub/
Jimmy Schaub

Inventor(s) : Wei *et al.*
Serial No. : 16/824,572
Filed : March 19, 2020

Attorney Docket No.: 33320.03087.US26/ 3087C
Amendment and Response

AMENDMENTS TO THE SPECIFICATION:

Page and line numbers are designated with reference to the specification as originally filed, on March 19, 2020. Please amend the specification as follows:

Replace the paragraph beginning at page 1, line 33, with the following amended paragraph:

Hyaluronan (hyaluronic acid; HA) is a polypeptide that is found in the extracellular matrix of many cells, especially in soft connective tissues. HA also is found predominantly in skin, cartilage, and in synovial fluid in mammals. Hyaluronan also is the main constituent of the vitreous of the eye. HA has a role in various physiological processes, such as in water and plasma protein homeostasis (Laurent TC *et al.* (1992) *FASEB J* 6: 2397-2404). Certain diseases are associated with expression and/or production of hyaluronan. Hyaluronan-degrading enzymes, such as hyaluronidases, are enzymes that degrade hyaluronan. By catalyzing HA degradation, hyaluronan-degrading enzymes (*e.g.*, hyaluronidases) can be used to treat diseases or disorders associated with accumulation of HA or other glycosaminoglycans. Also, since HA is a major component of the interstitial barrier, hyaluronan-degrading enzymes (*e.g.*, hyaluronidase) increase tissue permeability and therefore can be used to increase the dispersion and delivery of therapeutic agents. Various hyaluronidases have been used therapeutically (*e.g.*, hyaluronidases sold under the trademarks Hydase[®][[TM]](bovine testicular hyaluronidase), Vitrase[®][[TM]] (ovine hyaluronidase), and Wydase[®][[TM]](bovine hyaluronidase)), typically as dispersing and spreading agents in combination with other therapeutic agents. Many of these are ovine or bovine forms, which can be immunogenic for treatment of humans. Improved hyaluronan-degrading enzymes, such as hyaluronidases, and compositions thereof that can be used for treatment are needed.

Replace the paragraph beginning at page 52, line 28, with the following amended paragraph:

As used herein, soluble human PH20 (sHuPH20) includes human PH20 polypeptides that lack a contiguous sequence of amino acids from the C-terminus of human PH20 that includes all or a portion of the glycosylphosphatidylinositol (GPI) anchor sequence (C-terminally truncated PH20 polypeptides) such that upon expression, the polypeptides are soluble under physiological conditions. For example, soluble human PH20 polypeptides are C-terminally truncated polypeptides of human PH20 set forth as SEQ ID NO:6 in its precursor form or in SEQ ID NO:7 in its mature form lacking the signal sequence, or allelic variants thereof (*e.g.* set forth in any of SEQ ID NOS: 68-72). Solubility can be assessed by any

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suitable method that demonstrates solubility under physiologic conditions. Exemplary of such methods is the Triton® X-114 assay, that assesses partitioning into the aqueous phase and that is described above. In addition, a soluble human PH20 polypeptide is, if produced in CHO cells, such as CHO-S cells, a polypeptide that is expressed and is secreted into the cell culture medium. Soluble human PH20 polypeptides, however, are not limited to those produced in CHO cells, but can be produced in any cell or by any method, including recombinant expression and polypeptide synthesis. Reference to secretion in CHO cells is definitional. Hence, if a polypeptide could be expressed and secreted in CHO cells and is soluble in the media, *i.e.*, partitions into the aqueous phase when extracted with Triton® X-114 detergent, it is a soluble PH20 polypeptide whether or not it is so-produced. The precursor polypeptides for sHuPH20 polypeptides can include a signal sequence, such as a heterologous or non-heterologous (*i.e.*, native) signal sequence. Exemplary of the precursors are those that include a signal sequence, such as the native 35 amino acid signal sequence at amino acid positions 1-35 (see, *e.g.*, amino acids 1-35 of SEQ ID NO:6).

Replace the paragraph beginning at page 75, line 25, with the following amended paragraph:

As used herein, “fast-acting insulin” refers to any insulin that exhibits peak insulin levels at or about not more than four hours following subcutaneous administration to a subject. Fast-acting insulins include any insulin or any fast-acting insulin composition for acute administration to a diabetic subject in response to an actual, perceived, or anticipated hyperglycemic condition in the subject arising at the time of, or within about four hours following, administration of the fast-acting insulin (such as a prandial hyperglycemic condition resulting or anticipated to result from, consumption of a meal), whereby the fast-acting insulin is able to prevent, control or ameliorate the acute hyperglycemic condition. Fast-acting insulins include recombinant insulins and isolated insulins (also referred to as “regular” insulins) such as the insulin sold as human insulin, porcine insulins and bovine insulins, as well as rapid acting insulin analogs (also termed fast-acting insulin analogs herein) designed to be rapid acting by virtue of amino acid changes. Exemplary regular insulin preparations include, but are not limited to, human regular insulins, such as those sold under the trademarks Humulin® R, Novolin® R and Velosulin®, Insulin Human, USP and Insulin Human Injection, USP, as well as acid formulations of insulin, such as, for example, Toronto Insulin, Old Insulin, and Clear Insulin, and regular pig insulins, such as Iletin II® insulin (porcine insulin).

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Regular insulins typically have an onset of action of between 30 minutes to an hour, and a peak insulin level of 2-5 hours post administration.

Replace the paragraph beginning at page 84, line 32, with the following amended paragraph:

PH20 can exist in membrane-bound or membrane-associated form, or can be secreted into the media when expressed from cells, and thereby can exist in soluble form. Soluble PH20 can be detected and discriminated from insoluble, membrane-bound PH20 using methods well known in the art, including, but not limited to, those using a Triton® X-114 assay. In this assay, soluble PH20 hyaluronidases partition into the aqueous phase of a Triton® X-114 detergent solution warmed to 37 °C (Bordier *et al.*, (1981) J. Biol. Chem., 256:1604-7) while membrane-anchored PH20 hyaluronidases partition into the detergent rich phase. Thus, in addition to using algorithms to assess whether a PH20 polypeptide is naturally GPI-anchored and hence membrane-bound, solubility experiments also can be performed.

Replace the paragraph beginning at page 85, line 4, with the following amended paragraph:

Soluble PH20 enzymes include hyaluronidases that contain a GPI-anchor attachment signal sequence, but that are loosely attached to the membrane such that they do not contain a phospholipase sensitive anchor. For example, soluble PH20 polypeptides include ovine or bovine PH20. Various forms of such soluble PH20 hyaluronidases have been prepared and approved for therapeutic use in subjects, including humans. For example, animal-derived hyaluronidase preparations include Vitrase® hyaluronidase (ISTA Pharmaceuticals), which is a purified ovine testicular hyaluronidase, and Amphadase® hyaluronidase (Amphastar Pharmaceuticals), which is a bovine testicular hyaluronidase. Soluble PH20 enzymes also include truncated forms of non-human or human membrane-associated PH20 hyaluronidases that lack one or more amino acid residues of a glycosylphosphatidylinositol (GPI) anchor attachment signal sequence and that retain hyaluronidase activity (see *e.g.*, U.S. Patent No. 7,767,429; U.S. Publication No. US20100143457). Thus, instead of having a GPI-anchor covalently attached to the C-terminus of the protein in the ER and being anchored to the extracellular leaflet of the plasma membrane, these polypeptides are secreted when expressed from cells and are soluble. In instances where the soluble hyaluronan degrading enzyme retains a portion of the GPI anchor attachment signal sequence, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more amino acid residues in the GPI-anchor attachment signal sequence can be retained, provided the polypeptide is soluble (*i.e.*, secreted when expressed from cells) and active.

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Replace the paragraph beginning at page 86, line 23, with the following amended paragraph:

In particular, a soluble human PH20 polypeptide is a polypeptide that is truncated after amino acid 482 of the sequence set forth in SEQ ID NO:6. Such a polypeptide can be generated from a nucleic acid molecule containing a signal sequence and encoding amino acids 36-482, for example, as set forth in SEQ ID NO:1 (containing an IgG kappa signal sequence) or SEQ ID NO:67 (containing the native signal sequence). Post translational processing removes the signal sequence, leaving a 447 amino acid soluble recombinant human PH20 (SEQ ID NO:3). A product produced upon expression of a vector set forth in SEQ ID NO:4 or 5, and containing a nucleic acid molecule set forth in SEQ ID NO:67, results in a secreted product, designated rHuPH20, in the culture medium that exhibits heterogeneity at the C-terminus such that the product includes a mixture of species that can include any one or more of SEQ ID NOS: 3 and 44-48 in various abundance. Typically, rHuPH20 is produced in cells that facilitate correct N-glycosylation to retain activity, such as mammalian cells, for example CHO cells (*e.g.*, DG44 CHO cells). Hylenex® hyaluronidase (Halozyme) is a human recombinant hyaluronidase produced by genetically engineered Chinese Hamster Ovary (CHO) cells containing nucleic acid encoding a truncated human PH20 polypeptide (designated rHuPH20).

Replace the paragraph beginning at page 174, line 15, with the following amended paragraph:

Single dose formulations of PH20 are known in the art. For example, Hylenex® recombinant hyaluronidase (hyaluronidase human injection) contains, per mL, 8.5 mg NaCl (145 mM), 1.4 mg dibasic sodium phosphate (9.9 mM), 1.0 mg human albumin, 0.9 mg edetate disodium (2.4 mM), 0.3 mg CaCl₂ (2.7 mM) and NaOH to adjust the pH to 7.4. Other formulations of human soluble hyaluronidase, such as the rHuPH20 formulations described in U.S. Pat. Pub. No. US2011/0053247, include 130 mM NaCl, 10 mM Hepes, pH 7.0; or 10 mM histidine, 130 mM NaCl, pH 6.0. Any of the modified PH20 polypeptides provided herein can be similarly formulated.

Replace the paragraph beginning at page 179, line 1, with the following amended paragraph:

In particular examples herein, the formulations contain one or more detergents, such as surfactants, to maintain the stability of the active agent(s) (*e.g.*, PH20 hyaluronidase). For example, surfactants can inhibit aggregation of PH20 and minimize absorptive loss. The

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surfactants generally are non-ionic surfactants. Surfactants that can be included in the formulations herein include, but are not limited to, partial and fatty acid esters and ethers of polyhydric alcohols such as of glycerol, or sorbitol, poloxamers and polysorbates. For example, exemplary surfactants in the -formulations herein include any one or more of poloxamer 188 (PLURONICS® poloxamer such as PLURONIC® F68 poloxamer), TETRONICS® surfactant, polysorbate 20, polysorbate 80, PEG 400, PEG 3000, Tween® surfactant (e.g., Tween® 20 or Tween® 80 surfactants), Triton® X-100 surfactant, SPAN® surfactant, MYRJ® surfactant, BRIJ® surfactant, CREMOPHOR® surfactant, polypropylene glycols or polyethylene glycols. In some examples, the formulations herein contain poloxamer 188, polysorbate 20, polysorbate 80, generally poloxamer 188 (pluronic F68). The formulations provided herein generally contain at least one surfactant, such as 1, 2 or 3 surfactants.

Replace the paragraph beginning at page 196, line 14, with the following amended paragraph:

The solubility of a PH20 polypeptide can be determined by any method known to one of the skill in the art. One method for determining solubility is detergent partitioning. For example, a soluble PH20 polypeptide can be distinguished, for example, by its partitioning into the aqueous phase of a Triton® X-114 detergent solution at 37 °C (Bordier et al., (1981) *J. Biol. Chem.*, 256:1604-1607). Membrane-anchored polypeptides, such as lipid-anchored hyaluronidases, including GPI-anchored hyaluronidases, will partition into the detergent-rich phase, but will partition into the detergent-poor or aqueous phase following treatment with Phospholipase C. Phospholipase C is an enzyme that cleaves the phospho-glycerol bond found in GPI-anchored proteins. Treatment with PLC will cause release of GPI-linked proteins from the outer cell membrane.

Replace the paragraph beginning at page 198, line 20, with the following amended paragraph:

Other methods and uses of a modified PH20 polypeptide include any that are known to one of skill in the art. For example, various forms of PH20 hyaluronidases have been prepared and approved for therapeutic use in humans. For example, animal-derived hyaluronidase preparations include Vitrase® hyaluronidase (ISTA Pharmaceuticals), a purified ovine testicular hyaluronidase, and Amphadase® hyaluronidase (Amphastar Pharmaceuticals), a bovine testicular hyaluronidase. Hylenex® hyaluronidase (Halozyme Therapeutics) is a human recombinant hyaluronidase produced by genetically engineered Chinese Hamster Ovary

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(CHO) cells containing nucleic acid encoding for soluble rHuPH20 (see e.g., U.S. Patent No. 7,767,429). Approved therapeutic uses for hyaluronidases include use as an adjuvant to increase the absorption and dispersion of other therapeutic agents for hypodermoclysis (subcutaneous fluid administration), and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents. In addition to these indications, hyaluronidases can be used as a therapeutic or cosmetic agent for the treatment of additional diseases and conditions. For example, hyaluronidase is commonly used, for example, for peribulbar block in local anesthesia prior ophthalmic surgery. The presence of the enzyme prevents the need for additional blocks and reduces the time to the onset of akinesia (loss of eye movement). Peribulbar and sub-Tenon's block are the most common applications of hyaluronidase for ophthalmic procedures. Hyaluronidase also can promote akinesia in cosmetic surgery, such as blepharoplasties and face lifts. It is understood that soluble PH20 hyaluronidases provided herein, including esPH20 hyaluronidases, can be used in any method of treatment or combination therapy for which a PH20 hyaluronidase is used (see e.g., U.S. Publication Nos. US20040268425; US20050260186; US20060104968; and U.S. Appl. Serial Nos. 12/381,844, published as U.S. Publication No. US20100074885; 12/386,249, published as U.S. Publication No. US20090311237; 12/387,225, published as U.S. Publication No. US20090304665; and 12/386,222, published as U.S. Publication No. US2010003238, each incorporated by reference in their entirety).

Replace the paragraph beginning at page 205, line 19, with the following amended paragraph:

Exemplary antibodies or other therapeutic agents include, but are not limited to, Cetuximab (*e.g.*, IMC-C225; Erbitux®); Trastuzumab (*e.g.*, Herceptin®); Rituximab (*e.g.*, Rituxan®; MabThera®); Bevacizumab (*e.g.*, Avastin®); Alemtuzumab (*e.g.*, Campath®; Campath-1H®; Mabcampath®); Panitumumab (*e.g.*, ABX-EGF; Vectibix®); Ranibizumab (*e.g.*, Lucentis®); Ibritumomab; Ibritumomab tiuxetan (*e.g.*, Zevalin®); Tositumomab; Iodine I 131 Tositumomab (*e.g.*, BEXXAR®); Catumaxomab (*e.g.*, Removab®); Gemtuzumab; Gemtuzumab ozogamicin (*e.g.*, Mylotarg®); Abatacept (*e.g.*, CTLA4-Ig; Orencia®); Belatacept (*e.g.*, L104EA29YIg; LEA29Y; LEA); Ipilimumab (*e.g.*, MDX-010; MDX-101); Tremelimumab (*e.g.*, ticilimumab; CP-675,206); PRS-010 (see *e.g.*, US20090042785); PRS-050 (US7585940; US20090305982); Aflibercept (VEGF Trap, AVE005; Holash *et al.*, (2002) *PNAS* 99:11393-11398); Volociximab (M200); F200 (Chimeric (human/murine) IgG4 Fab fragment of Volociximab (M200)); MORAb-009 Mouse/human chimeric

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IgG1(US20050054048); Soluble fusion protein: Anti-mesothelin Fv linked to a truncated Pseudomonas exotoxin A (SS1P (CAT-5001); US20070189962); Cixutumumab (IMC-A12); Nimotuzumab (h-R3) (Spicer (2005) *Curr Opin Mol Ther* 7:182-191); Zalutumumab (HuMax-EGFR; Lammerts van Bueren *et al.* (2008) *PNAS* 105:6109-14); Necitumumab IMC-11F8 (Li *et al.* (2008) *Structure* 16:216-227); Sym004 (Pedersen *et al.* 2010 *Cancer Res* 70:588-597); and mAb-425.

Replace the paragraph beginning at page 218, line 29, with the following amended paragraph:

The concentrated, diafiltered harvest was inactivated for virus. Prior to viral inactivation, a solution of 10% Triton® X-100 detergent, and 3% tri (n-butyl) phosphate (TNBP) was prepared. The concentrated, diafiltered harvest was exposed to 1% Triton® X-100 detergent, and 0.3% TNBP for 1 hour in a 36 L glass reaction vessel immediately prior to purification on the Q column.

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AMENDMENTS TO THE CLAIMS:

Please amend claims 1, 6, 8, 9, 11, 13 and 20, as follows. This listing of claims replaces all prior versions, and listings of claims, in the application.

LISTING OF CLAIMS:

1. (Currently Amended) A modified PH20 polypeptide, comprising one or more amino acid replacements in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of sequence of amino acids set forth in SEQ ID NOs: 3, 7 and 32-66;

the modified PH20 polypeptide exhibits increased hyaluronidase activity compared to the unmodified PH20 polypeptide not containing the amino acid replacement(s);

the amino acid replacement(s) confer(s) the increased hyaluronidase activity;

the amino acid replacement(s) is at a position corresponding to 313 with reference to amino acid positions ~~of set forth in~~ SEQ ID NO:3, which confers increased hyaluronidase activity;

corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the sequence of amino acids set forth in SEQ ID NO:3; and

the modified PH20 polypeptide has at least 91% sequence identity to the amino acid sequence selected from the group consisting of sequence of amino acids set forth as SEQ ID NOs: 3, 7 ~~and~~ 32-66.

2. (Cancelled)

3. (Original) The modified PH20 polypeptide of claim 1, wherein the replacement is selected from among A at a position corresponding to position 313; G at a position corresponding to position 313; H at a position corresponding to position 313; K at a position corresponding to position 313; P at a position corresponding to position 313; R at a position corresponding to position 313; T at a position corresponding to position 313; and Y at a position corresponding to position 313.

4. (Cancelled)

5. (Original) The modified PH20 polypeptide of claim 3, wherein the replacement at the position corresponding to 313 is K.

6. (Currently Amended) The modified PH20 polypeptide of claim 1, wherein the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of ~~sequence of amino acids set forth in~~ SEQ ID NOs: 3, 7 ~~and~~ 32-66.

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7. (Cancelled)
8. (Currently Amended) The modified PH20 polypeptide of claim 3, wherein the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of ~~sequence of amino acids set forth in~~ SEQ ID NOs: 3, 7 ~~and~~ 32-66.
9. (Currently Amended) The modified PH20 polypeptide of claim 1, wherein the modified PH20 polypeptide has at least 95% sequence identity to the amino acid sequence selected from the group consisting of ~~sequence of amino acids set forth as~~ SEQ ID NOs: 3, 7 ~~and~~ 32-66.
10. (Previously Presented) The modified PH20 polypeptide of claim 1, wherein the modified PH20 polypeptide has at least 95% sequence identity to SEQ ID NO:35.
11. (Currently Amended) The modified PH20 polypeptide of claim 5, wherein the unmodified PH20 polypeptide consists of the amino acid sequence of ~~sequence of amino acids set forth in~~ SEQ ID NO:35.
12. (Original) The modified PH20 polypeptide of claim 1, wherein the modified PH20 polypeptide exhibits increased hyaluronidase activity that is at least 120% of the hyaluronidase activity compared to the unmodified PH20 polypeptide not containing the amino acid replacement or replacements.
13. (Currently Amended) A modified PH20 polypeptide, comprising the amino acid sequence selected from the group consisting of ~~a sequence of amino acids set forth in any of~~ SEQ ID ~~NOs~~ NOS: 591-598, or a sequence of amino acids that exhibits at least 91% sequence identity to a sequence of amino acids set forth in any of SEQ ID ~~NOs~~ NOS: 591-598 and that contains the amino acid replacement at residue 313 compared to corresponding positions in the amino acid sequence selected from the group consisting of ~~a polypeptide of any of~~ SEQ ID ~~NOs~~ NOS: 3 and 32-66.
14. (Original) The modified PH20 polypeptide of claim 1 that comprises one or more of a modification selected from among glycosylation, sialation, albumination, farnesylation, carboxylation, hydroxylation, and phosphorylation.
15. (Original) The modified PH20 polypeptide of claim 1 that comprises an N-acetylglucosamine moiety linked to each of at least three asparagine (N) residues.
16. (Original) The modified PH20 polypeptide of claim 1 that is conjugated to a polymer.
17. (Original) The modified PH20 polypeptide of claim 16, wherein the polymer is dextran or polyethylene glycol (PEG).

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18. (Original) The modified PH20 polypeptide of claim 1, further comprising a heterologous signal sequence.

19. (Original) A chimeric polypeptide comprising the modified PH20 polypeptide of claim 1.

20. (Currently Amended) A pharmaceutical composition, comprising ~~thea~~ modified PH20 polypeptide of claim 1.

21. (Withdrawn) A method of treatment, comprising administering a pharmaceutical composition of claim 20, wherein the method is selected from a method that treats an excess of glycosaminoglycans; a tumor; glycosaminoglycan accumulation in the brain; a cardiovascular disorder; an ophthalmic disorder; pulmonary disease or edema; and a method of increasing delivery of therapeutic agents.

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REMARKS

Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 50-0911. If a Petition for Extension of Time is needed, this paper is to be considered such Petition.

A Supplemental Information Disclosure Statement is filed under separate cover.

Claims 1, 3, 5, 6 and 8-21 are pending. Claims 1, 3, 5, 6 and 8-20 have been examined. Claim 21, which is withdrawn from consideration as drawn to non-elected subject matter, is retained for possible joinder upon allowance of the product claims on which it depends. Claims 1, 6, 8, 9, 11, 13 and 20 are amended to address the Examiner's objections. Claims 6 and 8 also are amended to delete reference to SEQ ID NO: 7. No new matter is added.

OBJECTIONS TO THE SPECIFICATION

Use of Trademarks

The Examiner states that the trademarks Hydase™, Vitrase™ and Wydase™ referenced in the specification, at page 2, line 1, should be capitalized and accompanied by the generic terminology. Applicant respectfully submits that the use of trademarks in the specification generally is in compliance with the Office's policies regarding such use. The use of trademarks in patent applications is addressed in the Manual of Patent Examining Procedures (MPEP), §608.01(v), "Marks Used in Commerce and Trade Names." As the cited section describes (*see* Part II, "Proprietary Nature of Marks Used in Commerce," (emphasis added)):

Marks should be identified by capitalizing each letter of the mark (in the case of word or letter marks) *or otherwise indicating the description of the mark (in the case of marks in the form of a symbol or device or other nontextual form)*

This is borne out in form paragraph 6.20 recited in the cited section, which provides the following Examiner Note (emphasis added):

1. Capitalize each letter of the word in the bracket *or, where appropriate, include a proper symbol indicating use in commerce such as TM, SM, or [®] following the word.*

Applicant respectfully submits that in the instant specification, trademarks are designated by their appropriate symbols. Trademarks generally are properly used as adjectives referencing source throughout the specification. There is clear reference to the generic terminology for the trademarks and, in some instances, the owner of the trademark (*e.g.*, Halozyme Therapeutics is the owner of the Hylenex® trademark) or indications that the product is "sold under" a particular trademark name. These are acceptable ways of designating trademarks, as noted in the above-cited section of the MPEP. For Example, at page 52, lines 6-8, the specification recites:

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Examples of commercially available bovine or ovine soluble hyaluronidases are **Vitraser[®] hyaluronidase (ovine hyaluronidase) and Amphadase[®] hyaluronidase (bovine hyaluronidase)** (emphasis added)

Each is identified with a generic term.

