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L49          4 FILE EMBASE
TOTAL FOR ALL FILES
L50          10 S L25 AND L40
L51          0 FILE MEDLINE
L52          0 FILE BIOSIS
L53          0 FILE CAPLUS
L54          0 FILE EMBASE
TOTAL FOR ALL FILES
L55          0 S L50 AND L5
L56          0 FILE MEDLINE
L57          0 FILE BIOSIS
L58          0 FILE CAPLUS
L59          0 FILE EMBASE
TOTAL FOR ALL FILES
L60          0 S L50 AND L10
L61          0 FILE MEDLINE
L62          0 FILE BIOSIS
L63          0 FILE CAPLUS
L64          0 FILE EMBASE
TOTAL FOR ALL FILES
L65          0 S L50 AND L15
L66          0 FILE MEDLINE
L67          0 FILE BIOSIS
L68          0 FILE CAPLUS
L69          0 FILE EMBASE
TOTAL FOR ALL FILES
L70          0 S L50 AND L20
L71          1 FILE MEDLINE
L72          0 FILE BIOSIS
L73          4 FILE CAPLUS
L74          3 FILE EMBASE
TOTAL FOR ALL FILES
L75          8 S L25 AND L5
L76          0 FILE MEDLINE
L77          0 FILE BIOSIS
L78          0 FILE CAPLUS
L79          0 FILE EMBASE
TOTAL FOR ALL FILES
L80          0 S L25 AND L10
L81          1 FILE MEDLINE
L82          1 FILE BIOSIS
L83          5 FILE CAPLUS
L84          1 FILE EMBASE
TOTAL FOR ALL FILES
L85          8 S L25 AND L15
L86          3 FILE MEDLINE
L87          0 FILE BIOSIS
L88          4 FILE CAPLUS
L89          2 FILE EMBASE
TOTAL FOR ALL FILES
L90          9 S L25 AND L20
L91          6 DUP REM L90 (3 DUPLICATES REMOVED)
L92          5 DUP REM L85 (3 DUPLICATES REMOVED)
L93          5 DUP REM L50 (5 DUPLICATES REMOVED)

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/340,786	06/23/2023	Ge WEI	63995-01-5105-US-17	6432
28977 7590 04/26/2024 Morgan, Lewis & Bockius LLP (PH) 2222 Market Street Philadelphia, PA 19103			EXAMINER WANG, CHANG YU	
			ART UNIT 1649	PAPER NUMBER
			NOTIFICATION DATE 04/26/2024	DELIVERY MODE 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):

judith.troilo@morganlewis.com
phpatentcorrespondence@morganlewis.com

Notice of Pre-AIA or AIA Status

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

DETAILED ACTION

RESPONSE TO AMENDMENT

Status of Application/Amendments/claims

2. Applicant's amendment filed April 3, 2024 is acknowledged. Claims 4, 11-13 and 19-22 are cancelled. Claims 1, 3 and 23 are amended. Claims 1-3, 5-10, 14-18 and 23 are pending. Claims 18 and 23 are withdrawn with traverse (filed 12/13/2023) from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on December 13, 2023.
3. Claims 1-3, 5-10 and 14-17 are under examination with respect to SEQ ID NO:35, D (aspartic acid), polypeptide/protein/antibody in this office action.
4. Applicant's arguments filed on April 3, 2024 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections/Objections Withdrawn

5. The objection to claim 1 is withdrawn in response to Applicant's amendment to the claim.

The rejection of claim 4 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite is moot because the claim is canceled.

The rejection of claim 4 under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement is moot because the claim is canceled.

The rejection of claims 3-4 under 35 U.S.C. 102(a)(1) as being anticipated by Kim et al. (Funct. Integr. Genomics, 2011; 11:507-517. DOI 10.1007/s10142-011-0220-9) is withdrawn in response to Applicant's amendment to the claims and cancellation of claim 4.

The rejection of claims 3-4 under 35 U.S.C. 102(a)(1) as being anticipated by Lin et al. (Proc. Natl. Acad. Sci. U.S.A., 1993; 90:10071-10075) is withdrawn in response to Applicant's amendment to the claims and cancellation of claim 4. .

The rejection of claims 1-10 and 14-17 on the ground of nonstatutory double patenting as being unpatentable over claims 1-18 of US10865400 is withdrawn in response to Applicant's approved terminal disclaimer and cancellation of claim 4.

The provisional rejection of claims 1-10 and 14-17 on the ground of nonstatutory double patenting as being unpatentable over claims 1-35 of Application No. 18/068418 is withdrawn in response to Applicant's approved terminal disclaimer and cancellation of claim 4.

Claim Rejections/Objections Maintained

In view of the amendment filed on April 3, 2024, the following rejections are maintained.

Claim Rejections - 35 USC § 112

6. 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, 5-10 and 14-17 stand 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. The rejection is maintained for the reasons made of record and the reasons set forth below.

Response to Arguments

On p. 4 of the response, Applicant argues that the rejection has been overcome in view of amendment to claim 1.