At page 75, line 36 to page 76, line 1, the specification recites:

Exemplary regular insulin preparations include, but are not limited to, **human regular insulins, such as those sold under the trademarks Humulin[®] R, Novolin[®] R and Velosulin[®]** (emphasis added)

At page 76, lines 15-18, the specification recites:

Exemplary **rapid acting insulin analogs include**, but are not limited to, for example, **insulin lispro (e.g., Humalog[®] insulin), insulin aspart (e.g., NovoLog[®] insulin), and insulin glulisine (e.g., Apidra[®] insulin) the fast-acting insulin composition sold as VIAject[®] and VIAtab[®]** (see, e.g., U.S. Pat. No. 7,279,457). (emphasis added)

At page 84, lines 19-21, the specification recites:

Original bovine testicular extract preparations included, for example, **extracts sold under the trademarks Wydase[®], Hylase[®], "Dessau," Neopermease[®], Alidase[®] and Hyazyme[®].** (emphasis added)

Nevertheless, to advance prosecution, the specification is amended. For example, at page 2, the specification is amended so that Hydase[®], Vitraser[®] and Wydase[®], which designate the marks by appropriate symbols, are followed by marks by generic terms, as required by the Examiner or are referenced as trademarks. Additional recitations of trademarks in the specification, at paragraphs beginning on pages 52, 75, 84, 85, 86, 174, 196, 198, and 216, are amended to employ the trademarks as adjectives and/or to contain generic terminology. All other recitations of trademarks throughout the application are designated by appropriate symbols, and contain the generic terminology, and, thus, do not require amendment.

Use of Sequence Identifiers

The Examiner states that the term "SEQ ID NOS" should be replaced with "SEQ ID NOs" at page 3, line 20, and throughout the specification. Applicant is not aware of any rule stating that reference to multiple sequence identity numbers must be denoted as "SEQ ID NOs" and not "SEQ ID NOS." A search of the USPTO database of issued patents identifies hundreds of issued patents in which multiple sequence identifiers are denoted as "SEQ ID NOS" in the specification and/or the claims. A few exemplary issued patents that refer to "SEQ ID NOS" in the specification and/or the claims are as follows: 7,999,070; 8,741,565; 7,456,273; 7,993,849; 7,091,323; 7,432,364; 8,900,829; 7,951,563; 7,932,031; 8,685,689; 8,227,231; and 9,447,401. Applicant therefore respectfully asks withdrawal of this objection, or provision of regulation or rule setting forth this requirement.

OBJECTIONS TO THE CLAIMS

The Examiner objects to several of the claims on various grounds, each of which are addressed below:

(1) In Claim 1, the Examiner states that the recitation "...unmodified PH20 polypeptide consists of the **sequence of amino acids set forth as** SEQ ID NO: 3, 7 or 32-66" should be changed to "...unmodified PH20 polypeptide consists of the **amino acid sequence selected from the group consisting of** SEQ ID NOs: 3, 7 and 32-66." (emphasis added).

Applicant respectfully disagrees with the requirement to replace the recitation "sequence of amino acids" with "amino acid sequence" and submits that the language as recited in the claims accurately characterizes the unmodified PH20 polypeptide. In the phrase "sequence of amino acids," the prepositional phrase "of amino acids" modifies the noun "sequence," thus rendering it clear that the sequence is an amino acid sequence. The phrase "unmodified PH20 polypeptide consists of" precedes "sequence of amino acids," rendering clear that the unmodified PH20 polypeptide consists of the sequence of amino acids set forth as the recited SEQ ID NOs.

The instant application is a continuation of U.S. application Serial No. 15/226,489, which is a divisional of U.S. application Serial No. 13/694,731, now U.S. Patent No. 9,447,401. Issued U.S. Patent No. 9,447,401 includes claims directed to modified PH20 polypeptides; the claims recite "sequence of amino acids" (see *e.g.*, claims 1, 2, 3). Insofar as the claims of the issued patent, which recite "sequence of amino acids," have been deemed patentable by the Patent Office, the claims of the instant application should not be objected to for reciting "sequence of amino acids."

The Examiner is reminded that, as set forth in 35 U.S.C. §282, an issued patent is presumptively valid and meets the requirements of 35 U.S.C §112. MPEP §1701 states that the Examiner must give full faith and credit to determinations of the Patent Office and cannot denigrate the validity of an issued patent. The Examiner's rejection of the claims in the instant application denigrates the validity of issued claims in U.S. Patent No. 9,447,401.

In the interest of advancing prosecution, claim 1 is amended as required by the Examiner. Applicant has complied with the requirement of the Examiner, but notes that a polypeptide is comprised of a sequence of amino acids; it is not comprised of an amino acid sequence, which is a written representation of the amino acid sequence of a polypeptide. Nevertheless in view of the requirement by the Office to use this language, this language should be interpreted to refer to a physical polypeptide, not a written representation.

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(2) In claim 1, the Examiner states that the recitation "...amino acid positions set forth in SEQ ID NO:3" should be changed to "... amino acid positions of SEQ ID NO:3." Applicant respectfully disagrees, and submits that the language as recited in the claims accurately characterizes the amino acid positions. The positions of amino acids in a sequence is a property that represents the amino acid residues that make up a protein or polypeptide; it is not a property of a "SEQ ID NO:" A "SEQ ID NO:" merely is a label to designate a sequence. While a protein or polypeptide can be characterized by the sequences of their amino acid residues, and the "SEQ ID NOS" help to locate where in the Sequence Listing the sequences may be read, the "SEQ ID NOS" label amino acid sequences that are recited or set forth. A "SEQ ID NO" does not possess amino acid positions; it is a label. Applicant therefore respectfully submits that the language "amino acid positions set forth in SEQ ID NO:3" (*i.e.*, how the sequence identifying amino acid positions can be located) is accurate and need not be replaced with "amino acid positions of SEQ ID NO:3." In the interest of advancing prosecution, since the amendment is not substantive, claim 1 is amended as required by the Examiner.

(3) In claim 1, the Examiner states that the recitation "...91% sequence identity to the sequence of amino acids set forth as SEQ ID NO: 3, 7 or 32-66" should be changed to "... 91% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NO: 3, 7 and 32-66" (emphasis added). As detailed above in objection (1), Applicant submits that the language of the claims is clear and accurately characterizes the unmodified PH20 polypeptide. The recitation of "selected from among a, b, and c" is acceptable alternative language; there is no requirement in US patent laws to employ Markush language. Markush language is one form of acceptable language for reciting alternatives. Nevertheless, in the interest of advancing prosecution, claim 1 is amended as required by the Examiner.

(4) In claims 6 and 8, the Examiner states "...that unmodified PH20 polypeptide consists of the sequence of amino acids set forth in SEQ ID NO: 3, 7 or 32-66" should be changed to "...the [un]modified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NO: 3, 7 and 32-66" (emphasis added). As detailed above with respect to the rejections to claim 1, Applicant submits that the language of the claims is clear and accurately characterizes the unmodified PH20 polypeptide. In the interest of advancing prosecution, claims 6 and 8 are amended as required by the Examiner.

(5) In claim 9, the Examiner states "...identity to the sequence of amino acids set forth as SEQ ID NO: 3, 7 or 32-66" should be changed to "...identity to the amino acid sequence selected from the group consisting of SEQ ID NO: 3, 7 and 32-66" (emphasis added). As

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detailed above with respect to the objections to claim 1, Applicant submits that the language of the claims is clear and accurately characterizes the unmodified PH20 polypeptide. In the interest of advancing prosecution, claim 9 is amended as required by the Examiner.

(6) In claim 11, the Examiner states "...PH20 polypeptide consists of the sequence of amino acids set forth in SEQ ID NO:35" should be changed to "...PH20 polypeptide consists of the amino acid sequence of SEQ ID NO:35." As detailed above with respect to the objections to claim 1, Applicant submits that the language of the claims is clear and accurately characterizes the unmodified PH20 polypeptide. In the interest of advancing prosecution, claim 11 is amended as required by the Examiner.

(7) In claim 13, the Examiner states "...comprising a sequence of amino acid[s] set forth in any of SEQ ID NOS: 591-598" should be changed to "...comprising the amino acid sequence selected from the group consisting of SEQ ID NOS: 591-598." As detailed above with respect to the objections to claim 1, Applicant submits that the language of the claims is clear and accurately characterizes the unmodified PH20 polypeptide. In the interest of advancing prosecution, claim 13 is amended as required by the Examiner.

(8) In claim 13, the Examiner states "...in a polypeptide of any of SEQ ID NOS: 3 and 32-66" should be changed to "...in the amino acid sequence selected from the group consisting of SEQ ID NOS: 3 and 32-66." As detailed above with respect to the objections to claim 1, Applicant submits that the language of the claims is clear and accurately characterizes the unmodified PH20 polypeptide. In the interest of advancing prosecution, claim 13 is amended as required by the Examiner.

(9) In claim 13, the Examiner states "SEQ ID NOS" should be changed to "SEQ ID NOS." As stated above with respect to this objection to the specification, Applicant is not aware of any rule stating that reference to multiple sequence identity numbers must be denoted as "SEQ ID NOS" and not "SEQ ID NOS." In the interest of advancing prosecution, claim 13 is amended as required by the Examiner.

(10) In claim 20, the Examiner states "...a modified PH20 polypeptide of claim 1" should be changed to the modified PH20 polypeptide of claim 1." Claim 20 is amended as required by the Examiner, to address the rejection.

THE REJECTION OF CLAIMS 1, 3, 5-6 and 8-20 UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1, 3, 5-6 and 8-20 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite because claim 1 recites that "the unmodified PH20 polypeptide" is selected from "SEQ ID NO: 3, 7 or 32-66" which the Examiner asserts is of broader scope than the scope of

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the unmodified PH20 polypeptide of “SEQ ID NO:3,” which is recited later in the claim. The Examiner states that a broad range together with a narrow range that falls within the broad range is considered indefinite.

Claim 1 also is rejected as indefinite in the recitation “the unmodified PH20 polypeptide consists of the sequence of amino acids set forth in SEQ ID NO: 3, 7 or 32-66” because the sequences of SEQ ID NOS: 3 and 32-66 are allegedly modified, not unmodified PH20 polypeptides, because they are truncated forms of the full-length amino acid sequence of SEQ ID NO:7.

Reconsideration and withdrawal of these rejections respectfully is requested in view of the amendments to the claims and the following arguments.

Relevant Law

Claims are not read in a vacuum but instead are considered in light of the specification and the general understanding of the skilled artisan. *Rosemount, Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1547, 221 USPQ 1, 7 (Fed. Cir. 1984), *Caterpillar Tractor Co. v. Berco, S.p.A.*, 714 F.2d 1110, 1116, 219 USPQ 185, 188 (Fed. Cir. 1983). Claim language is satisfactory if it reasonably apprises those of skill in the art of the bounds of the claimed invention and is as precise as the subject matter permits. *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir.), cert. dismissed, 106 S.Ct. 340 (1985).

Any form of claim language is acceptable under 35 U.S.C. § 112, second paragraph if the scope of the claim is clear. *See, e.g., Application of Borkowski*, 422 F.2d 904, 908 (CCPA 1970) (“If the scope of subject matter embraced by a claim is clear, and if the applicant has not otherwise indicated that he intends that claim to be of a different scope, then the claim does particularly point out and distinctly claim the subject matter which the applicant regards as his invention.”) (citations omitted).

There are no requirements for terms to be defined in the claims when one of skill in the art can readily determine the meaning of the term based on the description and definitions provided in the specification. In this respect, an Applicant is entitled to be its own lexicographer (see, *e.g.*, MPEP 2111.01). The amount of detail required to be included in the claims depends on the particular subject matter and the prior art and is not to be viewed in the abstract, but in conjunction with whether the specification is in compliance with the first paragraph of 35 U.S.C. § 112. If the claims, read in light of the specification, reasonably

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apprise those skilled in the art of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more:

[i]t is not necessary that a claim recite each and every element needed for the practical utilization of the claimed subject matter (*Bendix Corp. v United States*, 600 F.2d 1364, 1369, 220 Ct. Cl. 507, 514, 204 USPQ 617, 621 (1979); *See, also, Carl Zeiss Stiftung v. Renishaw plc*, 20 USPQ2d 1094, 1101).

The Rejected Claims

Claims 1, 3, 5, 6 and 8-20 are rejected. Independent claim 1 recites:

A modified PH20 polypeptide, comprising one or more amino acid replacements in an unmodified PH20 polypeptide, wherein:
the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7 and 32-66;
the modified PH20 polypeptide exhibits increased hyaluronidase activity compared to the unmodified PH20 polypeptide not containing the amino acid replacement(s);
the amino acid replacement(s) confer(s) the increased hyaluronidase activity;
the amino acid replacement(s) is at a position corresponding to 313 with reference to amino acid positions of SEQ ID NO:3, which confers increased hyaluronidase activity;
corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the sequence of amino acids set forth in SEQ ID NO:3; and
the modified PH20 polypeptide has at least 91% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7 and 32-66.

Independent claim 13 recites:

A modified PH20 polypeptide, comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 591-598, or a sequence of amino acids that exhibits at least 91% sequence identity to a sequence of amino acids set forth in any of SEQ ID NOs: 591-598 and that contains the amino acid replacement at residue 313 compared to corresponding positions in the amino acid sequence selected from the group consisting of SEQ ID NOs: 3 and 32-66.

Claims 3, 5, 6, 8-12 and 14-20 ultimately depend on claim 1, and recite particulars of the modified or unmodified PH20 polypeptides. For example, claims 3 and 5 recite potential replacements at position 313. Claim 12 recites that the modified PH20 polypeptide exhibits increased hyaluronidase activity of at least 120%. Claim 14 recites that the PH20 polypeptide comprises a modification, such as glycosylation, sialation, albumination, farnesylation, carboxylation, hydroxylation, or phosphorylation. Claim 16 recites that the modified PH20 polypeptide is conjugated to a polymer and claim 17 recites that the polymer is dextran or polyethylene glycol (PEG). Claim 18 recites that the modified PH20 polypeptide comprises a heterologous signal sequence. Claim 19 recites a chimeric polypeptide comprising the modified PH20 polypeptide. Claim 20 recites a pharmaceutical composition comprising the modified PH20 polypeptide.

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Contrary to what is stated in the Office Action, claim 13 does not depend on claim 1. Claim 13, copied above, is an independent claim. Claim 13 does not recite the rejected language.

Analysis

“SEQ ID NO: 3, 7 or 32-66” and “with reference to amino acid positions set forth in SEQ ID NO:3”

The Examiner states that the recitation that “the unmodified PH20 polypeptide is selected from SEQ ID NO: 3, 7 or 32-66” has a broader scope than the “scope of the unmodified PH20 polypeptide of ‘SEQ ID NO:3’” which also is recited in the claim. The Examiner states that the claim is indefinite because it recites a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation, in the same claim.

Applicant respectfully disagrees and asserts the recitation is not indefinite. Claim 1 recites that the unmodified PH20 polypeptide consists of the SEQ ID NO: 3, 7, or 32-66. Claim 1 further recites that amino acid positions in the modified PH20 polypeptide are identified by alignment of the modified PH20 polypeptide with the polypeptide having the sequence of amino acids set forth in SEQ ID NO:3. SEQ ID NO: 3 is provided as a reference sequence to which the PH20 polypeptide is aligned to determine corresponding amino acid positions.

Throughout the application, the replacement(s) in an unmodified PH20 polypeptide is/are at a specified amino acid residue with reference to amino acid positions set forth in SEQ ID NO:3, where corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide set forth in SEQ ID NO:3. For example, at page 5, lines 25-33; at page 8, lines 10-17; and at page 11, lines 8-15, which recite that the position of amino acid replacement is identified with reference to SEQ ID NO: 3. Basis for SEQ ID NO:3 as a reference polypeptide also can be found at page 67, lines 7-22, of the application as-filed, which recite:

Hence, reference herein that a position or amino acid replacement corresponds to positions with reference to SEQ ID NO:3 also means that the position or amino acid replacement corresponds to positions with reference to any of SEQ ID NOS: 7 or 32-66, since the sequences therein are identical to the corresponding residues as set forth in SEQ ID NO:3. By aligning the sequences, one skilled in the art can identify corresponding residues, for example, using conserved and identical amino acid residues as guides. In general, to identify corresponding positions, the sequences of amino acids are aligned so that the highest order match is obtained (see, *e.g.*: *Computational Molecular Biology*, Lesk, A.M., ed., Oxford University Press, New York, 1988; *Biocomputing: Informatics and Genome Projects*, Smith, D.W., ed., Academic Press, New York, 1993; *Computer Analysis of Sequence Data, Part I*, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey, 1994; *Sequence Analysis in Molecular*

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Biology, von Heinje, G., Academic Press, 1987; and *Sequence Analysis Primer*, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; Carrillo *et al.* (1988) *SLAM J Applied Math* 48:1073). Figure 2 (A-L) exemplifies exemplary alignments and identification of exemplary corresponding residues for replacement.

Basis also can be found in the Figures, such as Figure 2, which depicts alignment of human soluble PH20 set forth as SEQ ID NO:3 with other PH20 polypeptides, such as PH20 polypeptides of other species.

Thus, SEQ ID NO:3 is a reference polypeptide for aligning the sequences to identify corresponding residues. SEQ ID NO: 3 is not recited in the claims to further limit the polypeptides whose sequences are set forth as SEQ ID NOS: 3, 7 and 32-66. SEQ ID NO: 3 is not recited as a subset of SEQ ID NOS: 3, 7, or 32-66. It is mature PH20 that serves as the reference polypeptide for purposes of aligning the polypeptides for numbering the residues. Thus, the claim does not recite broad and narrow ranges.

As noted above, the instant application is a continuation of U.S. application Serial No. 15/226,489, now U.S. Patent No. 10,865,400. U.S. Patent No. 10,865,400 references an unmodified PH20 polypeptide with the sequence set forth as any of “SEQ ID NOS: 3, 7, and 32-66” and also, in the same claim, recites that the “corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the sequence of amino acids set forth as SEQ ID NO:3.” For example, claim 1 of U.S. Patent No. 10,865,400 recites (**emphasis added**):

1. A modified PH20 polypeptide, comprising one or more amino acid replacements in an unmodified PH20 polypeptide, wherein:
the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NOS: 3, 7, and 32-66;
the modified PH20 polypeptide exhibits increased hyaluronidase activity that is at least 120% of the hyaluronidase activity compared to the unmodified PH20 polypeptide not containing the amino acid replacement(s); wherein:
the activity of the unmodified PH20 polypeptide not containing the replacement(s) is 100%;
hyaluronidase activity of the modified PH20 polypeptide and hyaluronidase activity of the unmodified PH20 polypeptide are measured under identical conditions;
the amino acid replacement(s) confer(s) the increased hyaluronidase activity;
at least one amino acid replacement confers the increased hyaluronidase activity, and is at a position corresponding to a position selected from 1, 15, 24, 27, 29, 30, 31, 32, 33, 37, 39, 48, 63, 67, 69, 71, 72, 73, 75, 87, 92, 93, 94, 118, 120, 135, 141, 147, 148, 150, 151, 152, 155, 156, 163, 164, 165, 170, 198, 209, 212, 215, 219, 233, 236, 247, 257, 259, 260, 263, 269, 271, 272, 276, 278, 282, 293, 305, 308, 313, 320, 324, 325, 326, 328, 353, 359, 371, 377, 380, 389, 392, 395, 405, 409, 410, 418, 425, 436, 437, 438, 441, 442, 446, and 447, with reference to amino acid positions set forth in SEQ ID NO:3;
corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the sequence of amino acids set forth as SEQ ID NO:3, with the proviso that if the modified PH20 polypeptide

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includes only a single amino acid replacement, the replacement does not correspond to amino acid replacement N219A with reference to amino acid positions set forth in SEQ ID NO:3; and

the modified PH20 polypeptide has at least 95% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOS: 3, 7, and 32-66.

The Examiner is, again, reminded that, as set forth in 35 U.S.C. §282, an issued patent is presumptively valid and meets the requirements of 35 U.S.C. §112. MPEP §1701 states that the Examiner must give full faith and credit to determinations of the Patent Office and cannot denigrate the validity of an issued patent. The Examiner's rejection of the claims in the instant application arguably denigrates the validity of issued claims in U.S. Patent No. 10,865,400 by alleging language is indefinite.

“the unmodified PH20 polypeptide consists of the sequence of amino acids set forth in SEQ ID NO: 3, 7 or 32-66”

The Examiner states that the recitation “the unmodified PH20 polypeptide consists of the sequence of amino acids set forth in SEQ ID NO: 3, 7 or 32-66” is unclear because the sequences of SEQ ID NOS: 3 and 32-66 are **modified**, not unmodified PH20 polypeptides, because they are truncated forms of the full-length amino acid sequence of SEQ ID NO:7. For definitional purposes of the claim, these polypeptides are unmodified because they do not include amino acid replacements or insertions.

Applicant respectfully disagrees and asserts that the recitation is not indefinite. For definitional purposes of the claim, these polypeptides are unmodified because they do not include amino acid replacements or insertions. Claim 1, from which the other rejected claims depend, recites that the modified PH20 polypeptide contains at least one amino acid replacement at a position selected from among positions recited in the claims in an unmodified PH20 polypeptide, which is defined with reference to SEQ ID NOS:3, 7 and 32-66. The modified PH20 polypeptide is “modified” because it contains a replacement. The claim defines SEQ ID NOS:3, 7 and 32-66 as the unmodified polypeptides; these polypeptides are unmodified because they do not contain the amino acid replacements that give rise to the increased activity.

Thus, claims 1, 6, 8, 9 and 13 recite that the modified PH20 polypeptide has at least one amino acid replacement relative to the unmodified polypeptides whose sequences are set forth in SEQ ID NOS: 3, 7 and 32-66. The unmodified PH20 polypeptide is “unmodified” because it does not contain a replacement at a position recited in the claims. Claims 1, 6, 8, 9 and 13 require that the unmodified PH20 polypeptide consists of the sequence of amino acids selected from the group consisting of SEQ ID NOS: 3, 7 and 32-66. None of the sequences set forth as

Inventor(s) : Wei *et al.*
Serial No. : 16/824,572
Filed : March 19, 2020

Attorney Docket No.: 33320.03087.US26/ 3087C
Amendment and Response

SEQ ID NO: 3, 7 or 32-66 contains a replacement at a position recited in the claims. The replacements are in the modified PH20 polypeptide. Thus, recitation of an “unmodified PH20 polypeptide” that “consists of the sequence of amino acids set forth in SEQ ID NO: 3, 7 or 32-66” is not unclear. As noted above, the claims are amended to address the Examiner’s Objections to the Claims, to recite the “amino acid sequence selected from the group consisting of SEQ ID NO: 3, 7 and 32-66.”

As noted above, the instant application is a continuation of U.S. application Serial No. 15/226,489, now U.S. Patent No. 10,865,400, which is a divisional of U.S. application Serial No. 13/694,731, now U.S. Patent No. 9,447,401. Each of U.S. Patent Nos. 9,447,401 and 10,865,400 references an unmodified PH20 polypeptide with the sequence set forth as any of “SEQ ID NOS: 3, 7, and 32-66.” For example, claim 2 of U.S. Patent No. 9,447,401 recites (emphasis added):

The modified PH20 polypeptide of claim 1, wherein:

the unmodified PH20 polypeptide is a soluble PH20 polypeptide that consists of the sequence of amino acids set forth in any of SEQ ID NOS: 3, 7 and 32-66.

Claim 1 of U.S. Patent No. 10,865,400 recites (emphasis added):

1. A modified PH20 polypeptide, comprising one or more amino acid replacements in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NOS: 3, 7, and 32-66;

the modified PH20 polypeptide exhibits increased hyaluronidase activity that is at least 120% of the hyaluronidase activity compared to the unmodified PH20 polypeptide not containing the amino acid replacement(s); wherein:

the activity of the unmodified PH20 polypeptide not containing the replacement(s) is 100%;

hyaluronidase activity of the modified PH20 polypeptide and hyaluronidase activity of the unmodified PH20 polypeptide are measured under identical conditions;

the amino acid replacement(s) confer(s) the increased hyaluronidase activity;

at least one amino acid replacement confers the increased hyaluronidase activity, and is at a position corresponding to a position selected from 1, 15, 24, 27, 29, 30, 31, 32, 33, 37, 39, 48, 63, 67, 69, 71, 72, 73, 75, 87, 92, 93, 94, 118, 120, 135, 141, 147, 148, 150, 151, 152, 155, 156, 163, 164, 165, 170, 198, 209, 212, 215, 219, 233, 236, 247, 257, 259, 260, 263, 269, 271, 272, 276, 278, 282, 293, 305, 308, 313, 320, 324, 325, 326, 328, 353, 359, 371, 377, 380, 389, 392, 395, 405, 409, 410, 418, 425, 436, 437, 438, 441, 442, 446, and 447, with reference to amino acid positions set forth in SEQ ID NO:3;

corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the sequence of amino acids set forth as SEQ ID NO:3, with the proviso that if the modified PH20 polypeptide includes only a single amino acid replacement, the replacement does not correspond to amino acid replacement N219A with reference to amino acid positions set forth in SEQ ID NO:3; and

the modified PH20 polypeptide has at least 95% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOS: 3, 7, and 32-66.

Inventor(s) : Wei *et al.*
Serial No. : 16/824,572
Filed : March 19, 2020

Attorney Docket No.: 33320.03087.US26/ 3087C
Amendment and Response

This language is clear;

As set forth in 35 U.S.C. §282, an issued patent is presumptively valid and meets the requirements of 35 U.S.C. §112. MPEP §1701 states that the Examiner must give full faith and credit to determinations of the Patent Office and cannot denigrate the validity of an issued patent. The Examiner's rejection of the claims in the instant application arguably denigrates the validity of issued claims in U.S. Patent Nos. 9,447,401 and 10,865,400 by alleging language in issued claims in parent applications that rely on the same specification is indefinite.

REJECTION FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1, 3, 5-6, 8-17 and 20 are provisionally rejected on the ground of obviousness-type double patenting as being unpatentable over claims 1, 2, 6-14 and 19 of allowed Application No. 15/226,489, now issued Patent No. 10,865,400. A terminal disclaimer has been filed.

* * *

Consideration of the above remarks, entry of this amendment, and allowance of the application, respectfully are requested.

Respectfully submitted,
/Stephanie Seidman/
Stephanie Seidman
Reg. No. 33,779

Attorney Docket No. 33320.03087.US26/ 3087C
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Electronic Acknowledgement Receipt	
EFS ID:	41757135
Application Number:	16824572
International Application Number:	
Confirmation Number:	1431
Title of Invention:	PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF
First Named Inventor/Applicant Name:	Ge WEI
Customer Number:	13565
Filer:	Stephanie L. Seidman/Jimmy Schaub
Filer Authorized By:	Stephanie L. Seidman
Attorney Docket Number:	33320.03087.US26/3087C
Receipt Date:	27-JAN-2021
Filing Date:	19-MAR-2020
Time Stamp:	18:24:54
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment		no			
File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	3087Ctra.pdf	139353	no	1
			863d849e207cf012f13981828979b5b6b5af62ae		
Warnings:					

Information:					
2		3087Camb.pdf	316911	yes	23
			ac65dc7b7aa9168c1c34f2bee65cb6203626dc49		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Specification		2	8	
	Claims		9	11	
	Applicant Arguments/Remarks Made in an Amendment		12	23	
Warnings:					
Information:					
Total Files Size (in bytes):			456264		
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>					

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors	: Wei <i>et al.</i>	Art Unit	: 1656
Serial No.	: 16/824,572	Examiner	: Liu, Samuel W.
Filed	: March 19, 2020	Conf. No.	: 1431
		Cust. No.	: 13565
Title	: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF		

Mail Stop Amendment

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

Dear Sir:

Responsive to the *Office Action*, mailed October 27, 2020, transmitted herewith is an *Amendment and Response* (23 pages) for filing in connection with the above-identified application.

☒ The Commissioner is hereby authorized to charge any fees that may be due in connection with this paper or with this application during its entire pendency to Deposit Account No. 50-0911.

Respectfully submitted,

/Stephanie Seidman/

Stephanie Seidman
Reg. No. 33,779

Attorney Docket No.: 33320.03087.US26/3087C

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CERTIFICATE OF TRANSMISSION VIA EFS-WEB

I hereby certify that this paper is being transmitted via the Electronic Filing System (EFS-WEB) to the United States Patent and Trademark Office on **January 27, 2021**.

/Jimmy Schaub/
Jimmy Schaub

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors	: Wei <i>et al.</i>	Art Unit	: 1656
Serial No.	: 16/824,572	Examiner	: Liu, Samuel W.
Filed	: March 19, 2020	Conf. No.	: 1431
		Cust. No.	: 13565
Title	: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF		

Mail Stop Amendment

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT IN
ACCORDANCE WITH 37 C.F.R. §§ 1.97-1.98**

Dear Sir:

Because this Supplemental Information Disclosure Statement is filed after the receipt of a First Office Action on the Merits for the above-captioned application, the Commissioner is authorized to charge the fee for filing the Supplemental Information Disclosure Statement to Deposit Account No. 50-0911.

In accordance with the duty of disclosure imposed by 37 C.F.R. § 1.56 to inform the Patent Office of all information known by Applicant or Applicant's representative that may be material to the examination of the subject application, Applicant's representative hereby provides this Supplemental Information Disclosure Statement that is prepared in accordance with 37 C.F.R. §§ 1.97-1.98. A Form PTO-1449 (1 page) and copies of the cited non-U.S. patent documents are provided herewith in connection with the above-captioned application.

The documents cited on the Form PTO-1449 are in the English language. Hence, in accordance with the requirements of 37 C.F.R. § 1.98, no further explanation of the listed items is necessary.

Although these documents and applications are made known to the Patent and Trademark Office in compliance with Applicant's duty of disclosure, such disclosure is not to be construed as an admission by Applicant or Applicant's representative that any of the documents, singly or in any combination thereof, is effective as prior art against the subject application. In accordance with 37 C.F.R. § 1.97(g) and (h), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 C.F.R. § 1.56(b) exists.

CERTIFICATE OF TRANSMISSION VIA EFS-WEB

I hereby certify that this paper is being transmitted via the Electronic Filing System (EFS-WEB) to the United States Patent and Trademark Office on January 27, 2021.

/Hyun Jeung Ji/
Hyun Jeung Ji

Inventors : Wei *et al.*
Serial No. : 16/824,572
Filed : March 19, 2020

Attorney Docket No.: 33320.03087.US26/3087C
Supplemental Information Disclosure Statement

Applicant respectfully requests that the Examiner review the foregoing documents and they be made of record in the file history of the above-captioned application.

Respectfully submitted,

/Stephanie Seidman/

Stephanie Seidman

Reg. No. 33,779

Attorney Docket No.: 33320.03087.US26/3087C

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Substitute Form PTO-1449 (Modified)		U.S. Department of Commerce Patent and Trademark Office		Attorney Docket No. 33320.03087.US26/ 3087C		Application No. 16/824,572	
List of Patents and Publications for Applicant's Information Disclosure Statement (37 CFR §1.98(b))				Inventors <i>Wei et al.</i>			
				Filing Date March 19, 2020		Group Art Unit 1656	
U.S. Patent Documents							
Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
	AA	2020/0318091	10/08/2020	Wei et al.	424	094.620	06/25/2020
	AB	2020/0368330	11/26/2020	Frost et al.	424	078.170	07/16/2020

Foreign Patent Documents or Published Foreign Patent Applications						
Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Translation	
					Yes	No
None						

Other Documents (include Author, Title, Date, and Place of Publication)		
Examiner Initial	Desig. ID	Document
	AC	Letter/Written Disclosure of the Information Disclosure Statement for the above-referenced application, filed herewith on January 27, 2021, 2 pages.
	AD	Rosengren et al., "Clinical Immunogenicity of rHuPH20, a Hyaluronidase Enabling Subcutaneous Drug Administration," AAPS J. 17(5):1144-56 (2015).
	AE	Written Submissions, filed Oct. 09, 2020, responsive to Hearing Notice, issued Aug. 10, 2020, in connection with Indian Patent Application No. 6272/DELNP/2014, 27 pages.
	AF	Amended claims and abstract, filed Nov. 19, 2020, responsive to Examiner request, in connection with Indian Patent Application No. 6272/DELNP/2014, 22 pages.
	AG	Certificate of Grant, issued Dec. 28, 2020, in connection with Indian Patent Application No. 6272/DELNP/2014, 1 page.
	AH	Certificate of Grant, issued Oct. 01, 2020, in connection with Israeli Patent Application No. 233192, 3 pages.
	AI	Notification Prior to Acceptance, dated Dec. 14, 2020, issued in connection with Israeli Patent Application No. 274798 [English reporting letter; original document as issued in Hebrew; and English translation of allowed claims], 10 pages.

Examiner Signature	Date Considered
EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

Electronic Patent Application Fee Transmittal				
Application Number:		16824572		
Filing Date:		19-Mar-2020		
Title of Invention:		PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF		
First Named Inventor/Applicant Name:		Ge WEI		
Filer:		Stephanie L. Seidman/Hyun Jeung Ji		
Attorney Docket Number:		33320.03087.US26/3087C		
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	260	260
Total in USD (\$)				260

Electronic Acknowledgement Receipt	
EFS ID:	41764196
Application Number:	16824572
International Application Number:	
Confirmation Number:	1431
Title of Invention:	PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF
First Named Inventor/Applicant Name:	Ge WEI
Customer Number:	13565
Filer:	Stephanie L. Seidman/Hyun Jeung Ji
Filer Authorized By:	Stephanie L. Seidman
Attorney Docket Number:	33320.03087.US26/3087C
Receipt Date:	27-JAN-2021
Filing Date:	19-MAR-2020
Time Stamp:	18:53:17
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$260
RAM confirmation Number	E20211QI53488768
Deposit Account	500911
Authorized User	Hyun Jeung Ji
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.16 (National application filing, search, and examination fees) 37 CFR 1.17 (Patent application and reexamination processing fees)	

37 CFR 1.19 (Document supply fees)					
37 CFR 1.20 (Post Issuance fees)					
37 CFR 1.21 (Miscellaneous fees and charges)					
File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	3087Ctra.pdf	25259	no	1
			834dd21edb27c3908ac1d0a90f035e0985050e72		
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	3087Cids.pdf	29508	no	2
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Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Information Disclosure Statement (IDS) Form (SB08)	3087Cp49.pdf	33441	no	1
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Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
4	Non Patent Literature	AC.pdf	101371	no	2
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Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
5	Non Patent Literature	AD.pdf	12073777	no	13
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Warnings:					
Information:					
6	Non Patent Literature	AE.pdf	15848148	no	27
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Warnings:					
Information:					
7	Non Patent Literature	AF.pdf	9475115	no	22
			7441ab6f44375e72109a783279b405229bb6a1a8		
Warnings:					
Information:					
8	Non Patent Literature	AG.pdf	1363172	no	1
			eaec5385c85f1694b1c28374cb49f59bac8a7f1e		
Warnings:					
Information:					
9	Non Patent Literature	AH.pdf	1318167	no	3
			76be670f99747a871beaab89f343900ae202ba7e		
Warnings:					
Information:					
10	Non Patent Literature	AI.pdf	5907433	no	10
			3732ec5e50d7a6f5fa3ccb0360390030ce2f0752		
Warnings:					
Information:					
11	Fee Worksheet (SB06)	fee-info.pdf	30813	no	2
			46c42f2f9df8f4a734e4269479aa07321cce9e49		
Warnings:					
Information:					
Total Files Size (in bytes):			46206204		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors : Wei *et al.* Art Unit : 1656
Serial No. : 16/824,572 Examiner : Liu, Samuel W.
Filed : March 19, 2020 Conf. No. : 1431
Cust. No. : 13565
Title : **PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES
THEREOF**

Mail Stop Amendment

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT TRANSMITTAL
LETTER**

Dear Sir:

Transmitted herewith are a Supplemental Information Disclosure Statement (2 pages), Form PTO-1449 (1 page), and cited non-U.S. patent documents for filing in connection with the above-identified application. Because this Supplemental Information Disclosure Statement is filed after the receipt of a First Office Action on the Merits in the above-referenced application, the Commissioner is authorized to charge Deposit Account No. 50-0911, as stated below:

☒ The Commissioner is hereby authorized to charge any fees that may be due in connection with this paper or with this application during its entire pendency to Deposit Account No. 50-0911.

Respectfully submitted,

/Stephanie Seidman/

Stephanie Seidman
Reg. No. 33,779

Attorney Docket No.: 33320.03087.US26/3087C

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CERTIFICATE OF TRANSMISSION VIA EFS-WEB

I hereby certify that this paper is being transmitted via the Electronic Filing System (EFS-WEB) to the United States Patent and Trademark Office on January 27, 2021.

/Hyun Jeung Ji/
Hyun Jeung Ji



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

13565 7590 02/18/2021
Dentons US LLP
4655 Executive Drive
Suite 700
San Diego, CA 92121

EXAMINER

LIU, SAMUEL W

ART UNIT

PAPER NUMBER

1656

DATE MAILED: 02/18/2021

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/824,572	03/19/2020	Ge WEI	33320.03087.US26/3087C	1431

TITLE OF INVENTION: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$0.00	\$1200	05/18/2021

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

13565 7590 02/18/2021
Dentons US LLP
4655 Executive Drive
Suite 700
San Diego, CA 92121

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/824,572	03/19/2020	Ge WEI	33320.03087.US26/3087C	1431

TITLE OF INVENTION: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$0.00	\$1200	05/18/2021

EXAMINER	ART UNIT	CLASS-SUBCLASS
LIU, SAMUEL W	1656	435-069100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

1 _____

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☐ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies _____

4b. Method of Payment: (Please first reapply any previously paid fee shown above)

☐ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. Change in Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment. **NOTE:** If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____

Date _____

Typed or printed name _____

Registration No. _____



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/824,572	03/19/2020	Ge WEI	33320.03087.US26/3087C	1431
13565	7590	02/18/2021	EXAMINER	
Dentons US LLP 4655 Executive Drive Suite 700 San Diego, CA 92121			LIU, SAMUEL W	
			ART UNIT	PAPER NUMBER
			1656	
DATE MAILED: 02/18/2021				

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.** Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b) (2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 16/824,572	Applicant(s) WEI et al.	
	Examiner SAMUEL W LIU	Art Unit 1656	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to 1/27/2021 & 2/10/2021.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are 1,3,5-6 and 8-20. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
Certified copies:
a) ☐ All b) ☐ Some *c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).
* Certified copies not received: ____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.
Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892) 2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date <u>1/27/2021</u> . 3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____. 4. ☒ Interview Summary (PTO-413), Paper No./Mail Date. <u>2/10/2021</u> .	5. ☒ Examiner's Amendment/Comment 6. ☒ Examiner's Statement of Reasons for Allowance 7. ☐ Other _____.
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/SAMUEL W LIU/ Examiner, Art Unit 1656	/SCARLETT Y GOON/ QAS, Art Unit 1600
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Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

The amendment filed 1/27/2021 which amends claims 1, 6, 8, 9, 11, 13 and 20 has been entered. Claims 2, 4 and 7 were canceled by the amendment filed 8/24/2020.

The terminal disclaimer filed on 1/27/2021 disclaiming the terminal portion of any patent granted on this application, which would extend beyond the expiration date of US Pat. No. 10865400, which was issued from Application No. 15226489 ('489), has been reviewed and accepted. The '489 is the reference application for the ODP rejection set forth in the Office action mailed 10/27/2020.

The reference cited in the IDS filed 1/27/2021 have been considered by Examiner.

The following office action is applied to the pending claims 1, 3, 5, 6, and 8-21.

EXAMINER' S AMENDMENT

An Examiner' s Amendment to the record appears below. Should the change and/or additions be unacceptable to Applicant, an amendment may be filed as provided by 37 C.F.R. § 1.312. To ensure consideration of such an amendment, it **MUST** be submitted no later than payment of the Issue Fee. Authorization for this Examiner' s Amendment was given in communication with Stephanie Seidman on 2/10/2021. Applicants agreed to cancel claim 21 for considering allowability of this case.

Cancel claim 21.

The statement of withdrawal of rejections:

The 112(b) rejection of claims 1, 3, 5, 6, and 8-20 is withdrawn in light of that the applicant's argument set forth in pages 16-23 of the response filed 1/27/2021 is persuasive.

The provisional ODP rejection of claims 1, 3, 5, 6, 8-17 and 20 over Application No.15226489 ('489) is withdrawn in light of the applicants' submission (filed 1/27/2021) of the terminal disclaimer over US Pat. No. 10865400 which was issued from application '489.

The following is an examiner's statement of reasons for allowance:

The closest prior art is the reference "Lin et al." (*Proc. Natl. Acad. Sci USA* (1993) 90, 10071-10075). The reference teach a variant PH20 polypeptide having 99.7% sequence identity to instant unmodified SEQ ID NO:3 (see sequence alignment below, wherein Qy is SEQ ID NO:3, and Db is the PH20 polypeptide of Lin); however, this reference neither teaches that the variant PH20 comprising the substitution at position 313 in the modified PH20 polypeptide of **claim 1** nor teaches that the variant polypeptide having at least 91% sequence identity to any one of mutant PH20 polypeptide of SEQ ID NOs:591-598 in **claim 9**; each of the mutant PH20

polypeptides of SEQ ID NOs:591-598 comprises the following amino acid substitutions at position 313: M313A, M313G, M313H, M313K, M313P, M313R, M313T and M313Y, respectively. There is no guidance for making the particular modification (amino acid substitution) at position 313 in a unmodified PH20 polypeptide to arrive at the claimed products of claims 1 and 9.

sperm protein PH-20 - human;
R; Lin, Y et al.; Proc. Natl. Acad. Sci. U.S.A. 90, 10071-10075, 1993;
Query Match 99.7%; Length 509;

```
Qy      1 LNFRAAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSLFSFIGSPRINATGQGVITIFYVDR 60
      |||
Db      36 LNFRAAPPVIPNVAFLWAWNAPSEFCLGKFDEPLDMSLFSFIGSPRINATGQGVITIFYVDR 95

Qy      61 LGYYPYIDSITGVTVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVIDWEEWRPTWA 120
      |||
Db      96 LGYYPYIDSITGVTVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVIDWEEWRPTWA 155

Qy     121 RNWKPKDVYKNRSIELVQQQNVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRPNHL 180
      |||
Db     156 RNWKPKDVYKNRSIELVQQQNVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRPNHL 215

Qy     181 WGYLFPDCYNHHYKPGYNGSCFNVEIKRNDLSWLWNESTALYPSIYLNTQQSFVAAT 240
      |||
Db     216 WGYLFPDCYNHHYKPGYNGSCFNVEIKRNDLSWLWNESTALYPSIYLNTQQSFVAAT 275

Qy     241 LYVRNRVREAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDELVYTFGETVALGASG 300
      |||
Db     276 LYVRNRVREAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDELVYTFGETVALGASG 335

Qy     301 IVIWGTLSIMRSMKSCLLLDNYMETILNPYIINVTLAAKMCSQVLCQEQGVCIRKNWNSS 360
      |||
Db     336 IVIWGTLSIMRSMKSCLLLDNYMETILNPYIINVTLAAKMCSQVLCQEQGVCIRKNWNSS 395

Qy     361 DYHLNPDNFAIQLEKGGKFTVRGKPTLEDLEQFSEKFCSCYSTLSCKEKADVKTDAV 420
      |||
Db     396 DYHLNPDNFAIQLEKGGKFTVRGKPTLEDLEQFSEKFCSCYSTLSCKEKADVKTDAV 455

Qy     421 DVCIADGVCIDAFLKPPMETEEPQIFY 447
      |||
Db     456 DVCIADGVCIDAFLKPPMETEEPQIFY 482
```

After further search, it is found that the amended claim 1 and claim 13 are free from prior art and allowable.

Therefore, claims 1, 3, 5, 6, and 8-20 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL W LIU whose telephone number is (571)272-0949. The examiner can normally be reached on M-F 8:30 am-5:30 pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <https://ppair-my.uspto.gov/pair/PrivatePair>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samuel Wei Liu/
Patent Examiner, Art Unit 1656
February 10, 2021

/SCARLETT Y GOON/
QAS, Art Unit 1600

<i>Examiner-Initiated Interview Summary</i>	Application No. 16/824,572	Applicant(s) WEI et al.		
	Examiner SAMUEL W LIU	Art Unit 1656	AIA (First Inventor to File) Status No	Page 1 of 1

All Participants (applicant, applicants representative, PTO personnel)	Title	Type
SAMUEL W LIU	Examiner	Telephonic
Stephanie Seidman	Attorney of Record	

Date of Interview: 10 February 2021

Issues Discussed:

Other

Discussed patentability of claims 1, 3, 5, 6, and 8-21. Examiner pointed out that claims 1, 3, 5, 6 and 8-20 are allowable; however, the process claim 20 previously withdrawn from further consideration will not be rejoined. This is because, although the process of claim 21 employs the allowable product of claim 20 which depends from the allowed claim 1, claim 21, which is directed to a method of treatment using the allowable product of claim 21 for treating a disease or/and disorder such as a tumor, edema, a cardiovascular disorder and ophthalmic disorder condition and pulmonary disease, as written does not satisfy written description requirement and scope enablement requirement of 35 USC 112(a); and thus, claim 21 is not in the condition for allowance. Therefore, claim 21 is not rejoined and should be cancel for considering allowability in this case. Applicants' representative agreed to cancel claim 12.