Applicant's arguments have been fully considered but they are not found persuasive. Contrary to Applicant's arguments, the examiner asserts that based on MPEP§2171-MPEP§2173, claims 1-3, 5-10 and 14-17 are still indefinite because:

i. The limitation "wherein, when aligned, gaps at the N-terminus and C-terminus of the aligned sequences are non-identical..." is unclear because it is unclear as to where the gaps at the N-terminus and C-terminus of the aligned sequences are located, and how far from the end of the N-terminus and the end of the C-terminus would be considered as "gaps at the N-terminus and C-terminus of the aligned sequences". It is unclear as to where the gaps at the N-terminus and C-terminus are for the 5% mismatches of the amino acid sequence of SEQ ID NO:35. Thus, claim 1 is indefinite.

ii. The rest of the claims are indefinite as depending from an indefinite claim.

Accordingly, the rejection of claims 1-3, 5-10 and 14-17 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite is maintained.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112(a):
(a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-10 and 14-17 stand rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is maintained for the reasons made of record and the reasons set forth below.

Claims 1-3, 5-10 and 14-17 as amended encompass a genus of modified PH20 polypeptide comprising an amino acid sequence having at least 95% or 96% residues identical to the amino acid sequence of SEQ ID NO:35, with gaps at the N-terminus and C-terminus of the aligned sequences that are non-identical; and comprising a residue of D, N or R at position 324 corresponding to SEQ ID NO:3.

Claims 5-6 encompass a genus of the claimed modified PH20 polypeptide variants with an increased hyaluronidase activity or at least 120% hyaluronidase activity as compared to SEQ ID NO:3.

Claims 15-17 encompass a genus of therapeutically active agent, polypeptide/protein/antibody, nucleic acid, and drug/small molecule/organic molecule in combination with the claimed genus of the modified PH20 polypeptide variants in a pharmaceutical composition.

Response to Arguments

On p. 5-18 of the response, Applicant argues that the specification and the prior art provides around 7000 examples of modified PH20 polypeptides variants and soluble PH20 polypeptides of SEQ ID NOs: 3, 7 and 32-66, and detailed structures and functions of the modified PH20 polypeptides variants. Applicant further cites Tables 8-9, US10865400 (95% sequence identity), US7767429 and US10286044 (PH20 polypeptide variants and pharmaceutical compositions thereof), US9447401 (85% sequence identity), US11041149 and US11066656 (91% identity) and MPEP§1701 in support of the arguments.

Applicant's arguments have been fully considered but they are not found persuasive. Contrary to Applicant's arguments, the examiner asserts that based on MPEP §2163, MPEP §§2163.01-2163.03, the specification fails to provide sufficient description or information or evidence to demonstrate that Applicant is in possession of the claimed genus of modified PH20 polypeptide variants and pharmaceutical compositions thereof because:

i. Each case is judged and determined based on its own merits. Based on Applicant's own admission on p. 135-p.139, Table 5 and p. 276-p. 286, Table 10 of the instant specification, a single point mutation or mismatches at the N-terminus and C-terminus result in inactive mutants of PH20 polypeptides (see Tables 5 and 10 of the instant specification).

The specification fails to teach the structural and functional relationship or correlation between the claimed genus of modified PH20 polypeptide variants with 95% residues identical to SEQ ID NO:35, comprising gaps at the N-terminus and C-terminus of the aligned sequences that are non-identical and a residue of D, N or R at position 324 corresponding to SEQ ID NO:3 and the modified PH20 polypeptide of SEQ ID NO:3 or 35 or variants shown in tables 5 and 10 or table 9. It is not known whether a combination of 5% mismatches of the amino acid sequence of SEQ ID NO:35 and gaps at the N-terminus and C-terminus that are non-identical, and with a residue of D, N or R at position 324 corresponding to SEQ ID NO:3 within the modified PH20 polypeptide variants would result in inactive mutants because a single point mutation or mismatches at the N-terminus or C-terminus results in inactive mutants (see tables 5 and 10).

ii. Based on Applicant's own admission on p. 253-p. 275, Table 9 of the instant specification, a single point mutation at the N-terminus or C-terminus results in decreased hyaluronidase activity, for example L001E/F/G or N002A/C/G/L/P/Q/S (see table 9 of the instant specification).

The specification fails to teach the structural and functional relationship or correlation between the claimed genus of modified PH20 polypeptide variants and a

modified PH20 polypeptide comprising the sequence of SEQ ID NO:623 (E324N), SEQ ID NO:624 (E324R) or SEQ ID NO:3 with a mutation of E324D having an increased hyaluronidase activity as compared to wild type PH20 of SEQ ID NO:3 (see p. 258, table 9 of the instant specification).

It is not known whether a combination of 5% mismatches of the amino acid sequence of SEQ ID NO:35 and gaps at the N-terminus and C-terminus that are non-identical, and with a residue of D, N or R at position 324 corresponding to SEQ ID NO:3 within the modified PH20 polypeptide variants would result in inactive mutants or decreased hyaluronidase activity because a single point mutation or mismatches at the N-terminus or C-terminus results in inactive mutants or decreased hyaluronidase activity (see tables 5 and 9-10).