/SAMUEL W LIU/ Examiner, Art Unit 1656	
<p>Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04</p> <p>Please further see: MPEP 713.04 Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b) 37 CFR § 1.2 Business to be transacted in writing</p>	

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

Notice of References Cited	Application/Control No. 16/824,572	Applicant(s)/Patent Under Reexamination WEI et al.	
	Examiner SAMUEL W LIU	Art Unit 1656	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A					
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Lin et al. (1999) Molecular cloning of the human and monkey sperm surface protein PH-20, Proc. Natl. Acad. Sci. USA , Vol. 90, pages 10071-10075. (Year: 1999)
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

U.S. Patent and Trademark Office
PTO-892 (Rev. 01-2001)

Notice of References Cited

Part of Paper No. 20210210

<i>Search Notes</i> 	Application/Control No. 16/824,572	Applicant(s)/Patent Under Reexamination WEI et al.
	Examiner SAMUEL W LIU	Art Unit 1656

CPC - Searched*		
Symbol	Date	Examiner
C12N 9/2474	02/10/2021	SWL

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
STIC sequence search for SEQ ID NOs:3, 7, 32-39 and 591-598.	02/08/2021	SWL
WEST assignee and inventor name search with prior art search for (PH20 protein or hyaluronidase or EC 3.2.1.35) and PH20 variant or PH20mutant, or modified PH20 polypeptide / amino acid substitution at residue 313.	02/10/2021	SWL
PALM inventor name search.	02/08/2021	SWL

/SAMUEL W LIU/ Examiner, Art Unit 1656	
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<i>Search Notes</i> 	Application/Control No. 16/824,572	Applicant(s)/Patent Under Reexamination WEI et al.
	Examiner SAMUEL W LIU	Art Unit 1656

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	PGPUB text (interference) search for PH20 protein or hyaluronidase or EC 3.2.1.35) and and PH20 variant or PH20 mutant, or modified PH20 polypeptide / amino acid substitution at residue 313 .	02/10/2021	SWL

/SAMUEL W LIU/ Examiner, Art Unit 1656	
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Issue Classification 	Application/Control No. 16/824,572	Applicant(s)/Patent Under Reexamination WEI et al.
	Examiner SAMUEL W LIU	Art Unit 1656

CPC						
Symbol					Type	Version
C12N	/	9	/	2474	F	2013-01-01
A61K	/	38	/	47	I	2013-01-01
A61K	/	38	/	28	I	2013-01-01
A61K	/	45	/	06	I	2013-01-01
C12Y	/	302	/	01035	I	2013-01-01
A61K	/	9	/	0019	I	2013-01-01
A61K	/	47	/	10	I	2013-01-01
C12Q	/	1	/	34	I	2013-01-01
G01N	/	2333	/	926	A	2013-01-01
G01N	/	2333	/	928	A	2013-01-01
Y02A	/	50	/	30	A	2018-01-01
A61K	/	38	/	00	A	2013-01-01

CPC Combination Sets								
Symbol					Type	Set	Ranking	Version
A61K	/	38	/	28	I	1	1	2013-01-01
A61K	/	2300	/	00	I	1	2	2013-01-01
A61K	/	38	/	47	I	2	1	2013-01-01
A61K	/	2300	/	00	I	2	2	2013-01-01

/SAMUEL W LIU/ Examiner, Art Unit 1656 (Assistant Examiner)	11 February 2021 (Date)	Total Claims Allowed: 17	
/SCARLETT Y GOON/ QAS, Art Unit 1600 (Primary Examiner)	12 February 2021 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

Issue Classification 	Application/Control No. 16/824,572	Applicant(s)/Patent Under Reexamination WEI et al.	
	Examiner SAMUEL W LIU	Art Unit 1656	

INTERNATIONAL CLASSIFICATION			
CLAIMED			
C12N	/	9	/ 26
C12N	/	15	/ 09
NON-CLAIMED			
A61K	/	38	/ 00

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

/SAMUEL W LIU/ Examiner, Art Unit 1656 (Assistant Examiner)	11 February 2021 (Date)	Total Claims Allowed: 17	
/SCARLETT Y GOON/ QAS, Art Unit 1600 (Primary Examiner)	12 February 2021 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

Issue Classification 	Application/Control No. 16/824,572	Applicant(s)/Patent Under Reexamination WEI et al.
	Examiner SAMUEL W LIU	Art Unit 1656

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47															
CLAIMS															
Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	17	13												
2	3	10	14												
3	5	11	15												
6	6	12	16												
5	8	13	17												
7	9	14	18												
8	10	15	19												
4	11	16	20												
9	12														

/SAMUEL W LIU/ Examiner, Art Unit 1656 (Assistant Examiner)	11 February 2021 (Date)	Total Claims Allowed: 17	
/SCARLETT Y GOON/ QAS, Art Unit 1600 (Primary Examiner)	12 February 2021 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none



UNITED STATES PATENT AND TRADEMARK OFFICE

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BIB DATA SHEET

CONFIRMATION NO. 1431

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.		
16/824,572	03/19/2020	435	1656	33320.03087.US26/3087C		
RULE						
APPLICANTS HALOZYME, INC., San Diego, CA; INVENTORS Ge WEI, San Diego, CA; H. Michael Shepard, San Diego, CA; Qiping Zhao, San Diego, CA; Robert James Connor, Oceanside, CA; ** CONTINUING DATA ***** This application is a CON of 15/226,489 08/02/2016 PAT 10865400 which is a DIV of 13/694,731 12/28/2012 PAT 9447401 which claims benefit of 61/796,208 11/01/2012 and claims benefit of 61/631,313 12/30/2011 This application 16/824,572 03/19/2020 is a DIV of 13/694,731 12/28/2012 PAT 9447401 which claims benefit of 61/796,208 11/01/2012 and claims benefit of 61/631,313 12/30/2011 ** FOREIGN APPLICATIONS ***** ** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** 05/01/2020						
Foreign Priority claimed ☐ Yes ☒ No 35 USC 119(a-d) conditions met ☐ Yes ☒ No Verified and /SAMUEL W LIU/ Acknowledged Examiner's Signature		☐ Met after Allowance Initials	STATE OR COUNTRY CA	SHEETS DRAWINGS 13	TOTAL CLAIMS 21	INDEPENDENT CLAIMS 2
ADDRESS Dentons US LLP 4655 Executive Drive Suite 700 San Diego, CA 92121 UNITED STATES						
TITLE PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF						
FILING FEE RECEIVED 3420	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:			☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit		

WEST Search History for Application 16824572

Creation Date: 2021021101:57

Interference Searches

Query	DB	Hits	Op.	Plur.	Thes.	Date
(PH20 near1 (protein or polypeptide) or hyaluronidase or EC 3.2.1.35) and (variant or mutant or recombinant \$ 3 or engineered or modified or mutated or substitut \$ 3)	PGPB	11816	ADJ	YES		02-11-2021
((PH20 near1 (protein or polypeptide) or hyaluronidase or EC 3.2.1.35) and (variant or mutant or recombinant \$ 3 or engineered or modified or mutated or substitut \$ 3)) and PH20 and (replacement or substitut \$ 3) with (amino acid or residue or position)	PGPB	173	ADJ	YES		02-11-2021
((PH20 near1 (protein or polypeptide) or hyaluronidase or EC 3.2.1.35) and (variant or mutant or recombinant \$ 3 or engineered or modified or mutated or substitut \$ 3) and PH20 and (replacement or substitut \$ 3) with (amino acid or residue or position)) and PH20 same (replacement or substitut \$ 3) with (amino acid or residue or position) with 313	PGPB	5	ADJ	YES		02-11-2021
((PH20 near1 (protein or polypeptide) or hyaluronidase or EC 3.2.1.35) and (variant or mutant or recombinant \$ 3 or engineered or modified or mutated or substitut \$ 3) and PH20 and (replacement or substitut \$ 3) with (amino acid or residue or position) and PH20 same (replacement or substitut \$ 3) with (amino acid or residue or position) with 313) and PH20 (protein or polypeptide)	PGPB	5	ADJ	YES		02-11-2021

Prior Art Searches

Query	DB	Hits	Op.	Plur.	Thes.	Date
(HALOZYME adj INC) and (PH20 or hyaluronidase or EC 3.2.1.35)	PGPB, USPT, USOC	110	ADJ	YES		02-11-2021
(HALOZYME adj INC and (PH20 or hyaluronidase or EC 3.2.1.35)) and PH20 with	PGPB, USPT,	74	ADJ	YES		02-11-2021

(variant or mutant or mutated or modified or recombinant\$3 or engineered or substitute\$4)	USOC					
(HALOZYME adj INC and (PH20 or hyaluronidase or EC 3.2.1.35) and PH20 with (variant or mutant or mutated or modified or recombinant\$3 or engineered or substitute\$4)) and (replac\$5 or substitute\$3) with (position or residue or amino acid) near1 313	PGPB, USPT, USOC	5	ADJ	YES		02-11-2021
WEI-GE.in. or SHEPARD-H-MICHAEL.in. or ZHAO-QIPING.in or CONNOR-ROBERT-JAMES.in.	PGPB, USPT, USOC	316	ADJ	YES		02-11-2021
(WEI-GE.in. or SHEPARD-H-MICHAEL.in. or ZHAO-QIPING.in or CONNOR-ROBERT-JAMES.in.) and PH20 with (variant or mutant or mutated or modified or recombinant\$3 or engineered or substitute\$4)	PGPB, USPT, USOC	33	ADJ	YES		02-11-2021
(WEI-GE.in. or SHEPARD-H-MICHAEL.in. or ZHAO-QIPING.in or CONNOR-ROBERT-JAMES.in. and PH20 with (variant or mutant or mutated or modified or recombinant\$3 or engineered or substitute\$4) and PH20 with (variant or mutant or mutated or modified or recombinant\$3 or engineered or substitute)) and (replac\$5 or substitut\$3) with (position or residue or amino acid) near1 313	PGPB, USPT, USOC	7	ADJ	YES		02-11-2021
(PH20 adj (polypeptide or protein) or hyaluronidase or EC 3.2.1.35)	PGPB, USPT, USOC	19864	ADJ	YES		02-11-2021
((PH20 adj (polypeptide or protein) or hyaluronidase or EC 3.2.1.35)) and H20 with (variant or mutant or mutated or modified or recombinant\$3 or engineered or substitut\$4)	PGPB, USPT, USOC	5	ADJ	YES		02-11-2021
(PH20 near1 (protein or polypeptide) or hyaluronidase or EC 3.2.1.35) and (variant or mutant or recombinant\$3 or engineered or modified or mutated or substitut\$3)	PGPB, USPT, USOC	18689	ADJ	YES		02-11-2021
((PH20 near1 (protein or polypeptide) or hyaluronidase or EC 3.2.1.35) and (variant or mutant or recombinant\$3 or engineered or modified or mutated or substitut\$3)) and PH20 near1 (protein or polypeptide)	PGPB, USPT, USOC	109	ADJ	YES		02-11-2021
((PH20 near1 (protein or polypeptide) or hyaluronidase or EC 3.2.1.35) and (variant or mutant or recombinant\$3 or engineered or	PGPB, USPT, USOC	7	ADJ	YES		02-11-2021

modified or mutated or substitut\$3) and PH20 near1 (protein or polypeptide)) and PH20 same (replac\$5 or substitut\$3) with (amino acid or residue or position) with 313						
((PH20 near1 (protein or polypeptide) or hyaluronidase or EC 3.2.1.35) and (variant or mutant or recombinant\$3 or engineered or modified or mutated or substitut\$3) and PH20 near1 (protein or polypeptide) and PH20 same (replac\$5 or substitut\$3) with (amino acid or residue or position) with 313) and PH20 with (replac\$5 or substitut\$3) with (amino acid or residue or position) near1 313	PGPB, USPT, USOC	7	ADJ	YES		02-11-2021

Hit List

First Hit

Interference Search

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Fwd Refs

Bkwd Refs

Generate OC

Search Results - Record(s) 1 through 5 of 5 returned.

☐ 1. Document ID: US 20200318091 A1

L4: Entry 1 of 5

File: PGPB

Oct 8, 2020

PGPUB-DOCUMENT-NUMBER: 20200318091
PGPUB-FILING-TYPE:
DOCUMENT-IDENTIFIER: US 20200318091 A1

TITLE: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF

PUBLICATION-DATE: June 25, 2020

PATENT-FAMILY-ID: 47595052

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
WEI; GE	SAN DIEGO	CA	US
SHEPARD; H. MICHAEL	SAN DIEGO	CA	US
ZHAO; QIPING	SAN DIEGO	CA	US
CONNOR; ROBERT JAMES	OCEANSIDE	CA	US

APPLICANT-INFORMATION:

NAME	CITY	STATE	COUNTRY	AUTHORITY	TYPE
HALOZYME, INC.	SAN DIEGO	CA	US		

APPL-NO: 16/912590 [PALM] [DAV] [US Family]
DATE FILED: June 25, 2020

US-CL-CURRENT: 1/1

CPC-CURRENT:

TYPE	CPC	DATE
CPCI	<u>C 12 Y 302/01035</u>	20130101
CPCI	<u>A 61 K 38/47</u>	20130101
CPCI	<u>A 61 P 3/04</u>	20180101
CPCI	<u>A 61 P 35/00</u>	20180101
CPCI	<u>A 61 K 45/06</u>	20130101
CPCI	<u>C 12 Q 1/34</u>	20130101
CPCI	<u>A 61 P 11/00</u>	20180101
CPCI	<u>A 61 K 38/28</u>	20130101
CPCI	<u>A 61 P 3/10</u>	20180101
CPCI	<u>A 61 K 9/0019</u>	20130101
CPCI	<u>A 61 K 47/10</u>	20130101

CPCI A 61 P 27/02 20180101
CPCI A 61 P 29/00 20180101
CPCI C 12 N 9/2474 20130101
CPCI A 61 P 43/00 20180101
CPCI A 61 K 38/28 20130101
CPCI A 61 K 2300/00 20130101
CPCI A 61 K 38/47 20130101
CPCI A 61 K 2300/00 20130101
CPCA G 01 N 2333/926 20130101
CPCA A 61 K 38/00 20130101
CPCA G 01 N 2333/928 20130101
CPCA Y 02 A 50/30 20180101

CPC-COMBINATION-SET(S) :

TYPE RANK CPC
CPCC 1 A 61 K 38/28
2 A 61 K 2300/00
CPCC 1 A 61 K 38/47
2 A 61 K 2300/00

ABSTRACT:

Modified PH20 hyaluronidase polypeptides, including modified polypeptides that exhibit increased stability and/or increased activity, are provided. Also provided are compositions and formulations and uses thereof.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Figures	Claims	KWIC	Drawings
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☐ 2. Document ID: US 20200255814 A1

L4: Entry 2 of 5

File: PGPB

Aug 13, 2020

PGPUB-DOCUMENT-NUMBER: 20200255814

PGPUB-FILING-TYPE:

DOCUMENT-IDENTIFIER: US 20200255814 A1

TITLE: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF

PUBLICATION-DATE: March 19, 2020

PATENT-FAMILY-ID: 47595052

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
WEI; Ge	San Diego	CA	US
Shepard; H. Michael	San Diego	CA	US
Zhao; Qiping	San Diego	CA	US
Connor; Robert James	Oceanside	CA	US

APPLICANT-INFORMATION:

NAME	CITY	STATE	COUNTRY	AUTHORITY	TYPE
HALOZYME, INC.	San Diego	CA	US		

APPL-NO: 16/824572 [PALM] [DAV] [US Family]
DATE FILED: March 19, 2020

US-CL-CURRENT: 1/1

CPC-CURRENT:

TYPE	CPC	DATE
CPCI	<u>A 61 K 9/0019</u>	20130101
CPCI	<u>A 61 P 35/00</u>	20180101
CPCI	<u>A 61 P 3/04</u>	20180101
CPCI	<u>A 61 P 3/10</u>	20180101
CPCI	<u>A 61 K 47/10</u>	20130101
CPCI	<u>A 61 P 11/00</u>	20180101
CPCI	<u>A 61 P 27/02</u>	20180101
CPCI	<u>C 12 Q 1/34</u>	20130101
CPCI	<u>C 12 Y 302/01035</u>	20130101
CPCI	<u>A 61 P 43/00</u>	20180101
CPCI	<u>A 61 K 38/47</u>	20130101
CPCI	<u>A 61 P 29/00</u>	20180101
CPCI	<u>A 61 K 45/06</u>	20130101
CPCI	<u>A 61 K 38/28</u>	20130101
CPCI	<u>C 12 N 9/2474</u>	20130101
CPCI	<u>A 61 K 38/28</u>	20130101
CPCI	<u>A 61 K 2300/00</u>	20130101
CPCI	<u>A 61 K 38/47</u>	20130101
CPCI	<u>A 61 K 2300/00</u>	20130101
CPCA	<u>Y 02 A 50/30</u>	20180101
CPCA	<u>G 01 N 2333/928</u>	20130101
CPCA	<u>A 61 K 38/00</u>	20130101
CPCA	<u>G 01 N 2333/926</u>	20130101

CPC-COMBINATION-SET(S) :

TYPE	RANK	CPC
CPCC	1	<u>A 61 K 38/28</u>
	2	<u>A 61 K 2300/00</u>
CPCC	1	<u>A 61 K 38/47</u>
	2	<u>A 61 K 2300/00</u>

ABSTRACT:

Modified PH20 hyaluronidase polypeptides, including modified polypeptides that exhibit increased stability and/or increased activity, are provided. Also provided are compositions and formulations and uses thereof.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Claims	KIMC	Draw De
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☐ 3. Document ID: US 20160362670 A1

L4: Entry 3 of 5

File: PGPB

Dec 15, 2016

PGPUB-DOCUMENT-NUMBER: 20160362670

PGPUB-FILING-TYPE:

DOCUMENT-IDENTIFIER: US 20160362670 A1

TITLE: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF

PUBLICATION-DATE: August 2, 2016

PATENT-FAMILY-ID: 47595052

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Wei; Ge	San Diego	CA	US
Shepard; H. Michael	San Diego	CA	US
Zhao; Qiping	San Diego	CA	US
Connor; Robert James	Oceanside	CA	US

APPLICANT-INFORMATION:

NAME	CITY	STATE	COUNTRY	AUTHORITY	TYPE
HALOZYME, INC.	San Diego	CA	US		

APPL-NO: 15/226489 [PAIM] [DAV] [US Family]

DATE FILED: August 2, 2016

US-CL-CURRENT: 1/1

CPC-CURRENT:

TYPE	CPC	DATE
CPCI	<u>A 61 P 3/04</u>	20180101
CPCI	<u>A 61 P 43/00</u>	20180101
CPCI	<u>A 61 K 47/10</u>	20130101
CPCI	<u>A 61 P 3/10</u>	20180101
CPCI	<u>A 61 K 45/06</u>	20130101
CPCI	<u>A 61 K 38/47</u>	20130101
CPCI	<u>A 61 K 38/28</u>	20130101
CPCI	<u>A 61 P 27/02</u>	20180101
CPCI	<u>A 61 P 29/00</u>	20180101
CPCI	<u>A 61 P 11/00</u>	20180101
CPCI	<u>C 12 Q 1/34</u>	20130101
CPCI	<u>C 12 Y 302/01035</u>	20130101
CPCI	<u>A 61 P 35/00</u>	20180101
CPCI	<u>A 61 K 9/0019</u>	20130101
CPCI	<u>C 12 N 9/2474</u>	20130101
CPCI	<u>A 61 K 38/28</u>	20130101
CPCI	<u>A 61 K 2300/00</u>	20130101
CPCI	<u>A 61 K 38/47</u>	20130101
CPCI	<u>A 61 K 2300/00</u>	20130101
CPCA	<u>G 01 N 2333/928</u>	20130101
CPCA	<u>Y 02 A 50/30</u>	20180101
CPCA	<u>A 61 K 38/00</u>	20130101
CPCA	<u>G 01 N 2333/926</u>	20130101

CPC-COMBINATION-SET(S) :

TYPE	RANK	CPC
CPCC	1	<u>A 61 K 38/28</u>
	2	<u>A 61 K 2300/00</u>
CPCC	1	<u>A 61 K 38/47</u>
	2	<u>A 61 K 2300/00</u>

ABSTRACT:

Modified PH20 hyaluronidase polypeptides, including modified polypeptides that exhibit increased stability and/or increased activity, are provided. Also provided are compositions and formulations and uses thereof.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Claims	KMC	Draw De
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4. Document ID: US 20140178330 A9

L4: Entry 4 of 5

File: PGPB

Jun 26, 2014

PGPUB-DOCUMENT-NUMBER: 20140178330
PGPUB-FILING-TYPE: us-republication-corrected
DOCUMENT-IDENTIFIER: US 20140178330 A9

TITLE: PH20 Polypeptide Variants, Formulations And Uses Thereof

PUBLICATION-DATE: December 28, 2012

PRIOR-PUBLICATION-INFORMATION:

DOCUMENT-IDENTIFIER DOCUMENT-DATE
US 20130302275 A1 November 14, 2013

PATENT-FAMILY-ID: 47595052

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Wei; Ge	San Diego	CA	US
Shepard; H. Michael	San Diego	CA	US
Zhao; Qiping	San Diego	CA	US
Connor; Robert James	Oceanside	CA	US

APPLICANT-INFORMATION:

NAME	CITY	STATE	COUNTRY	AUTHORITY	TYPE
Wei; Ge	San Diego	CA	US		
Shepard; H. Michael	San Diego	CA	US		
Zhao; Qiping	San Diego	CA	US		
Connor; Robert James	Oceanside	CA	US		

APPL-NO: 13/694731 [PALM] [DAV] [US Family]

DATE FILED: December 28, 2012

US-CL-CURRENT: 424/85.2, 424/130.1, 424/209.1, 424/225.1, 424/85.5, 424/85.6,
424/85.7, 424/94.62, 435/18, 435/201, 435/320.1, 435/325, 536/23.2

CPC-CURRENT:

TYPE	CPC	DATE
CPCI	<u>A 61 K 47/10</u>	20130101
CPCI	<u>A 61 K 9/0019</u>	20130101
CPCI	<u>A 61 K 38/28</u>	20130101
CPCI	<u>A 61 K 38/47</u>	20130101
CPCI	<u>C 12 N 9/2474</u>	20130101
CPCI	<u>A 61 P 35/00</u>	20180101

CPCI A 61 P 3/10 20180101
 CPCI A 61 P 3/04 20180101
 CPCI A 61 P 11/00 20180101
 CPCI A 61 P 43/00 20180101
 CPCI A 61 P 29/00 20180101
 CPCI C 12 Q 1/34 20130101
 CPCI A 61 K 45/06 20130101
 CPCI C 12 Y 302/01035 20130101
 CPCI A 61 P 27/02 20180101
 CPCI A 61 K 38/28 20130101
 CPCI A 61 K 2300/00 20130101
 CPCI A 61 K 38/47 20130101
 CPCI A 61 K 2300/00 20130101
 CPCA G 01 N 2333/926 20130101
 CPCA Y 02 A 50/30 20180101
 CPCA A 61 K 38/00 20130101
 CPCA G 01 N 2333/928 20130101

CPC-COMBINATION-SET(S) :

TYPE RANK CPC
 CPCC 1 A 61 K 38/28
 2 A 61 K 2300/00
 CPCC 1 A 61 K 38/47
 2 A 61 K 2300/00

ABSTRACT:

Modified PH20 hyaluronidase polypeptides, including modified polypeptides that exhibit increased stability and/or increased activity, are provided. Also provided are compositions and formulations and uses thereof.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Claims	KMC	Draw De
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☐ 5. Document ID: US 20130302275 A1

L4: Entry 5 of 5

File: PGPB

Nov 14, 2013

PGPUB-DOCUMENT-NUMBER: 20130302275

PGPUB-FILING-TYPE:

DOCUMENT-IDENTIFIER: US 20130302275 A1

TITLE: PH20 Polypeptide Variants, Formulations And Uses Thereof

PUBLICATION-DATE: December 28, 2012

PATENT-FAMILY-ID: 47595052

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Wei; Ge	San Diego	CA	US
Shepard; H. Michael	San Diego	CA	US
Zhao; Qiping	San Diego	CA	US
Connor; Robert James	Oceanside	CA	US

APPLICANT-INFORMATION:

NAME	CITY	STATE	COUNTRY	AUTHORITY	TYPE
Wei; Ge	San Diego	CA	US		
Shepard; H. Michael	San Diego	CA	US		
Zhao; Qiping	San Diego	CA	US		
Connor; Robert James	Oceanside	CA	US		

APPL-NO: 13/694731 [PALM] [DAV] [US Family]
 DATE FILED: December 28, 2012

US-CL-CURRENT: 424/85.2; 424/130.1, 424/209.1, 424/225.1, 424/85.5, 424/85.6,
424/85.7, 424/94.62, 435/18, 435/201, 435/320.1, 435/325, 536/23.2

CPC-CURRENT:

TYPE	CPC	DATE
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CPCI	A <u>61</u> K <u>45/06</u>	20130101
CPCI	A <u>61</u> P <u>11/00</u>	20180101
CPCI	A <u>61</u> P <u>29/00</u>	20180101
CPCI	C <u>12</u> Y <u>302/01035</u>	20130101
CPCI	A <u>61</u> P <u>35/00</u>	20180101
CPCI	A <u>61</u> K <u>9/0019</u>	20130101
CPCI	A <u>61</u> K <u>38/47</u>	20130101
CPCI	A <u>61</u> P <u>3/10</u>	20180101
CPCI	A <u>61</u> P <u>27/02</u>	20180101
CPCI	C <u>12</u> Q <u>1/34</u>	20130101
CPCI	A <u>61</u> K <u>38/28</u>	20130101
CPCI	A <u>61</u> P <u>43/00</u>	20180101
CPCI	A <u>61</u> K <u>38/28</u>	20130101
CPCI	A <u>61</u> K <u>2300/00</u>	20130101
CPCI	A <u>61</u> K <u>38/47</u>	20130101
CPCI	A <u>61</u> K <u>2300/00</u>	20130101
CPCA	A <u>61</u> K <u>38/00</u>	20130101
CPCA	G <u>01</u> N <u>2333/926</u>	20130101
CPCA	G <u>01</u> N <u>2333/928</u>	20130101
CPCA	Y <u>02</u> A <u>50/30</u>	20180101

CPC-COMBINATION-SET(S) :

TYPE	RANK	CPC
CPCC	1	A <u>61</u> K <u>38/28</u>
	2	A <u>61</u> K <u>2300/00</u>
CPCC	1	A <u>61</u> K <u>38/47</u>
	2	A <u>61</u> K <u>2300/00</u>

ABSTRACT:

Modified PH20 hyaluronidase polypeptides, including modified polypeptides that exhibit increased stability and/or increased activity, are provided. Also provided are compositions and formulations and uses thereof.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Claims	KWC	Draw De
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Term	Documents
PH20	368
PH20S	12
PROTEIN	542892
PROTEINS	483354
POLYPEPTIDE	224928
POLYPEPTIDES	186046
((PH20 ADJ (POLYPEPTIDE OR PROTEIN)) AND 3).PGPB.	5
(L3 and PH20 (protein or polypeptide)).PGPB.	5

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PH20 (polypeptide or protein) and amino acid substitution 313



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ph20 polypeptide variants, formulations and uses thereof

Aug 13, 2020 — A modified PH20 polypeptide, comprising a sequence of amino acids set forth in ... that contains the amino acid replacement at residue 309 and/or 313 compared to ... such as in water and plasma protein homeostasis (Laurent T C et al. ... The modification can be an amino acid replacement (substitution), ...

patents.google.com > patent

US5721348A - DNA encoding PH-20 proteins - Google Patents

Preferably, the sperm surface protein is the PH-20 protein. ... The derived amino acid sequence contains all the tryptic peptide sequences obtained ... identical and 74% similar (includes conservative substitutions) to guinea pig PH-20. ... NAME/KEY: CDS(B) LOCATION: 313..1848(x) SEQUENCE DESCRIPTION: SEQ ID ...

[www.ncbi.nlm.nih.gov](https://www.ncbi.nlm.nih.gov/books) > books > NBK22364

Primary Structure: Amino Acids Are Linked by Peptide Bonds ...

Jump to **Proteins Have Unique Amino Acid Sequences That Are ...** — Indeed, the complete amino acid sequences of more ... The amino acid sequence of a protein is often ... from a change in a single amino acid within a protein.
Missing: PH20 313

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Structure-activity relationships of alphaIIb 313-320 derived ...

Structure-activity relationships of alphaIIb 313-320 derived peptide inhibitors of ... of platelets, can interact with a variety of adhesive proteins including fibrinogen, ... the sequence 313-320 aiming to evaluate the contribution of each amino acid in ... It was found that the substitution of Y313, M314, E315 or S316 by A does not ...
Missing: PH20 | Must include: PH20

hupo.org > resources > Documents

Proteolytic Cleavage—Mechanisms, Function, and - HUPO

by T Klein · 2018 · Cited by 63 · Related articles

Dec 21, 2017 — enzymatic hydrolysis of a peptide bond in a peptide or protein substrate ... the amino acid or metal ion catalyzing the peptide-bond cleavage. ... were partially mediated by PH-20 or -30 (fertilin α and ... BioMetals 2001, 14, 271–313. ... Substitution of the S1 Site and Adjacent Loops Reconstitutes Esterase.

www2.chemistry.msu.edu > reusch > virttextjml > protein2

Proteins - MSU chemistry

If the amine and carboxylic acid functional groups in amino acids join ... This keeps the peptide links relatively planar and resistant to conformational change. ... The different amino acids that make up a peptide or protein, and the order in which ...
Missing: PH20 313

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ProAlanase is an Effective Alternative to Trypsin for Proteomics ...

cuts proteins after or before specific amino acids. ... must be performed at low pH (20). ... deduce peptide sequences directly from high-quality MS/MS ... taining species-specific amino acid substitutions (supple- ... Acta 1863, 303–313, 57.

edoc.unibas.ch > DissB_6004

Crystal structure determination of hyaluronidase, a major bee ... - edoc



PH20 (polypeptide or protein) and amino acid substitution 313



terminal end; whereas the Cys222-Cys313 bridge joins the sec... synthetic 10-mer peptide comprising the entire epitope (Arg138-Glu152) is.

People also ask

How are polypeptides formed from amino acids?



How many peptide bonds are in 100 amino acids?



What does polypeptide mean?



How do amino acids connect to peptide bonds?



Feedback

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Acute pH-dependent Regulation of AE2-mediated Anion Exchange

...

Aia ((A)6) and individual amino acid substitutions to investigate the ... The anion exchangers AE1, AE2, and AE3 are polypeptide products of the SLC4 ... ple cytoskeletal proteins, glycolytic enzymes, and hemoglobin ... mutants P313A and H317A, and the double mutant H314A/ H317A. ... activity by pH (28). However, the ...

www.michigan.gov › documents › exploreiabscience

Introduction to Proteins and Amino Acids

Proteins are made up of smaller units called amino acids, which are building ... by peptide bonds forming a long chain of proteins. ... to a change in the amino acid sequence of the protein. Even changing just one amino acid in a protein's ...

Missing: PH20 313

Ad • www.acrobiosystems.com/ph20

Human Ph20, His Tag - ACROBiosystems

Ph20 High purity, Bioactivity validated by ELISA, Free Protocol Offered. Recombinant **proteins** designed for biological medicine R&D. Free protocols offered. 200+ Biotinylated **Protein**. Best Biotinylated **Protein**. Active & Bulk in Stock. Next Day Shipping.

Searches related to PH20 (polypeptide or protein) and amino acid substitution 313

hydrolysis of proteins into peptides and amino acids

which level of protein structure is formed by the weak bonds between oxygen and hydrogen atoms

the linear sequence of amino acids within a protein is considered the

two amino acids joined together by a peptide bond is called this

distinguish between a protein and a polypeptide

amino acids in proteins are joined together by

where are amino acids joined together to make polypeptides

the relation between amino acid and polypeptide is similar to the relation between

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Substitute Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No. 33320.03087.US26/ 3087C	Application No. 16/824,572
List of Patents and Publications for Applicant's Information Disclosure Statement (37 CFR §1.98(b))		Inventors Wei <i>et al.</i>	
		Filing Date March 19, 2020	Group Art Unit 1656

U.S. Patent Documents

Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
	AA	2020/0318091	10/08/2020	Wei et al.	424	094.620	06/25/2020
	AB	2020/0368330	11/26/2020	Frost et al.	424	078.170	07/16/2020

Foreign Patent Documents or Published Foreign Patent Applications

Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Translation	
					Yes	No
None						

Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig. ID	Document
	AC	Letter/Written Disclosure of the Information Disclosure Statement for the above-referenced application, filed herewith on January 27, 2021, 2 pages.
	AD	Rosengren et al., "Clinical Immunogenicity of rHuPII20, a Hyaluronidase Enabling Subcutaneous Drug Administration," AAPS J. 17(5):1144-56 (2015).
	AE	Written Submissions, filed Oct. 09, 2020, responsive to Hearing Notice, issued Aug. 10, 2020, in connection with Indian Patent Application No. 6272/DELNP/2014, 27 pages.
	AF	Amended claims and abstract, filed Nov. 19, 2020, responsive to Examiner request, in connection with Indian Patent Application No. 6272/DELNP/2014, 22 pages.
	AG	Certificate of Grant, issued Dec. 28, 2020, in connection with Indian Patent Application No. 6272/DELNP/2014, 1 page.
	AH	Certificate of Grant, issued Oct. 01, 2020, in connection with Israeli Patent Application No. 233192, 3 pages.
	AI	Notification Prior to Acceptance, dated Dec. 14, 2020, issued in connection with Israeli Patent Application No. 274798 [English reporting letter; original document as issued in Hebrew; and English translation of allowed claims], 10 pages.

Examiner Signature /SAMUEL W LIU/	Date Considered 02/08/2021
EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

APPL-NO: 16/824572 [PALM] [DAV] [US Family]
DATE FILED: March 19, 2020

US-CL-CURRENT: 1/1

CPC-CURRENT:

TYPE	CPC	DATE
CPCI	<u>A 61 K 9/0019</u>	20130101
CPCI	<u>A 61 P 35/00</u>	20180101
CPCI	<u>A 61 P 3/04</u>	20180101
CPCI	<u>A 61 P 3/10</u>	20180101
CPCI	<u>A 61 K 47/10</u>	20130101
CPCI	<u>A 61 P 11/00</u>	20180101
CPCI	<u>A 61 P 27/02</u>	20180101
CPCI	<u>C 12 Q 1/34</u>	20130101
CPCI	<u>C 12 Y 302/01035</u>	20130101
CPCI	<u>A 61 P 43/00</u>	20180101
CPCI	<u>A 61 K 38/47</u>	20130101
CPCI	<u>A 61 P 29/00</u>	20180101
CPCI	<u>A 61 K 45/06</u>	20130101
CPCI	<u>A 61 K 38/28</u>	20130101
CPCI	<u>C 12 N 9/2474</u>	20130101
CPCI	<u>A 61 K 38/28</u>	20130101
CPCI	<u>A 61 K 2300/00</u>	20130101
CPCI	<u>A 61 K 38/47</u>	20130101
CPCI	<u>A 61 K 2300/00</u>	20130101
CPCA	<u>Y 02 A 50/30</u>	20180101
CPCA	<u>G 01 N 2333/928</u>	20130101
CPCA	<u>A 61 K 38/00</u>	20130101
CPCA	<u>G 01 N 2333/926</u>	20130101

CPC-COMBINATION-SET(S) :

TYPE	RANK	CPC
CPCC	1	<u>A 61 K 38/28</u>
	2	<u>A 61 K 2300/00</u>
CPCC	1	<u>A 61 K 38/47</u>
	2	<u>A 61 K 2300/00</u>

ABSTRACT:

Modified PH20 hyaluronidase polypeptides, including modified polypeptides that exhibit increased stability and/or increased activity, are provided. Also provided are compositions and formulations and uses thereof.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Claims	KIMC	Draw De
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☐ 3. Document ID: US 20160362670 A1

L8: Entry 3 of 7

File: PGPB

Dec 15, 2016

PGPUB-DOCUMENT-NUMBER: 20160362670

PGPUB-FILING-TYPE:

DOCUMENT-IDENTIFIER: US 20160362670 A1

TITLE: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF

PUBLICATION-DATE: August 2, 2016

PATENT-FAMILY-ID: 47595052

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Wei; Ge	San Diego	CA	US
Shepard; H. Michael	San Diego	CA	US
Zhao; Qiping	San Diego	CA	US
Connor; Robert James	Oceanside	CA	US

APPLICANT-INFORMATION:

NAME	CITY	STATE	COUNTRY	AUTHORITY	TYPE
HALOZYME, INC.	San Diego	CA	US		

APPL-NO: 15/226489 [PAIM] [DAV] [US Family]

DATE FILED: August 2, 2016

US-CL-CURRENT: 1/1

CPC-CURRENT:

TYPE	CPC	DATE
CPCI	<u>A 61 P 3/04</u>	20180101
CPCI	<u>A 61 P 43/00</u>	20180101
CPCI	<u>A 61 K 47/10</u>	20130101
CPCI	<u>A 61 P 3/10</u>	20180101
CPCI	<u>A 61 K 45/06</u>	20130101
CPCI	<u>A 61 K 38/47</u>	20130101
CPCI	<u>A 61 K 38/28</u>	20130101
CPCI	<u>A 61 P 27/02</u>	20180101
CPCI	<u>A 61 P 29/00</u>	20180101
CPCI	<u>A 61 P 11/00</u>	20180101
CPCI	<u>C 12 Q 1/34</u>	20130101
CPCI	<u>C 12 Y 302/01035</u>	20130101
CPCI	<u>A 61 P 35/00</u>	20180101
CPCI	<u>A 61 K 9/0019</u>	20130101
CPCI	<u>C 12 N 9/2474</u>	20130101
CPCI	<u>A 61 K 38/28</u>	20130101
CPCI	<u>A 61 K 2300/00</u>	20130101
CPCI	<u>A 61 K 38/47</u>	20130101
CPCI	<u>A 61 K 2300/00</u>	20130101
CPCA	<u>G 01 N 2333/928</u>	20130101
CPCA	<u>Y 02 A 50/30</u>	20180101
CPCA	<u>A 61 K 38/00</u>	20130101
CPCA	<u>G 01 N 2333/926</u>	20130101

CPC-COMBINATION-SET(S) :

TYPE	RANK	CPC
CPCC	1	<u>A 61 K 38/28</u>
	2	<u>A 61 K 2300/00</u>
CPCC	1	<u>A 61 K 38/47</u>
	2	<u>A 61 K 2300/00</u>

ABSTRACT:

Modified PH20 hyaluronidase polypeptides, including modified polypeptides that exhibit increased stability and/or increased activity, are provided. Also provided are compositions and formulations and uses thereof.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Claims	KMC	Draw De
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4. Document ID: US 20140178330 A9

L8: Entry 4 of 7

File: PGPB

Jun 26, 2014

PGPUB-DOCUMENT-NUMBER: 20140178330
PGPUB-FILING-TYPE: us-republication-corrected
DOCUMENT-IDENTIFIER: US 20140178330 A9

TITLE: PH20 Polypeptide Variants, Formulations And Uses Thereof

PUBLICATION-DATE: December 28, 2012

PRIOR-PUBLICATION-INFORMATION:

DOCUMENT-IDENTIFIER DOCUMENT-DATE
US 20130302275 A1 November 14, 2013

PATENT-FAMILY-ID: 47595052

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Wei; Ge	San Diego	CA	US
Shepard; H. Michael	San Diego	CA	US
Zhao; Qiping	San Diego	CA	US
Connor; Robert James	Oceanside	CA	US

APPLICANT-INFORMATION:

NAME	CITY	STATE	COUNTRY	AUTHORITY	TYPE
Wei; Ge	San Diego	CA	US		
Shepard; H. Michael	San Diego	CA	US		
Zhao; Qiping	San Diego	CA	US		
Connor; Robert James	Oceanside	CA	US		

APPL-NO: 13/694731 [PALM] [DAV] [US Family]
DATE FILED: December 28, 2012

US-CL-CURRENT: 424/85.2, 424/130.1, 424/209.1, 424/225.1, 424/85.5, 424/85.6,
424/85.7, 424/94.62, 435/18, 435/201, 435/320.1, 435/325, 536/23.2

CPC-CURRENT:

TYPE	CPC	DATE
CPCI	<u>A 61 K 47/10</u>	20130101
CPCI	<u>A 61 K 9/0019</u>	20130101
CPCI	<u>A 61 K 38/28</u>	20130101
CPCI	<u>A 61 K 38/47</u>	20130101
CPCI	<u>C 12 N 9/2474</u>	20130101
CPCI	<u>A 61 P 35/00</u>	20180101

CPCI A 61 P 3/10 20180101
 CPCI A 61 P 3/04 20180101
 CPCI A 61 P 11/00 20180101
 CPCI A 61 P 43/00 20180101
 CPCI A 61 P 29/00 20180101
 CPCI C 12 Q 1/34 20130101
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 CPCA G 01 N 2333/926 20130101
 CPCA Y 02 A 50/30 20180101
 CPCA A 61 K 38/00 20130101
 CPCA G 01 N 2333/928 20130101

CPC-COMBINATION-SET(S) :

TYPE RANK CPC
 CPCC 1 A 61 K 38/28
 2 A 61 K 2300/00
 CPCC 1 A 61 K 38/47
 2 A 61 K 2300/00

ABSTRACT:

Modified PH20 hyaluronidase polypeptides, including modified polypeptides that exhibit increased stability and/or increased activity, are provided. Also provided are compositions and formulations and uses thereof.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Claims	KMC	Draw De
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☐ 5. Document ID: US 20130302275 A1

L8: Entry 5 of 7

File: PGPB

Nov 14, 2013

PGPUB-DOCUMENT-NUMBER: 20130302275

PGPUB-FILING-TYPE:

DOCUMENT-IDENTIFIER: US 20130302275 A1

TITLE: PH20 Polypeptide Variants, Formulations And Uses Thereof

PUBLICATION-DATE: December 28, 2012

PATENT-FAMILY-ID: 47595052

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Wei; Ge	San Diego	CA	US
Shepard; H. Michael	San Diego	CA	US
Zhao; Qiping	San Diego	CA	US
Connor; Robert James	Oceanside	CA	US

APPLICANT-INFORMATION:

NAME	CITY	STATE	COUNTRY	AUTHORITY	TYPE
Wei; Ge	San Diego	CA	US		
Shepard; H. Michael	San Diego	CA	US		
Zhao; Qiping	San Diego	CA	US		
Connor; Robert James	Oceanside	CA	US		

APPL-NO: 13/694731 [PALM] [DAV] [US Family]
 DATE FILED: December 28, 2012

US-CL-CURRENT: 424/85.2; 424/130.1, 424/209.1, 424/225.1, 424/85.5, 424/85.6,
424/85.7, 424/94.62, 435/18, 435/201, 435/320.1, 435/325, 536/23.2

CPC-CURRENT:

TYPE	CPC	DATE
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CPCI	A <u>61</u> K <u>47/10</u>	20130101
CPCI	C <u>12</u> N <u>9/2474</u>	20130101
CPCI	A <u>61</u> K <u>45/06</u>	20130101
CPCI	A <u>61</u> P <u>11/00</u>	20180101
CPCI	A <u>61</u> P <u>29/00</u>	20180101
CPCI	C <u>12</u> Y <u>302/01035</u>	20130101
CPCI	A <u>61</u> P <u>35/00</u>	20180101
CPCI	A <u>61</u> K <u>9/0019</u>	20130101
CPCI	A <u>61</u> K <u>38/47</u>	20130101
CPCI	A <u>61</u> P <u>3/10</u>	20180101
CPCI	A <u>61</u> P <u>27/02</u>	20180101
CPCI	C <u>12</u> Q <u>1/34</u>	20130101
CPCI	A <u>61</u> K <u>38/28</u>	20130101
CPCI	A <u>61</u> P <u>43/00</u>	20180101
CPCI	A <u>61</u> K <u>38/28</u>	20130101
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CPCA	A <u>61</u> K <u>38/00</u>	20130101
CPCA	G <u>01</u> N <u>2333/926</u>	20130101
CPCA	G <u>01</u> N <u>2333/928</u>	20130101
CPCA	Y <u>02</u> A <u>50/30</u>	20180101

CPC-COMBINATION-SET(S) :

TYPE	RANK	CPC
CPCC	1	A <u>61</u> K <u>38/28</u>
	2	A <u>61</u> K <u>2300/00</u>
CPCC	1	A <u>61</u> K <u>38/47</u>
	2	A <u>61</u> K <u>2300/00</u>

ABSTRACT:

Modified PH20 hyaluronidase polypeptides, including modified polypeptides that exhibit increased stability and/or increased activity, are provided. Also provided are compositions and formulations and uses thereof.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Claims	KWC	Draw De
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6. Document ID: US 10865400 B2

L8: Entry 6 of 7

File: USPT

Dec 15, 2020

US-PAT-NO: 10865400

DOCUMENT-IDENTIFIER: US 10865400 B2

TITLE: PH20 polypeptide variants, formulations and uses thereof

DATE-ISSUED: December 15, 2020

PRIOR-PUBLICATION-INFORMATION:

DOCUMENT-IDENTIFIER DOCUMENT-DATE

US 20160362670 A1 December 15, 2016

PATENT-FAMILY-ID: 47595052

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Wei; Ge	San Diego	CA		US
Shepard; H. Michael	San Diego	CA		US
Zhao; Qiping	San Diego	CA		US
Connor; Robert James	Oceanside	CA		US

APPLICANT-INFORMATION:

NAME	CITY	STATE	COUNTRY	AUTHORITY	TYPE
HALOZYME, INC.	San Diego	CA	US		

APPL-NO: 15/226489 [PALM] [DAV] [US Family]

DATE FILED: August 2, 2016

US-CL-CURRENT: 1/1

CPC-CURRENT:

TYPE	CPC	DATE
CPCI	<u>A 61 K 9/0019</u>	20130101
CPCI	<u>A 61 P 3/04</u>	20180101
CPCI	<u>A 61 P 35/00</u>	20180101
CPCI	<u>A 61 P 3/10</u>	20180101
CPCI	<u>A 61 P 29/00</u>	20180101
CPCI	<u>C 12 Y 302/01035</u>	20130101
CPCI	<u>C 12 N 9/2474</u>	20130101
CPCI	<u>A 61 K 47/10</u>	20130101
CPCI	<u>A 61 K 45/06</u>	20130101
CPCI	<u>A 61 K 38/47</u>	20130101
CPCI	<u>A 61 P 27/02</u>	20180101
CPCI	<u>A 61 P 43/00</u>	20180101
CPCI	<u>A 61 P 11/00</u>	20180101
CPCI	<u>C 12 Q 1/34</u>	20130101
CPCI	<u>A 61 K 38/28</u>	20130101
CPCI	<u>A 61 K 38/28</u>	20130101
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CPCI	<u>A 61 K 2300/00</u>	20130101

CPCA G 01 N 2333/928 20130101
 CPCA A 61 K 38/00 20130101
 CPCA G 01 N 2333/926 20130101
 CPCA Y 02 A 50/30 20180101

CPC-COMBINATION-SET(S) :

TYPE RANK CPC
 CPCC 1 A 61 K 38/28
 2 A 61 K 2300/00
 CPCC 1 A 61 K 38/47
 2 A 61 K 2300/00

ABSTRACT:

Modified PH20 hyaluronidase polypeptides, including modified polypeptides that exhibit increased stability and/or increased activity, are provided. Also provided are compositions and formulations and uses thereof.

18 Claims, 13 Drawing figures
 Exemplary Claim Number: 1
 Number of Drawing Sheets: 13

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Figures	Claims	KMC	Draw De
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☐ 7. Document ID: US 9447401 B2

L8: Entry 7 of 7

File: USPT

Sep 20, 2016

US-PAT-NO: 9447401

DOCUMENT-IDENTIFIER: US 9447401 B2

****Please see Images for: (Certificate of Correction) ****

TITLE: PH20 polypeptide variants, formulations and uses thereof

DATE-ISSUED: September 20, 2016

PRIOR-PUBLICATION-INFORMATION:

DOCUMENT-IDENTIFIER DOCUMENT-DATE

US 20130302275 A1 November 14, 2013

US 20140178330 A9 June 26, 2014

PATENT-FAMILY-ID: 47595052

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Wei; Ge	San Diego	CA		US
Shepard; H. Michael	San Diego	CA		US
Zhao; Qiping	San Diego	CA		US
Connor; Robert James	Oceanside	CA		US

APPLICANT-INFORMATION:

NAME	CITY	STATE	COUNTRY	AUTHORITY	TYPE
Wei; Ge	San Diego	CA	US		

Shepard; H. Michael San Diego CA US
 Zhao; Qiping San Diego CA US
 Connor; Robert James Oceanside CA US

APPL-NO: 13/694731 [PALM] [DAV] [US Family]
 DATE FILED: December 28, 2012

US-CL-CURRENT: 1/1

CPC-CURRENT:

TYPE	CPC	DATE
CPCI	A <u>61</u> P <u>27/02</u>	20180101
CPCI	A <u>61</u> K <u>45/06</u>	20130101
CPCI	A <u>61</u> K <u>9/0019</u>	20130101
CPCI	A <u>61</u> P <u>35/00</u>	20180101
CPCI	C <u>12</u> Y <u>302/01035</u>	20130101
CPCI	A <u>61</u> P <u>3/04</u>	20180101
CPCI	C <u>12</u> N <u>9/2474</u>	20130101
CPCI	A <u>61</u> K <u>38/28</u>	20130101
CPCI	A <u>61</u> P <u>11/00</u>	20180101
CPCI	A <u>61</u> P <u>3/10</u>	20180101
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CPCI	A <u>61</u> K <u>47/10</u>	20130101
CPCI	C <u>12</u> Q <u>1/34</u>	20130101
CPCI	A <u>61</u> P <u>29/00</u>	20180101
CPCI	A <u>61</u> P <u>43/00</u>	20180101
CPCI	A <u>61</u> K <u>38/28</u>	20130101
CPCI	A <u>61</u> K <u>2300/00</u>	20130101
CPCI	A <u>61</u> K <u>38/47</u>	20130101
CPCI	A <u>61</u> K <u>2300/00</u>	20130101
CPCA	G <u>01</u> N <u>2333/926</u>	20130101
CPCA	A <u>61</u> K <u>38/00</u>	20130101
CPCA	G <u>01</u> N <u>2333/928</u>	20130101
CPCA	Y <u>02</u> A <u>50/30</u>	20180101

CPC-COMBINATION-SET(S) :

TYPE	RANK	CPC
CPCC	1	A <u>61</u> K <u>38/28</u>
	2	A <u>61</u> K <u>2300/00</u>
CPCC	1	A <u>61</u> K <u>38/47</u>
	2	A <u>61</u> K <u>2300/00</u>

ABSTRACT:

Modified PH20 hyaluronidase polypeptides, including modified polypeptides that exhibit increased stability and/or increased activity, are provided. Also provided are compositions and formulations and uses thereof.

49 Claims, 13 Drawing figures
 Exemplary Claim Number: 1
 Number of Drawing Sheets: 13

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Claims	KMC	Draw
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Term	Documents
PH20	626
PH20S	16
AMINO	1263962
AMINOES	4
AMINOS	2226
AMINOE	550
ACID	2822539
ACIDS	1663405
RESIDUE	1029029
RESIDUES	617736
POSITION	8774177
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Web Search History

date, time	web site	search string
2/11/2021 4:18:21 AM	Google	PH20 protein or hyaluronidase or EC 3.2.1.35
2/11/2021 4:19:07 AM	Google	PH20 (variant or modified or mutant) and amino acid substitution
2/11/2021 4:20:52 AM	Google	PH20 and amino acid substitution at residue 313
2/11/2021 4:22:25 AM	Google	PH20 (polypeptide or protein) and amino acid substitution 313

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s)	: Ge Wei <i>et al.</i>	Art Unit	: 1656
Serial No.	: 16/824,572	Examiner	: Samuel W. Liu
Filed	: March 19, 2020	Conf. No.	: 1431
		Cust. No.	: 13565
Title	: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF		

Mail Stop Missing Parts

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

REQUEST FOR CORRECTED FILING RECEIPT

Dear Sir:

Transmitted herewith is this *Request for Corrected Filing Receipt*, a copy of the *Filing Receipt*, mailed May 4, 2020, with annotated corrections, and an updated *Application Data Sheet*, marked to show the changes to the residence and mailing address information of inventor H. Michael Shepard.

Please update the second Inventor's City and State of Residence to read as follows:

H. Michael Shepard, Springfield, OR;

Applicant requests the city and state of the residence of inventor H. Michael Shepard be updated from "San Diego, CA" to "Springfield, OR". A marked-up updated *Application Data Sheet* (ADS) is filed herewith to provide the Office with H. Michael Shepard's new residence and mailing address information.

Applicant respectfully requests provision of an updated filing receipt to reflect the updated information.

Respectfully submitted,

/Stephanie Seidman/

Stephanie Seidman

Reg. No. 33,779

Attorney Docket No. 33320.03087.US26/3087C

Address all correspondence to: 13565

Stephanie Seidman

Dentons US LLP

4655 Executive Drive, Suite 700

San Diego, California 92121

Telephone: (619) 595-8010

Facsimile: (619) 595-8135

email: stephanie.seidman@dentons.com

CERTIFICATE OF TRANSMISSION VIA EFS-WEB

I hereby certify that this paper is being transmitted via the Electronic Filing System (EFS-WEB) to the United States Patent and Trademark Office on **May 05, 2021**.

/Rosalind E. Smith/

Rosalind E. Smith

Inventor(s) : Ge Wei *et al.*
Serial No. : 16/824,572
Filed : March 19, 2020

Attorney Docket No.: 33320.03087.US26/3087C
Request for Corrected Filing Receipt

Attachment 1

**Copy of *Updated Filing Receipt*, mailed May 4, 2020,
with Annotated Corrections**

COPY



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
16/824,572	03/19/2020	1652	3420	33320.03087.US26/3087C	21	2

CONFIRMATION NO. 1431

FILING RECEIPT



0000000116689249

13565
Dentons US LLP
4655 Executive Drive
Suite 700
San Diego, CA 92121

Date Mailed: 05/04/2020

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Ge WEI, San Diego, CA;
H. Michael Shepard, ~~San Diego, CA;~~ Springfield, OR;
Qiping Zhao, San Diego, CA;
Robert James Connor, Oceanside, CA;

Applicant(s)

HALOZYME, INC., San Diego, CA;

Power of Attorney:

Stephanie Seidman--33779
Frank Miskiel--53332
James Turner--74602

Domestic Priority data as claimed by applicant

This application is a CON of 15/226,489 08/02/2016
which is a DIV of 13/694,731 12/28/2012 PAT 9447401
which claims benefit of 61/796,208 11/01/2012
and claims benefit of 61/631,313 12/30/2011
This application 16/824,572
is a DIV of 13/694,731 12/28/2012 PAT 9447401
which claims benefit of 61/796,208 11/01/2012
and claims benefit of 61/631,313 12/30/2011

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.) - None.

Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 05/01/2020

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/824,572**

Projected Publication Date: 08/13/2020

Non-Publication Request: No

Early Publication Request: No
Title

PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF

Preliminary Class

435

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at <http://www.uspto.gov/web/offices/pac/doc/general/index.html>.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit <http://www.SelectUSA.gov> or call +1-202-482-6800.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	33320.03087.US26/3087C
		Application Number	<u>16/824,572</u>
Title of Invention	PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF		

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.

Inventor Information:

Inventor 1				
Legal Name				
Prefix	Given Name	Middle Name	Family Name	Suffix
	Ge		Wei	
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service				
City	San Diego	State/Province	CA	Country of Residence US
Mailing Address of Inventor:				
Address 1	11530 Miro Circle			
Address 2				
City	San Diego		State/Province	CA
Postal Code	92131		Country	US
Inventor 2				
Legal Name				
Prefix	Given Name	Middle Name	Family Name	Suffix
	H.	Michael	Shepard	
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service				
City	San Diego <u>Springfield</u>	State/Province	CA <u>OR</u>	Country of Residence US
Mailing Address of Inventor:				
Address 1	13225 Bavarian Drive <u>870 Mountaingate Drive</u>			
Address 2				
City	San Diego <u>Springfield</u>		State/Province	CA <u>OR</u>
Postal Code	92129 <u>97478</u>		Country	US
Inventor 3				
Legal Name				
Prefix	Given Name	Middle Name	Family Name	Suffix
	Qiping		Zhao	
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service				
City	San Diego	State/Province	CA	Country of Residence US
Mailing Address of Inventor:				
Address 1	11240 Windbrook Way			

Application Data Sheet 37 CFR 1.76		Attorney Docket Number		33320.03087.US26/3087C	
		Application Number		16/824,572	
Title of Invention		PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF			
Address 2					
City	San Diego		State/Province	CA	
Postal Code	92131		Country	US	
Inventor 4					
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Robert	James	Connor		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service					
City	Oceanside	State/Province	CA	Country of Residence	US
Mailing Address of Inventor:					
Address 1	451 Lexington Circle				
Address 2					
City	Oceanside		State/Province	CA	
Postal Code	92057		Country	US	
<i>All Inventors Must Be Listed – Add Additional Inventor Information blocks for each inventor.</i>					

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).	
Customer Number	13565
Email Address	stephanie.seidman@dentons.com
Email Address	mlaipsd@dentons.com

Application Information:

Title of the Invention	PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF		
Attorney Docket Number	33320.03087.US26/3087C	Small Entity Status Claimed	☐
Application Type	☒ Nonprovisional ☐ Provisional		
Subject Matter	☒ Utility ☐ Plant ☐ Design		
Total Number of Drawing Sheets (if any)	13	Suggested Figure for Publication (if any)	

Representative Information:

Please Select One:	☐ Customer Number	☒ US Patent Practitioner	☐ Limited Recognition (37 CFR 11.9)		
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Stephanie		Seidman		
Registration Number:		33,779			
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Frank	J.	Miskiel		
Registration Number:		53,332			
Prefix	Given Name	Middle Name	Family Name	Suffix	

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	33320.03087.US26/3087C	
		Application Number	<u>16/824,572</u>	
Title of Invention	PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF			
	James	M.	Turner	
Registration Number:	74,602			

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

Present Application No.		Continuity Type	Prior Application Number		Filing Date (YYYY-MM-DD)
Present Application No.	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
<i>This application</i>	Is a Continuation of	15/226,489	2016-08-02	<u>10,865,400</u>	<u>2020-12-15</u>
Prior Application No. 15/226,489 - Status:			☒ Patented ☐ Pending ☐ Abandoned ☐ Expired		
Application No.	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15/226,489	is a Divisional of	13/694,731	2012-12-28	9,447,401	2016-09-20
Prior Application No. 13/694,731 - Status:			☒ Patented ☐ Pending ☐ Abandoned ☐ Expired		
Application Number	Continuity Type	Prior Application Number		Filing Date (YYYY-MM-DD)	
13/694,731	claims priority to	61/796,208		2012-11-01	
Prior Application No. 61/796,208 - Status:			☐ Patented ☐ Pending ☐ Abandoned ☒ Expired		
Application Number	Continuity Type	Prior Application Number		Filing Date (YYYY-MM-DD)	
13/694,731	claims priority to	61/631,313		2011-12-30	
Prior Application No. 61/631,313 - Status:			☐ Patented ☐ Pending ☐ Abandoned ☒ Expired		
Application No.	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
<i>This application</i>	is a Divisional of	13/694,731	2012-12-28	9,447,401	2016-09-20
Prior Application No. 13/694,731 - Status:			☒ Patented ☐ Pending ☐ Abandoned ☐ Expired		
Application Number	Continuity Type	Prior Application Number		Filing Date (YYYY-MM-DD)	
13/694,731	claims priority to	61/796,208		2012-11-01	
Prior Application No. 61/796,208 - Status:			☐ Patented ☐ Pending ☐ Abandoned ☒ Expired		
Application Number	Continuity Type	Prior Application Number		Filing Date (YYYY-MM-DD)	
13/694,731	claims priority to	61/631,313		2011-12-30	
Prior Application No. 61/631,313 - Status:			☐ Patented ☐ Pending ☐ Abandoned ☒ Expired		

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55.

Application Number	Country	Filing Date (YYYY-MM-DD)	Priority Claimed	Access Code (if applicable)
			☐ Yes ☐ No	

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	33320.03087.US26/3087C
		Application Number	<u>16/824,572</u>
Title of Invention	PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF		

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications:

- ☐ If checked, this application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant must opt-out of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h) (1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby grants the USPTO authority to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

- ☐ **A.** Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.
- ☐ **B.** Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	33320.03087.US26/3087C
		Application Number	<u>16/824,572</u>
Title of Invention	PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF		

person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

☒ Assignee ☐ Legal Representative under 35 U.S.C. 117 ☐ Joint Inventor

☐ Person to whom the inventor is obligated to assign ☐ Person who shows sufficient proprietary interest

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

☐ Deceased ☐ Legally incapacitated

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name: HALOZYME, INC.

Mailing Address Information For Applicant:

Address 1 11388 Sorrento Valley Road

Address 2

City San Diego **State/Province** CA

Country US **Postal Code** 92121

Phone Number 858-794-8889 **Fax Number** 858-704-8311

Email Address

If needed, Additional Applicant Data may be added within this form.

Signature:

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications

Signature	/Stephanie Seidman/	Date (YYYY-MM-DD)	2021-05-05
First Name	Stephanie	Last Name	Seidman
		Registration Number	33,779

Additional Signatures may be added within this form.

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Electronic Acknowledgement Receipt	
EFS ID:	42642244
Application Number:	16824572
International Application Number:	
Confirmation Number:	1431
Title of Invention:	PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF
First Named Inventor/Applicant Name:	Ge WEI
Customer Number:	13565
Filer:	Stephanie L. Seidman/Rosalind Smith
Filer Authorized By:	Stephanie L. Seidman
Attorney Docket Number:	33320.03087.US26/3087C
Receipt Date:	05-MAY-2021
Filing Date:	19-MAR-2020
Time Stamp:	13:41:27
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment		no			
File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	3087Ctra_05-05-21.pdf	137632	no	1
			e1dbc56573f48170af3752cc2c32a450e8059821		
Warnings:					

Information:					
2	Request for Corrected Filing Receipt	3087Crcfr_05-05-21.pdf	400033	no	6
			7622d7f3c66bdd192d67221f16decce2090be96a		
Warnings:					
Information:					
3	Application Data Sheet	3087Cads_05-05-21.pdf	160607	no	5
			4514c64d05ff56291a8b69b9fd3313b291578d9a		
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
Total Files Size (in bytes):			698272		
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>					

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s)	: Ge Wei <i>et al.</i>	Art Unit	: 1656
Serial No.	: 16/824,572	Examiner	: Samuel W. Liu
Filed	: March 19, 2020	Conf. No.	: 1431
		Cust. No.	: 13565
Title	: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF		

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

Dear Sir:

Transmitted herewith are a *Request for Corrected Filing Receipt*, a copy of the *Filing Receipt*, mailed May 4, 2020, with annotated corrections, and an updated *Application Data Sheet*, for filing in connection with the above-captioned application.

The residence and mailing address of inventor H. Michael Shepard has changed and provision of an updated Filing Receipt is requested to reflect the updated information. A marked-up updated *Application Data Sheet* is filed herewith to provide the Office with inventor H. Michael Shepard's change of address.

A fee for filing this request should not be due. However, should it be determined that a fee for filing these papers is required, the Commissioner is authorized to charge Deposit Account No. 50-0911, as stated below.

☒ The Commissioner is hereby authorized to charge any fees that may be due in connection with this and the attached papers or with this application during its entire pendency to Deposit Account No. 50-0911.

Respectfully submitted,

/Stephanie Seidman/
Stephanie Seidman
Reg. No. 33,779

Attorney Docket No. 33320.03087.US26/3087C
Address all correspondence to: 13565
Stephanie Seidman
Dentons US LLP
4655 Executive Drive, Suite 700
San Diego, CA 92121
Telephone: (619) 595-8010
Facsimile: (619) 595-8135
email: stephanie.seidman@dentons.com

CERTIFICATE OF TRANSMISSION VIA EFS-WEB

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/Rosalind E. Smith/
Rosalind E. Smith



UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
16/824,572	03/19/2020	1656	3420	33320.03087.US26/3087C	21	2

CONFIRMATION NO. 1431

CORRECTED FILING RECEIPT



0000000123417381

13565
Dentons US LLP
4655 Executive Drive
Suite 700
San Diego, CA 92121

Date Mailed: 05/07/2021

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Ge WEI, San Diego, CA;
H. Michael Shepard, Springfield, OR;
Qiping Zhao, San Diego, CA;
Robert James Connor, Oceanside, CA;

Applicant(s)

HALOZYME, INC., San Diego, CA;

Power of Attorney:

Stephanie Seidman--33779
Frank Miskiel--53332
James Turner--74602

Domestic Priority data as claimed by applicant

This application is a CON of 15/226,489 08/02/2016 PAT 10865400
which is a DIV of 13/694,731 12/28/2012 PAT 9447401
which claims benefit of 61/796,208 11/01/2012
and claims benefit of 61/631,313 12/30/2011
This application 16/824,572
is a DIV of 13/694,731 12/28/2012 PAT 9447401
which claims benefit of 61/796,208 11/01/2012
and claims benefit of 61/631,313 12/30/2011

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 05/01/2020

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/824,572**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No
Title

PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF

Preliminary Class

435

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at <http://www.uspto.gov/web/offices/pac/doc/general/index.html>.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor	: Ge WEI <i>et al.</i>	Art Unit	: 1656
Serial No.	: 16/824,572	Examiner	: Samuel W. LIU
Filed	: March 19, 2020	Conf. No.	: 1431
		Cust. No.	: 13565
Title	: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF		

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P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

Dear Sir:

Transmitted herewith are *Comments Responsive to the Statement of Reasons for Allowance* (5 pages), a *PTOL-85 Part B-Fee Transmittal Form* (1 page in duplicate), with an authorization to charge the Deposit Account for the issue fee, publication fee, and order for 14 copies of the patent (Large Entity Status), for filing in connection with the above-identified application.

- ☒ The Commissioner is hereby authorized to charge any fees that may be due in connection with this paper or with this application during its entire pendency to Deposit Account No. 50-0911.

Respectfully submitted,

/Stephanie Seidman/
Stephanie Seidman
Reg. No. 33,779

Attorney Docket No. 33320.03087.US26/3087C
Address all correspondence to: 13565
Stephanie Seidman
Dentons US LLP
4655 Executive Drive, Ste. 700
San Diego, California 92121
Telephone: (619) 595-8010
Facsimile: (619) 595-8135
email: stephanie.seidman@dentons.com

CERTIFICATE OF TRANSMISSION BY EFS-WEB

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/Rosalind E. Smith/
Rosalind E. Smith

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02/18/2021

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Rosalind E. Smith

(Depositor's name)

/Rosalind E. Smith/

(Signature)

May 17, 2021

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/824,572	03/19/2020	Ge WEI	33320.03087.US26/3087C	1431

TITLE OF INVENTION: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF

APPLN. TYPE	ENTITY STATUS	ISSUE FEE	PUBLICATION FEE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
NONPROVISIONAL	UNDISCOUNTED	\$1200	\$0	\$0	\$1200	05/18/2021

EXAMINER	ART UNIT	CLASS-SUBCLASS
LIU, SAMUEL W.	1656	435-069100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. Use of a Customer Number is required.

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1. **Dentons US LLP**

2. **Stephanie Seidman**

3.

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the USPTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE (CITY and STATE OR COUNTRY)

Halozyme, Inc.

San Diego, California

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ individual ☒ corporation or other private group entity ☐ government

4a. The following fee(s) are enclosed:

☒ Issue Fee

☒ Publication Fee (No small entity discount permitted)

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☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number **50-0911**, (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

☐ a. Applicant claims MICRO ENTITY status. See 37 CFR 1.29.

☐ b. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

☐ c. Applicant changing to regular UNDISCOUNTED fee status.

a. NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

b. NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

c. NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

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(Authorized Signature) **/Stephanie Seidman/**

(Date) **May 17, 2021**

Typed or Printed Name **Stephanie Seidman**

Registration No. **33,779**

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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Rosalind E. Smith

(Depositor's name)

/Rosalind E. Smith/

(Signature)

May 17, 2021

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/824,572	03/19/2020	Ge WEI	33320.03087.US26/3087C	1431

TITLE OF INVENTION: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF

APPLN. TYPE	ENTITY STATUS	ISSUE FEE	PUBLICATION FEE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
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EXAMINER	ART UNIT	CLASS-SUBCLASS
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(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1. **Dentons US LLP**

2. **Stephanie Seidman**

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(B) RESIDENCE (CITY and STATE OR COUNTRY)

Halozyme, Inc.

San Diego, California

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ individual ☒ corporation or other private group entity ☐ government

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☐ b. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

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b. NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

c. NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

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(Authorized Signature) **/Stephanie Seidman/**

(Date) **May 17, 2021**

Typed or Printed Name **Stephanie Seidman**

Registration No. **33,779**

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	Wei <i>et al.</i>	Art Unit	: 1656
Serial No. :	16/824,572	Examiner	: Liu, Samuel W.
Filed	: March 19, 2020	Conf. No.	: 1431
		Cust. No.	: 13565
Title	: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF		

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U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

COMMENTS ON EXAMINER'S REASONS FOR ALLOWANCE

Dear Sir:

Responsive to the Examiner's Reasons for Allowance, set forth with the *Notice of Allowance*, mailed February 18, 2021, entry of the following comments into the file history of the above-captioned application respectfully is requested.

Remarks begin on page 2 of this paper.

CERTIFICATE OF TRANSMISSION VIA EFS-WEB

I hereby certify that this paper is being transmitted via the Electronic Filing System (EFS-WEB) to the United States Patent and Trademark Office on **May 17, 2021**.

/Rosalind E. Smith/

Rosalind E. Smith

REMARKS

Any fees that may be due in connection with this paper or this application during its entire pendency should be charged to Deposit Account No. 50-0911. If a Petition for extension of time is needed, this paper is to be considered such Petition.

Applicant acknowledges the *Notice of Allowance*, dated February 18, 2021, in which claims 1, 3, 5-6 and 8-20 are allowed.

Comments on Statement of Reasons for Allowance:

The Examiner provides comments and states that:

The closest prior art is the reference “Lin et al.” (*Proc. Natl. Acad. Sci USA* (1993) 90, 10071-10075). The reference teach [*sic.*] a variant PH20 polypeptide having 99.7% sequence identity to instant unmodified SEQ ID NO:3 (see sequence alignment below, wherein Qy is SEQ ID NO:3, and Db is the PH20 polypeptide of Lin); however, this reference neither teaches that the variant PH20 comprising the substitution at position 313 in the modified PH20 polypeptide of **claim 1** nor teaches that the variant polypeptide having at least 91% sequence identity to any one of mutant PH20 polypeptide of SEQ ID NOs:591-598 in **claim 9**; each of the mutant PH20 polypeptides of SEQ ID NOs:591-598 comprises the following amino acid substitutions at position 313: M313A, M313G, M313H, M313K, M313P, M313R, M313T and M313Y, respectively. There is no guidance for making the particular modification (amino acid substitution) at position 313 in a unmodified PH20 polypeptide to arrive at the claimed products of claims 1 and 9.

As a preliminary matter, it appears that the Examiner’s reference to claim 9 is in error. Claim 9 depends on claim 1 and is directed to the modified PH20 polypeptide of claim 1, wherein the modified PH20 polypeptide has at least 95% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7 and 32-66. There is no reference to SEQ ID NOs: 591-598 in claim 9. Applicant respectfully submits that the Examiner intended to reference independent claim 13 in the comments; the remarks below address the Examiner’s comments accordingly.

In accord with M.P.E.P. §1302.14, the Examiner’s reasons for allowance need not set forth all of the details why the claims are allowed. Applicant does not concede that the Examiner’s stated reasons for allowance are the only reasons for which the claims are allowable. As discussed below, the claims may be patentable for additional reasons.

Claim 1 and Dependent Claims

Claim 1 and its dependent claims are directed to a modified PH20 polypeptide, comprising one or more amino acid replacements in an unmodified PH20 polypeptide, wherein: the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7 and 32-66; the modified PH20 polypeptide exhibits increased hyaluronidase activity compared to the unmodified PH20 polypeptide not

containing the amino acid replacement(s); the amino acid replacement(s) confer(s) the increased hyaluronidase activity; the amino acid replacement(s) is at a position corresponding to 313 with reference to amino acid positions of SEQ ID NO: 3, which confers increased hyaluronidase activity; corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the sequence of amino acids set forth in SEQ ID NO: 3; and the modified PH20 polypeptide has at least 91% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7 and 32-66. Thus, the claims are directed to modified PH20 polypeptides that comprise one or more amino acid modifications, where one of the modifications is an amino acid replacement(s) at a position corresponding to 313. Claims also are directed to chimeric polypeptides and pharmaceutical compositions comprising the modified PH20 polypeptides.

Applicant agrees with the Examiner that neither Lin *et al.* (*Proc. Natl. Acad. Sci. U.S.A.* (1993) 90:10071-10075), nor any art of record, singly or in any combination, discloses, teaches or suggests a modified PH20 polypeptide that comprises an amino acid replacement(s) at position 313. Lin *et al.* is directed to the isolation of naturally-occurring human and cynomolgus monkey PH20 cDNA that encode human and cynomolgus monkey PH20. Lin *et al.* does not recognize that PH20 has hyaluronidase activity; Lin *et al.* refers to the protein as “sperm surface protein PH-20.” At the time of Lin *et al.* it was a protein that “has an essential function in sperm adhesion to the zona pellucida” of the guinea pig egg. Lin *et al.* states that the PH20 protein was isolated from primates to see if it had this function in primates and proposed its use in a vaccine contraceptive.

In accord with this understanding at the time, Lin *et al.* teaches that human PH20 may be used as an antigen for a human contraceptive vaccine. Lin *et al.* also fails to teach that PH20 is a glycoprotein. Lin *et al.* does not teach or suggest any modified forms of PH20, nor the effects of any modifications, particularly on hyaluronidase activity, which activity was not yet discovered in 1993. Thus, Lin *et al.*, alone or in combination with any other art of record, fails to teach or suggest the instantly claimed subject matter, including results achieved thereby. Lin *et al.* does not teach or suggest modified PH20 polypeptides. The instant application shows that replacements at the residue corresponding to residue 313 (with reference to SEQ ID NO:3) increases hyaluronidase activity. The instantly claimed modified PH20 polypeptides containing an amino acid replacement at this position exhibit increased hyaluronidase activity compared to a corresponding unmodified PH20 polypeptide not containing the amino acid replacement.

These results are taught in the extensive Working Examples provided in the instant application. For example, Example 4 provides the results of testing the effects of more than 6,700 modifications on activities/properties of soluble forms of the resulting PH20 polypeptides (see *e.g.*, Table 8). For example, results in Table 9 show that more than 600 of the tested modified polypeptides exhibit activity that is increased compared to wild type. Replacements at residue 313 are among the replacements that increase hyaluronidase activity.

There is no teaching or suggestion in Lin *et al.* of any modifications of the PH20 polypeptides, nor any that alter hyaluronidase activity, particularly since Lin *et al.* is concerned with using PH20 or antigenic portion thereof as a contraceptive. Thus, Lin *et al.*, provides no suggestion for generating modified PH20 polypeptides, nor the effects of any modifications on hyaluronidase activity, nor any reason to generate such polypeptides, or modify (*i.e.* with a polymer, *e.g.*, PEGylate) such modified PH20 polypeptides.

Claim 13

Independent claim 13 recites a modified PH20 polypeptide, comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 591-598, or a sequence of amino acids that exhibits at least 91% sequence identity to a sequence of amino acids set forth in any of SEQ ID NOs: 591-598 and that contains the amino acid replacement at residue 313 compared to corresponding positions in the amino acid sequence selected from the group consisting of SEQ ID NOs: 3 and 32-66.

Applicant agrees with the Examiner that neither Lin *et al.* (*Proc. Natl. Acad. Sci. U.S.A.* (1993) 90:10071-10075), nor any art of record, singly or in any combination, discloses, teaches or suggests a modified PH20 polypeptide having at least 91% sequence identity to a sequence of amino acids set forth in any of SEQ ID NOs: 591-598, which comprise the amino acid substitutions M313A, M313G, M313H, M313K, M313P, M313R, M313T and M313Y, respectively. Applicant respectfully submits that Lin *et al.*, alone or in combination with any other art of record, fails to teach or suggest other elements of the instantly claimed subject matter, or the results achieved thereby.

As discussed above, Lin *et al.* does not disclose, teach or suggest or even mention amino acid replacements in PH20 polypeptides, nor amino acid replacements at positions that result in a modified PH20 polypeptide with increased hyaluronidase activity. As described above, these results are demonstrated in the extensive Working Examples provided in the instant application. For example, the results in Table 9 show that the replacements M313R and M313K have a more than 2-fold increase in hyaluronidase activity. There is no teaching

Inventor(s): Wei *et al.*
Serial No. : 16/824,572
Filed : March 19, 2020

Attorney Docket No.: 33320.03087.US26/3087C
Comments on Reasons for Allowance

or suggestion in Lin *et al.* nor any art of record of modified PH20 polypeptides that exhibit altered hyaluronidase activity or other properties, nor any reason to generate such a polypeptide. Therefore, the art does not teach or suggest the instantly claimed PH20 polypeptides.

* * *

Entry of these remarks into the file history of the above-captioned application respectfully is requested.

Respectfully submitted,

/Stephanie Seidman/
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Reg. No. 33,779

Attorney Docket No.: 33320.03087.US26/3087C
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Electronic Patent Application Fee Transmittal				
Application Number:		16824572		
Filing Date:		19-Mar-2020		
Title of Invention:		PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF		
First Named Inventor/Applicant Name:		Ge WEI		
Filer:		Stephanie L. Seidman/Rosalind Smith		
Attorney Docket Number:		33320.03087.US26/3087C		
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
UTILITY APPL ISSUE FEE	1501	1	1200	1200
Extension-of-Time:				
Miscellaneous:				
PRINTED COPY OF PATENT - NO COLOR	8001	14	3	42
Total in USD (\$)				1242

Electronic Acknowledgement Receipt	
EFS ID:	42742179
Application Number:	16824572
International Application Number:	
Confirmation Number:	1431
Title of Invention:	PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF
First Named Inventor/Applicant Name:	Ge WEI
Customer Number:	13565
Filer:	Stephanie L. Seidman/Rosalind Smith
Filer Authorized By:	Stephanie L. Seidman
Attorney Docket Number:	33320.03087.US26/3087C
Receipt Date:	17-MAY-2021
Filing Date:	19-MAR-2020
Time Stamp:	17:12:17
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$1242
RAM confirmation Number	E20215GH13193202
Deposit Account	500911
Authorized User	Rosalind Smith
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.16 (National application filing, search, and examination fees) 37 CFR 1.17 (Patent application and reexamination processing fees)	

37 CFR 1.19 (Document supply fees)					
37 CFR 1.20 (Post Issuance fees)					
37 CFR 1.21 (Miscellaneous fees and charges)					
File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	3087Ctra_05-17-21.pdf	165178	no	1
			bbbb725700f7ae2ab20e092a6d96294e3c318964		
Warnings:					
Information:					
2	Issue Fee Payment (PTO-85B)	3087Cifp_05-17-21.pdf	318399	no	2
			fa1196e4f120c36e189e099fae36dbc6e1ce8dc		
Warnings:					
Information:					
3	Post Allowance Communication - Incoming	3087Ccra_05-17-21.pdf	158680	no	5
			86d29d1e2b53013e831c00b88986a612be775511		
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	33698	no	2
			c433a1ab2ea7ba57d4127cf49450c0549d5bb7a1		
Warnings:					
Information:					
Total Files Size (in bytes):			675955		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/824,572	06/22/2021	11041149	33320.03087.US26/3087C	1431

13565 7590 06/02/2021
Dentons US LLP
4655 Executive Drive
Suite 700
San Diego, CA 92121

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site <http://pair.uspto.gov> for additional applicants):

Ge WEI, San Diego, CA;
HALOZYME, INC., San Diego, CA;
H. Michael Shepard, Springfield, OR;
Qiping Zhao, San Diego, CA;
Robert James Connor, Oceanside, CA;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	Wei <i>et al.</i>	Art Unit	: 1656
Patent No.:	11,041,149	Examiner	: Liu, Samuel W.
Issue Date:	June 22, 2021	Conf. No.	: 1431
Serial No.:	16/824,572	Cust. No.	: 13565
Filed	: March 19, 2020		
Title	: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF		

Attn.: Certificate of Correction Branch

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION

Dear Sir:

Pursuant to 37 C.F.R. § 1.322, the patentee respectfully requests that a Certificate of Correction be issued for the above referenced patent to correct the following errors:

IN THE SPECIFICATION:

At column 160, line 29, please replace "Single dose formulations of PH20 are known in the art. For example, Hylenex® recombinant hyaluronidase (hyaluronidase human injection) contains, per mL, 8.5 mg NaCl (145 mM), 1.4 mg dibasic sodium phosphate (9.9 mM), 1.0 mg human albumin, 0.9 mg edetate disodium (2.4 mM), 0.3 mg CaCl₂ (2.7 mM) and NaOH to adjust the pH to 7.4. Other formulations of human soluble hyaluronidase, such as the rHuPH20 formulations described in U.S. Pat. Pub. No. US2011/0053247, include 130 mM NaCl, 10 mM Hepes, pH 7.0; or 10 mM histidine, 130 mM NaCl, pH 6.0. Any of the modified PH20 polypeptides provided herein can be similarly formulated."

with —In addition to a therapeutically effective amount of a modified PH20 polypeptide and/or other therapeutic agent, exemplary pharmaceutical compositions provided herein, including separately formulated- and co-formulated-PH20 containing formulations, can contain a concentration of NaCl and are prepared at a requisite pH to maintain the stability of the active agent(s) (e.g., PH20 hyaluronidase and/or other co-formulated therapeutic agent). For multi-dose formulations and other formulations stored for a prolonged time, the compositions generally also contain one or more preservatives. Further stabilizing agents and other excipients also can be included. Exemplary components are described below.—;

CERTIFICATE OF TRANSMISSION VIA EFS-WEB

I hereby certify that this paper is being transmitted via the Electronic Filing System (EFS-WEB) to the United States Patent and Trademark Office On **August 09, 2022**.

/Jimmy Schaub/
Jimmy Schaub

Inventor(s): Wei *et al.*
Patent No. : 11,041,149
Issue Date : June 22, 2021
Serial No. : 16/824,572
Filed : March 19, 2020

Attorney Docket No.: 33320.03087.US26/3087C
Request for Certificate of Correction Pursuant to
37 C.F.R. § 1.322

At column 177, line 36, please replace "Frost and Stem" with —Frost and Stern—;

At column 183, line 59, please replace "Lonafamibs" with —Lonafarnibs—;

At column 184, line 28, please replace "Tales" with —Talcs—;

IN THE CLAIMS:

Please replace claim 4 with the following amended claim:

4. The modified PH20 polypeptide of claim 3, wherein the unmodified PH20 polypeptide consists of the amino acid ~~sequence of~~ sequence of SEQ ID NO:35.

Please replace claim 16 with the following amended claim:

16. A pharmaceutical composition, comprising the ~~theft~~ modified PH20 polypeptide of claim 1.

Inventor(s): Wei *et al.*
Patent No. : 11,041,149
Issue Date : June 22, 2021
Serial No. : 16/824,572
Filed : March 19, 2020

Attorney Docket No.: 33320.03087.US26/3087C
Request for Certificate of Correction Pursuant to
37 C.F.R. § 1.322

REMARKS

A Certificate of Correction (Form PTO/SB/44) incorporating the above changes is included with this Request. Any fees that may be due can be charged to Deposit Account No. 50-0911.

IN THE SPECIFICATION

This Certificate of Correction seeks to correct a typographical error introduced by the PTO in the specification at column 160, line 29. The error is corrected by replacing the duplicate paragraph beginning at line 29 with "In addition to a therapeutically effective amount of a modified PH20 polypeptide and/or other therapeutic agent, exemplary pharmaceutical compositions provided herein, including separately formulated- and co-formulated-PH20 containing formulations, can contain a concentration of NaCl and are prepared at a requisite pH to maintain the stability of the active agent(s) (e.g., PH20 hyaluronidase and/or other co-formulated therapeutic agent). For multi-dose formulations and other formulations stored for a prolonged time, the compositions generally also contain one or more preservatives. Further stabilizing agents and other excipients also can be included. Exemplary components are described below." Basis for this correction can be found at page 174, line 23 of the specification as originally filed on March 19, 2020. A copy of page 174 of the specification as originally filed on March 19, 2020 is attached.

This Certificate of Correction seeks to correct a typographical error introduced by the PTO in the specification at column 177, line 36. The error is corrected by replacing "Frost and Stem" with "Frost and Stern," to correct the spelling of the surname of the author of the cited reference. Basis for this correction can be found at page 194, line 36 of the specification as originally filed on March 19, 2020. A copy of page 194 of the specification as originally filed on March 19, 2020 is attached.

This Certificate of Correction seeks to correct a typographical error introduced by the PTO in the specification at column 183, line 59. The error is corrected by replacing "Lonafamibs" with "Lonafarnibs," to correct the spelling error. Basis for this correction can be found at page 202, line 22 of the specification as originally filed on March 19, 2020. A copy of page 202 of the specification as originally filed on March 19, 2020 is attached.

Inventor(s): Wei *et al.*
Patent No. : 11,041,149
Issue Date : June 22, 2021
Serial No. : 16/824,572
Filed : March 19, 2020

Attorney Docket No.: 33320.03087.US26/3087C
Request for Certificate of Correction Pursuant to
37 C.F.R. § 1.322

This Certificate of Correction seeks to correct a typographical error introduced by the PTO in the specification at column 184, line 28. The error is corrected by replacing "Tales" with "Talcs," to correct the spelling error. Basis for this correction can be found at page 203, line 8 of the specification as originally filed on March 19, 2020. A copy of page 203 of the specification as originally filed on March 19, 2020 is attached.

IN THE CLAIMS

This Certificate of Correction also seeks to correct a typographical error introduced by the PTO in claim 4, at column 312, line 47. This error is corrected by removing the recitation "sequence of" immediately preceding the recitation "sequence of SEQ ID NO:35." Basis for this correction can be found in claim 11 as filed in the Amendment and Response filed on January 27, 2021. Claim 11 corresponds to claim 4 in the issued patent. A copy of the claims from the Amendment and Response filed on January 27, 2021 is attached.

This Certificate of Correction also seeks to correct a typographical error introduced by the PTO in claim 16, at column 313, line 19. This error is corrected by replacing the recitation "theft" with "the." Basis for this correction can be found in claim 20 as filed in the Amendment and Response filed on January 27, 2021. Claim 20 corresponds to claim 16 in the issued patent. A copy of the claims from the Amendment and Response filed on January 27, 2021 is attached.

* * *

These changes do not constitute new matter. Patentee respectfully requests correction of these errors by issuance of a Certificate of Correction.

Respectfully submitted,

/Stephanie Seidman/
Stephanie Seidman
Reg. No. 33,779

Attorney Docket No.: 33320.03087.US26/3087C
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Inventor(s): Wei *et al.*
Patent No. : 11,041,149
Issue Date : June 22, 2021
Serial No. : 16/824,572
Filed : March 19, 2020

Attorney Docket No.: 33320.03087.US26/3087C
Request for Certificate of Correction Pursuant to
37 C.F.R. §1.322

CERTIFICATE OF CORRECTION

Staple
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UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

Page 1 of 2

PATENT NO. : 11,041,149
 APPLICATION NO : 16/824,572
 DATED : MARCH 19, 2020
 INVENTOR(S) : WEI *ET AL.*

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

IN THE SPECIFICATION:

At column 160, line 29, please replace "Single dose formulations of PH20 are known in the art. For example, Hylenex® recombinant hyaluronidase (hyaluronidase human injection) contains, per mL, 8.5 mg NaCl (145 mM), 1.4 mg dibasic sodium phosphate (9.9 mM), 1.0 mg human albumin, 0.9 mg edetate disodium (2.4 mM), 0.3 mg CaCl₂ (2.7 mM) and NaOH to adjust the pH to 7.4. Other formulations of human soluble hyaluronidase, such as the rHuPH20 formulations described in U.S. Pat. Pub. No. US2011/0053247, include 130 mM NaCl, 10 mM Hepes, pH 7.0; or 10 mM histidine, 130 mM NaCl, pH 6.0. Any of the modified PH20 polypeptides provided herein can be similarly formulated."

with —In addition to a therapeutically effective amount of a modified PH20 polypeptide and/or other therapeutic agent, exemplary pharmaceutical compositions provided herein, including separately formulated- and co-formulated-PH20 containing formulations, can contain a concentration of NaCl and are prepared at a requisite pH to maintain the stability of the active agent(s) (e.g., PH20 hyaluronidase and/or other co-formulated therapeutic agent).

MAILING ADDRESS OF SENDER:

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 San Diego, CA, 92121

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

Page 2 of 2

PATENT NO. : 11,041,149
 APPLICATION NO : 16/824,572
 DATED : MARCH 19, 2020
 INVENTOR(S) : WEI *ET AL.*

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

For multi-dose formulations and other formulations stored for a prolonged time, the compositions generally also contain one or more preservatives. Further stabilizing agents and other excipients also can be included. Exemplary components are described below.—;

At column 177, line 36, please replace "Frost and Stem" with —Frost and Stern—;

At column 183, line 59, please replace "Lonafamibs" with —Lonafarnibs—;

At column 184, line 28, please replace "Tales" with —Talcs—;

IN THE CLAIMS:

Please replace claim 4 with the following amended claim:

4. The modified PH20 polypeptide of claim 3, wherein the unmodified PH20 polypeptide consists of the amino acid ~~sequence of~~ sequence of SEQ ID NO:35.

Please replace claim 16 with the following amended claim:

16. A pharmaceutical composition, comprising the ~~the~~ modified PH20 polypeptide of claim 1.

MAILING ADDRESS OF SENDER:

Stephanie Seidman
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 4655 Executive Drive, Suite 700
 San Diego, CA, 92121

Inventor(s): Wei *et al.*
Patent No. : 11,041,149
Issue Date : June 22, 2021
Serial No. : 16/824,572
Filed : March 19, 2020

Attorney Docket No.: 33320.03087.US26/3087C
Request for Certificate of Correction Pursuant to
37 C.F.R. §1.322

COPIES OF PAGES 174, 194, 202, AND 203 OF THE SPECIFICATION FILED ON
MARCH 19, 2020

COPY

powder. Subsequent sterile filtration of the solution followed by lyophilization under standard conditions known to those of skill in the art provides the desired formulation. A liquid formulation as described herein above can be prepared. The resulting mixture is sterile filtered or treated to remove particulates and to insure sterility, and apportioned into vials for lyophilization. For example, the lyophilized powder can be prepared by dissolving an excipient, such as dextrose, sorbitol, fructose, corn syrup, xylitol, glycerin, glucose, sucrose or other suitable agent, in a suitable buffer, such as citrate, sodium or potassium phosphate or other such buffer known to those of skill in the art. Then, a selected enzyme is added to the resulting mixture, and stirred until it dissolves.

Each vial is made to contain a single dosage or multiple dosages of the compound. The lyophilized powder can be stored under appropriate conditions, such as at about 4 °C to room temperature. Reconstitution of this lyophilized powder with an appropriate buffer solution provides a formulation for use in parenteral administration.

b. Exemplary Formulations

Single dose formulations of PH20 are known in the art. For example, Hylenex® recombinant (hyaluronidase human injection) contains, per mL, 8.5 mg NaCl (145 mM), 1.4 mg dibasic sodium phosphate (9.9 mM), 1.0 mg human albumin, 0.9 mg edetate disodium (2.4 mM), 0.3 mg CaCl₂ (2.7 mM) and NaOH to adjust the pH to 7.4. Other formulations of human soluble hyaluronidase, such as the rHuPH20 formulations described in U.S. Pat. Pub. No. US2011/0053247, include 130 mM NaCl, 10 mM Hepes, pH 7.0; or 10 mM histidine, 130 mM NaCl, pH 6.0. Any of the modified PH20 polypeptides provided herein can be similarly formulated.

In addition to a therapeutically effective amount of a modified PH20 polypeptide and/or other therapeutic agent, exemplary pharmaceutical compositions provided herein, including separately formulated- and co-formulated-PH20 containing formulations, can contain a concentration of NaCl and are prepared at a requisite pH to maintain the stability of the active agent(s) (e.g., PH20 hyaluronidase and/or other co-formulated therapeutic agent). For multi-dose formulations and other formulations stored for a prolonged time, the compositions generally also contain one or more preservatives. Further stabilizing agents and other excipients also can be included. Exemplary components are described below.

i. Salt (e.g. NaCl)

In examples herein, the pharmaceutical compositions provided herein contain a concentration of salt, such as sodium chloride (NaCl), to maintain the stability of the active agent(s) (e.g., PH20 hyaluronidase). Salt, such as NaCl, is generally required to retain PH20 stability and activity. Low salt concentrations of generally less than 120 mM can have deleterious effects on PH20 activity over time and depending on temperature conditions. Hence, the absence of salt (e.g. NaCl) or a low concentration of salt (e.g. NaCl) can result in

COPY

G. METHODS OF ASSESSING PH20 ACTIVITY AND STABILITY

Assays can be used to assess the stability and activity of the PH20 polypeptides provided herein. The assays can be used to assess the hyaluronidase activity of the PH20 polypeptide under particular conditions, temperature, and/or over time. Such assays can be used, for example, to determine the stability of the PH20 polypeptide under specific denaturation conditions, including, but not limited to, elevated temperatures greater than or about 30 °C (*e.g.*, 30 °C to 42 °C such as or about 37 °C), agitation, presence of excipients (*e.g.*, preservative), or low or no NaCl (salt). For example, stability under specific conditions can be monitored by assessing activity, solubility, and stability (*e.g.*, formation of aggregates, etc.) in the absence of exposure to the denaturation condition and then at various time points thereafter in the presence of the condition. Hence, stability can be assessed over time. Stability also can be assessed by comparing any one or more of activity, solubility or aggregation in the presence of one or more denaturation conditions compared to a native, wildtype or reference PH20 polypeptide. The assays also can be used make minor adjustments to the formulations provided herein while retaining the stability of both active agents.

1. Hyaluronidase Activity

The activity of a modified PH20 polypeptide can be assessed using methods well known in the art. For example, the USP XXII assay for hyaluronidase determines activity indirectly by measuring the amount of undegraded hyaluronic acid, or hyaluronan, (HA) substrate remaining after the enzyme is allowed to react with the HA for 30 min at 37 °C (USP XXII-NF XVII (1990) 644-645 United States Pharmacopeia Convention, Inc, Rockville, MD). A Hyaluronidase Reference Standard (USP) or National Formulary (NF) Standard Hyaluronidase solution can be used in an assay to ascertain the activity, in units, of any hyaluronidase. In one example, activity is measured using a microturbidity assay. This is based on the formation of an insoluble precipitate when hyaluronic acid binds with a reagent that precipitates it, such as acidified serum or cetylpyridinium chloride (CPC). The activity is measured by incubating hyaluronidase with sodium hyaluronate (hyaluronic acid) for a set period of time (*e.g.*, 10 minutes) and then precipitating the undigested sodium hyaluronate with the addition of acidified serum or CPC. The turbidity of the resulting sample is measured at 640 nm after an additional development period. The decrease in turbidity resulting from hyaluronidase activity on the sodium hyaluronate substrate is a measure of hyaluronidase enzymatic activity.

In another example, hyaluronidase activity is measured using a microtiter assay in which residual biotinylated hyaluronic acid is measured following incubation with hyaluronidase (see *e.g.*, Frost and Stern (1997) *Anal. Biochem.* 251:263-269, U.S. Pat. Publication No. 20050260186). The free carboxyl groups on the glucuronic acid residues of

CONF

- liposomals; Daunorubicins/Daunomycins; Daunorubicins; Decitabines; Denileukin Diftitoxes;
Dexniguldipines; Dexonas; Dexrazoxanes; Dezaguanines; Diaziquones; Dibrospidiums;
Dienogests; Dinalins; Disermolides; Docetaxels; Dofequidars; Doxifluridines; Doxorubicin
liposomals; Doxorubicin HCL; Doxorubicin HCL liposome injection; Doxorubicins;
5 Droloxifenes; Dromostanolone Propionates; Duazomycins; Ecomustines; Edatrexates;
Edotecarins; Eflornithines; Elacridars; Elinafides; Elliott's B Solutions; Elsamitrucins;
Emitefurs; Enloplatins; Enpromates; Enzastaurins; Epiropidines; Epirubicins; Epoetin alfas;
Eptaloprosts; Erbulozoles; Esorubicins; Estramustines; Etanidazoles; Etoglucids; Etoposide
phosphates; Etoposide VP-16s; Etoposides; Etoprines; Exemestanes; Exisulinds; Fadrozoles;
10 Fazarabines; Fenretinides; Filgrastims; Floxuridines; Fludarabines; Fluorouracils; 5-
fluorouracils; Fluoxymesterones; Flurocitabines; Fosquidones; Fostriecins; Fostriecins;
Fotretamines; Fulvestrants; Galarubicins; Galocitabines; Gemcitabines;
Gemtuzumabs/Ozogamicins; Geroquinols; Gimatecans; Gimeracils; Gloxazones;
Glufosfamides; Goserelin acetates; Hydroxyureas; Ibritumomabs/Tiuxetans; Idarubicins;
15 Ifosfamides; Ilmofofines; Ilomastats; Imatinib mesylates; Imexons; Improsulfans; Indisulams;
Inproquones; Interferon alfa-2as; Interferon alfa-2bs; Interferon Alfas; Interferon Betas;
Interferon Gammas; Interferons; Interleukin-2s and other Interleukins (including recombinant
Interleukins); Intoplicines; Iobenguanes [131-I]; Iproplatins; Irinotecans; Irsogladines;
Ixabepilones; Ketotrexates; L-Alanosines; Lanreotides; Lapatinibs; Ledoxantrones;
20 Letrozoles; Leucovorins; Leuprolides; Leuprorelin (Leuprolides); Levamisoles;
Lexacalcitols; Liarozoles; Lobaplatins; Lometrexols; Lomustines/CCNUs; Lomustines;
Lonafarnibs; Losoxantrones; Lurtotecans; Mafosfamides; Mannosulfans; Marimastats;
Masoprocals; Maytansines; Mechlorethamines; Mechlorethamines/Nitrogen mustards;
Megestrol acetates; Megestrols; Melengestrols; Melphalans; Melphalan L-PAMs; Menogarils;
25 Mepitiostanes; Mercaptopurines; 6-Mecaptopurine; Mesnas; Metesinds; Methotrexates;
Methoxsalens; Metomidates; Metoprines; Meturedepas; Miboplatins; Miproxifenes;
Misonidazoles; Mitindomides; Mitocarcins; Mitocromins; Mitoflaxones; Mitogillins;
Mitoguazones; Mitomalcins; Mitomycin Cs; Mitomycins; Mitonafides; Mitoquidones;
Mitospers; Mitotanes; Mitoxantrones; Mitozolomides; Mivobulins; Mizoribines;
30 Mofarotenes; Mopidamols; Mubritinibs; Mycophenolic Acids; Nandrolone Phenpropionates;
Nedaplatins; Nelarabines; Nemorubicins; Nitracrine; Nocodazoles; Nofetumomabs;
Nogalamycins; Nolatrexed; Nortopixantrones; Octreotides; Oprelvekins; Ormaplatins;
Ortaxels; Oteracils; Oxaliplatins; Oxisurans; Oxophenarsines; Paclitaxels; Pamidronates;
Patupilones; Pegademases; Pegaspargases; Pegfilgrastims; Peldesines; Peliomycins;
35 Pelitrexols; Pemetrexeds; Pentamustines; Pentostatins; Peplomycins; Perfosfamides;
Perifosines; Picoplatins; Pinafides; Pipobromans; Pipo sulfans; Pirfenidones; Piroxantrones;
Pixantrones; Plevitrexeds; Plicamycin Mithramycins; Plicamycins; Plomestanes;

COPY

- Plomestanes; Porfimer sodiums; Porfimers; Porfiromycins; Prednimustines; Procarbazines; Propamidines; Prospidiiums; Pumitepas; Puromycins; Pyrazofurins; Quinacrine; Ranimustines; Rasburicases; Riboprines; Ritrosulfans; Rituximabs; Rogletimides; Roquinimexs; Rufocromomycins; Sabarubicins; Safingols; Sargramostims; Satraplatins; 5 Sebriplatins; Semustines; Simtrazenes; Sizofirans; Sobuzoxanes; Sorafenibs; Sparfosates; Sparfosic Acids; Sparsomycins; Spirogermaniums; Spiromustines; Spiroplatins; Spiroplatins; Squalamines; Streptonigrins; Streptovarycins; Streptozocins; Sufosfamides; Sulofenurs; Sunitinib Malate; 6-TG; Tacedinalines; Talcs; Talisomycins; Tallimustines; Tamoxifens; Tariquidars; Tauromustines; Tecogalans; Tegafurs; Teloxantrones; Temoporfin; 10 Temozolomides; Teniposides/VM-26s; Teniposides; Teroxirones; Testolactones; Thiamiprines; Thioguanines; Thiotepas; Tiamiprines; Tiazofurins; Tilomisoles; Tilorones; Timcodars; Timonacics; Tirapazamines; Topixantrones; Topotecans; Toremifenes; Tositumomabs; Trabectedins (Ecteinascidin 743); Trastuzumabs; Trestolones; Tretinoin/ATRA; Triciribines; Trilostanes; Trimetrexates; Triplatin Tetranitrates; 15 Triptorelins; Trofosfamides; Tubulozoles; Ubenimexs; Uracil Mustards; Uredepas; Valrubicins; Valspodars; Vapreotides; Verteporfin; Vinblastines; Vincristines; Vindesines; Vinepidines; Vinflunines; Vinformides; Vinglycinates; Vinleucinols; Vinleurosines; Vinorelbines; Vinrosidines; Vintriptols; Vinzolidines; Vorozoles; Xanthomycin A's (Guamecyclines); Zeniplatins; Zilascorbs [2-H]; Zinostatins; Zoledronate; Zorubicins; and 20 Zosuquidars, for example:
- Aldesleukins (*e.g.*, PROLEUKIN®); Alemtuzumabs (*e.g.*, CAMPATH®); Alitretinoin (*e.g.*, PANRETIN®); Allopurinols (*e.g.*, ZYLOPRIM®); Altretamines (*e.g.*, HEXALEN®); Amifostines (*e.g.*, ETHYOL®); Anastrozoles (*e.g.*, ARIMIDEX®); Arsenic Trioxides (*e.g.*, TRISENOX®); Asparaginases (*e.g.*, ELSPAR®); BCG Live (*e.g.*, TICE® 25 BCG); Bexarotenes (*e.g.*, TARGRETIN®); Bevacizumab (AVASTIN®); Bleomycins (*e.g.*, BLENOXANE®); Busulfan intravenous (*e.g.*, BUSULFEX®); Busulfan orals (*e.g.*, MYLERAN™); Calusterones (*e.g.*, METHOSARB®); Capecitabines (*e.g.*, XELODA®); Carboplatins (*e.g.*, PARAPLATIN®); Carmustines (*e.g.*, BCNU®, BiCNU®); Carmustines with Polifeprosans (*e.g.*, GLIADEL® Wafer); Celecoxibs (*e.g.*, CELEBREX®); 30 Chlorambucils (*e.g.*, LEUKERAN®); Cisplatins (*e.g.*, PLATINOL®); Cladribines (*e.g.*, LEUSTATIN®, 2-CdA®); Cyclophosphamides (*e.g.*, CYTOXAN®, NEOSAR®); Cytarabines (*e.g.*, CYTOSAR-U®); Cytarabine liposomals (*e.g.*, DepoCyt®); Dacarbazines (*e.g.*, DTIC-Domeo); Dactinomycins (*e.g.*, COSMEGEN®); Darbepoetin Alfas (*e.g.*, ARANESP®); Daunorubicin liposomals (*e.g.*, DAUNOXOME®); 35 Daunorubicins/Daunomycins (*e.g.*, CERUBIDINE®); Denileukin Diftitoxes (*e.g.*, ONTAK®); Dexrazoxanes (*e.g.*, ZINECARD®); Docetaxels (*e.g.*, TAXOTERE®); Doxorubicins (*e.g.*, ADRIAMYCIN®, RUBEX®); Doxorubicin liposomals, including

Inventor(s): Wei *et al.*
Patent No. : 11,041,149
Issue Date : June 22, 2021
Serial No. : 16/824,572
Filed : March 19, 2020

Attorney Docket No.: 33320.03087.US26/3087C
Request for Certificate of Correction Pursuant to
37 C.F.R. §1.322

COPY OF THE CLAIMS FROM THE AMENDMENT AND RESPONSE, FILED ON
JANUARY 27, 2021

COF

Inventor(s) : Wei *et al.*
Serial No. : 16/824,572
Filed : March 19, 2020

Attorney Docket No.: 33320.03087.US26/ 3087C
Amendment and Response

AMENDMENTS TO THE CLAIMS:

Please amend claims 1, 6, 8, 9, 11, 13 and 20, as follows. This listing of claims replaces all prior versions, and listings of claims, in the application.

LISTING OF CLAIMS:

1. (Currently Amended) A modified PH20 polypeptide, comprising one or more amino acid replacements in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of sequence of amino acids set forth in SEQ ID NOs: 3, 7 and 32-66;

the modified PH20 polypeptide exhibits increased hyaluronidase activity compared to the unmodified PH20 polypeptide not containing the amino acid replacement(s);

the amino acid replacement(s) confer(s) the increased hyaluronidase activity;

the amino acid replacement(s) is at a position corresponding to 313 with reference to amino acid positions ~~of set forth in~~ SEQ ID NO:3, which confers increased hyaluronidase activity;

corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the sequence of amino acids set forth in SEQ ID NO:3; and

the modified PH20 polypeptide has at least 91% sequence identity to the amino acid sequence selected from the group consisting of sequence of amino acids set forth as SEQ ID NOs: 3, 7 ~~and~~ 32-66.

2. (Cancelled)

3. (Original) The modified PH20 polypeptide of claim 1, wherein the replacement is selected from among A at a position corresponding to position 313; G at a position corresponding to position 313; H at a position corresponding to position 313; K at a position corresponding to position 313; P at a position corresponding to position 313; R at a position corresponding to position 313; T at a position corresponding to position 313; and Y at a position corresponding to position 313.

4. (Cancelled)

5. (Original) The modified PH20 polypeptide of claim 3, wherein the replacement at the position corresponding to 313 is K.

6. (Currently Amended) The modified PH20 polypeptide of claim 1, wherein the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of sequence of amino acids set forth in SEQ ID NOs: 3, 7 ~~and~~ 32-66.

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Filed : March 19, 2020

Attorney Docket No.: 33320.03087.US26/ 3087C
Amendment and Response

7. (Cancelled)

8. (Currently Amended) The modified PH20 polypeptide of claim 3, wherein the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of sequence of amino acids set forth in SEQ ID NOs: 3, 7 and 32-66.

9. (Currently Amended) The modified PH20 polypeptide of claim 1, wherein the modified PH20 polypeptide has at least 95% sequence identity to the amino acid sequence selected from the group consisting of sequence of amino acids set forth as SEQ ID NOs: 3, 7 and 32-66.

10. (Previously Presented) The modified PH20 polypeptide of claim 1, wherein the modified PH20 polypeptide has at least 95% sequence identity to SEQ ID NO:35.

11. (Currently Amended) The modified PH20 polypeptide of claim 5, wherein the unmodified PH20 polypeptide consists of the amino acid sequence of sequence of amino acids set forth in SEQ ID NO:35.

12. (Original) The modified PH20 polypeptide of claim 1, wherein the modified PH20 polypeptide exhibits increased hyaluronidase activity that is at least 120% of the hyaluronidase activity compared to the unmodified PH20 polypeptide not containing the amino acid replacement or replacements.

13. (Currently Amended) A modified PH20 polypeptide, comprising the amino acid sequence selected from the group consisting of a sequence of amino acids set forth in any of SEQ ID NOS: 591-598, or a sequence of amino acids that exhibits at least 91% sequence identity to a sequence of amino acids set forth in any of SEQ ID NOS: 591-598 and that contains the amino acid replacement at residue 313 compared to corresponding positions in the amino acid sequence selected from the group consisting of a polypeptide of any of SEQ ID NOS: 3 and 32-66.

14. (Original) The modified PH20 polypeptide of claim 1 that comprises one or more of a modification selected from among glycosylation, sialation, albumination, farnesylation, carboxylation, hydroxylation, and phosphorylation.

15. (Original) The modified PH20 polypeptide of claim 1 that comprises an N-acetylglucosamine moiety linked to each of at least three asparagine (N) residues.

16. (Original) The modified PH20 polypeptide of claim 1 that is conjugated to a polymer.

17. (Original) The modified PH20 polypeptide of claim 16, wherein the polymer is dextran or polyethylene glycol (PEG).

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Inventor(s) : Wei *et al.*
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Attorney Docket No.: 33320.03087.US26/ 3087C
Amendment and Response

18. (Original) The modified PH20 polypeptide of claim 1, further comprising a heterologous signal sequence.

19. (Original) A chimeric polypeptide comprising the modified PH20 polypeptide of claim 1.

20. (Currently Amended) A pharmaceutical composition, comprising ~~thea~~ modified PH20 polypeptide of claim 1.

21. (Withdrawn) A method of treatment, comprising administering a pharmaceutical composition of claim 20, wherein the method is selected from a method that treats an excess of glycosaminoglycans; a tumor; glycosaminoglycan accumulation in the brain; a cardiovascular disorder; an ophthalmic disorder; pulmonary disease or edema; and a method of increasing delivery of therapeutic agents.

Electronic Acknowledgement Receipt	
EFS ID:	46374353
Application Number:	16824572
International Application Number:	
Confirmation Number:	1431
Title of Invention:	PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF
First Named Inventor/Applicant Name:	Ge WEI
Customer Number:	13565
Filer:	Stephanie L. Seidman/Jimmy Schaub
Filer Authorized By:	Stephanie L. Seidman
Attorney Docket Number:	33320.03087.US26/3087C
Receipt Date:	09-AUG-2022
Filing Date:	19-MAR-2020
Time Stamp:	17:40:35
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment		no			
File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	3087Ctra_000.pdf	136100	no	1
			396d22240d943b04de5428d4fc85c316e3bc8778		
Warnings:					

Information:					
2	Request for Certificate of Correction	3087Crcc_000_08-09-22.pdf	149308	no	4
			da4b0cf98a3573610a7f69b883ce649758b9ae60		
Warnings:					
Information:					
3	Request for Certificate of Correction	3087Ccoc.pdf	683785	no	12
			cca2112f8e63cbad81092d4b4fa5dc3ddc98e96c		
Warnings:					
Information:					
Total Files Size (in bytes):			969193		
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>					

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	Wei <i>et al.</i>	Art Unit	: 1656
Patent No.:	11,041,149	Examiner	: Liu, Samuel W.
Issue Date:	June 22, 2021	Conf. No.	: 1431
Serial No.:	16/824,572	Cust. No.	: 13565
Filed	: March 19, 2020		
Title	: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF		

Attn: Certificate of Correction Branch

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

Dear Sir:

Transmitted herewith are a Request for Certificate of Correction (4 pages); a Certificate of Correction (2 pages); copies of pages 174, 194, 202, and 203 of the Specification as originally filed on March 19, 2020 (4 pages); and a copy of the claims from the Amendment and Response, filed January 27, 2021 (3 pages).



The Commissioner is hereby authorized to charge any fees that may be due in connection with this and the attached papers or with this application during its entire pendency to Deposit Account No. 50-0911.

Respectfully submitted,

/Stephanie Seidman/

Stephanie Seidman

Reg. No. 33,779

Attorney Docket No.: 33320.03087.US26/3087C

Address all correspondence to: 13565

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CERTIFICATE OF TRANSMISSION VIA EFS-WEB

I hereby certify that this paper is being transmitted via the Electronic Filing System (EFS-WEB) to the United States Patent and Trademark Office On **August 09, 2022**.

/Jimmy Schaub/

Jimmy Schaub



UNITED STATES PATENT AND TRADEMARK OFFICE

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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/824,572	03/19/2020	Ge WEI	33320.03087.US26/3087C	1431
13565	7590	08/29/2022	EXAMINER	
Dentons US LLP 4655 Executive Drive Suite 700 San Diego, CA 92121			LIU, SAMUEL W	
			ART UNIT	PAPER NUMBER
			1656	
			NOTIFICATION DATE	DELIVERY MODE
			08/29/2022	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

MLAIPSD@Dentons.com
lucy.begalla@dentons.com
rosalind.smith@dentons.com



UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Patent No.: 11041149
Issue Date: 06/22/2021
Appl. No.: 16/824,572
Filed: 03/19/2020

PART (A) RESPONSE FOR CERTIFICATES OF CORRECTION

This is a decision on the Certificate of Correction request filed 09 August 2022.

The request for issuance of Certificate of Correction for the above-identified correction(s) under the provisions of 37 CFR 1.322 and/or 1.323 is hereby:

(Check one)

☒ Approved

☐ Approved in Part

☐ Denied

Comments: _____

PART (B) PETITION UNDER 37 CFR 1.324 OR 37 CFR 1.48

☐ This is a decision on the petition filed _____ to correct inventorship under 37 CFR 1.324.

☐ This is a decision on the request under 37 CFR 1.48, petition filed _____. In view of the fact that the patent has already issued, the request under 37 CFR 1.48 has been treated as a petition to correct inventorship under 37 CFR 1.324.

The petition is hereby:

☐ Granted

☐ Dismissed

Comment: _____

The patented filed is being forwarded to Certificate of Corrections Branch for issuance of a certificate naming only the actual inventor or inventors.

/MANJUNATH N RAO/
Supervisory Patent Examiner, Art Unit 1656
Technology Center 1600
Phone: (571)272-0939

Certificates of Correction Branch email: CustomerServiceCoC@uspto.gov CoC Central Phone Number: (703) 756-1814

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Dentons US LLP
4655 Executive Drive
Suite 700
San Diego, CA 92121



**Courtesy Reminder for
Application Serial No: 16/824,572**

Attorney Docket No: 33320.03087.US26/3087C
Customer Number: 13565
Date of Electronic Notification: 08/30/2022

This is a courtesy reminder that new correspondence is available for this application. If you have not done so already, please review the correspondence. The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

An email notification regarding the correspondence was sent to the following email address(es) associated with your customer number:

MLAIPSD@Dentons.com
lucy.begalla@dentons.com
rosalind.smith@dentons.com

To view your correspondence online or update your email addresses, please visit us anytime at <https://ppair-my.uspto.gov/pair/PrivatePair>. If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov or call 1-866-217-9197.

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 11,041,149 B2
APPLICATION NO. : 16/824572
DATED : June 22, 2021
INVENTOR(S) : Wei et al.

Page 1 of 2

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specification

At Column 160, Line 29, please replace “Single dose formulations of PH20 are known in the art. For example, Hylenex® recombinant hyaluronidase (hyaluronidase human injection) contains, per mL, 8.5 mg NaCl (145 mM), 1.4 mg dibasic sodium phosphate (9.9 mM), 1.0 mg human albumin, 0.9 mg edetate disodium (2.4 mM), 0.3 mg CaCl₂ (2.7 mM) and NaOH to adjust the pH to 7.4. Other formulations of human soluble hyaluronidase, such as the rHuPH20 formulations described in U.S. Pat. Pub. No. US2011/0053247, include 130 mM NaCl, 10 mM Hepes, pH 7.0; or 10 mM histidine, 130 mM NaCl, pH 6.0. Any of the modified PH20 polypeptides provided herein can be similarly formulated.” with —In addition to a therapeutically effective amount of a modified PH20 polypeptide and/or other therapeutic agent, exemplary pharmaceutical compositions provided herein, including separately formulated- and co-formulated-PH20 containing formulations, can contain a concentration of NaCl and are prepared at a requisite pH to maintain the stability of the active agent(s) (e.g., PH20 hyaluronidase and/or other co-formulated therapeutic agent).

For multi-dose formulations and other formulations stored for a prolonged time, the compositions generally also contain one or more preservatives. Further stabilizing agents and other excipients also can be included. Exemplary components are described below.—;

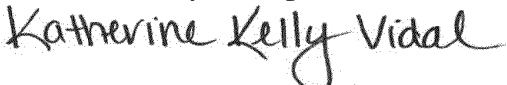
At Column 177, Line 36, please replace “Frost and Stem” with —Frost and Stern—;

At Column 183, Line 59, please replace “Lonafamibs” with —Lonafarnibs—;

At Column 184, Line 28, please replace “Tales” with —Tals—;

In the Claims

At Column 312, Lines 47-49, please replace Claim 4 with the following amended claim:
—4. The modified PH20 polypeptide of claim 3, wherein the unmodified PH20 polypeptide consists of the amino acid sequence of SEQ ID NO:35.—;

Signed and Sealed this
Thirteenth Day of September, 2022


Katherine Kelly Vidal
Director of the United States Patent and Trademark Office

CERTIFICATE OF CORRECTION (continued)
U.S. Pat. No. 11,041,149 B2

Page 2 of 2

At Column 313, Lines 19-20, please replace Claim 16 with the following amended claim:
—16. A pharmaceutical composition, comprising the modified PH20 polypeptide of claim 1.—.