The specification fails to provide what other common structures and sequences and features for the claimed modified PH20 polypeptide variants are, and what 5% amino acids and/or gaps at the N-terminus and C-terminus that are non-identical can or cannot be changed within the modified PH20 of SEQ ID NO:35 with 95% identity to SEQ ID NO:35 and comprising a residue D, N or R at position 324 corresponding to SEQ ID NO:3 in order to preserve the activity of PH20, or to increase hyaluronidase activity or increase at least 120% hyaluronidase activity as compared to SEQ ID NO:3.

iii. The specification provides no structural and functional relationship or correlation among the claimed genus of therapeutically active agent, the claimed genus of polypeptide/protein/antibody, the claimed genus of nucleic acid, and the claimed

drug/small molecule/organic molecule in combination with the claimed genus of modified PH20 polypeptide variants in the claimed pharmaceutical composition.

It is not known what the claimed genus of therapeutically active agent, polypeptide/protein/antibody, nucleic acid, and drugs/small molecules/organic molecules are and can be combined with the claimed genus of the modified PH20 polypeptide variants with 5% mismatches of the amino acid sequence of SEQ ID NO:35, gaps at the N-terminus and C-terminus that are non-identical, and with a residue of D, N or R at position 324 corresponding to SEQ ID NO:3 would result in inactive mutants or decreased hyaluronidase activity.

Since the common characteristics/features of other modified PH20 polypeptides with the claimed features are unknown and the common characteristics/features of the claimed genus of therapeutically active agent and the claimed genus of polypeptide/protein/antibody are also unknown, a skilled artisan cannot envision the functional correlations of the genus with the claimed invention in view of Burgess et al. (J of Cell Bio. 1990, 111:2129-2138, cited previously), Bowie et al. (see col 2, p. 1306, Bowie et al. Science, 1990, 247:1306-1310, cited previously), Pawson et al. (see p. 445 the second column, first paragraph, Pawson et al. 2003, Science 300:445-452, cited previously), Alaoui-Ismaili et al. (see p. 502, right col., 2th paragraph; Alaoui-Ismaili et al., Cytokine Growth Factor Rev. 2009; 20:501-507, cited previously) and Guo et al. (see p. 9207, left col., 2th paragraph, Guo et al., PNAS 2004; 101:9205-9210, cited previously).

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the

genus of modified PH20 polypeptides with the claimed features, the genus of therapeutically active agent, polypeptide/protein/antibody, nucleic acid, and drug/small molecule/organic molecule in combination with the claimed genus of modified PH20 polypeptide variants in the claimed pharmaceutical composition.

Based on MPEP § 2161.01 and §2163, “to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116”.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the ‘written description’ inquiry, whatever is now claimed.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116).

As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of other structurally and functionally undefined modified PH20 polypeptide variants having at least 95% residue identity to SEQ ID NO:35, gaps at the N-terminus and C-terminus that are non-identical and with a residue of D, N or R at position 324 corresponding to SEQ ID NO:3, the genus of other structurally and functionally undefined modified PH20 polypeptide variants having the

claimed features and with an increased hyaluronidase activity or at least 120% hyaluronidase activity as compared to SEQ ID NO:3 or the genus of structurally and functionally undefined therapeutically active agent, polypeptide/protein/antibody, nucleic acid, and drug/small molecule/organic molecule in combination with the claimed genus of modified PH20 polypeptide variants in the claimed pharmaceutical composition, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483 and *Centocor v. Abbott*, 636 F.3d1341 (Fed. Cir. 2011) and *AbbVie v. Janssen*, 759 F.3d 1285 (Fed. Cir.2014).

Therefore, the claimed modified PH20 polypeptide variants and compositions have not met the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115). Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement. See MPEP § 2161.01 and 2163.

Accordingly, the rejection of claims 1-3, 5-10 and 14-17 under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement is maintained.

Conclusion

8. NO CLAIM IS ALLOWED.

Sequence alignment

```
SEQ ID NO:3      1  LNFRAFFVIVNVFFLWANNAPSEFCLEGFDEFLDMSLFSFIGSPRINATGGVITIFYVDR 60
SEQ ID NO:35     1  LNFRAFFVIVNVFFLWANNAPSEFCLEGFDEFLDMSLFSFIGSPRINATGGVITIFYVDR 60
SEQ ID NO:32     1  LNFRAFFVIVNVFFLWANNAPSEFCLEGFDEFLDMSLFSFIGSPRINATGGVITIFYVDR 60

SEQ ID NO:3      61  LGYFFIIDSITGVTVNGGIPQKISLQDHLDRKKDITFMPVDHLGMAVIDWEEWRPTWA 120
SEQ ID NO:35     61  LGYFFIIDSITGVTVNGGIPQKISLQDHLDRKKDITFMPVDHLGMAVIDWEEWRPTWA 120
SEQ ID NO:32     61  LGYFFIIDSITGVTVNGGIPQKISLQDHLDRKKDITFMPVDHLGMAVIDWEEWRPTWA 120

SEQ ID NO:3      121  RNNKFDVYKNNRSIELVQQQNVQLSLTEATEKAKQEFKAGKDFLVETIKLSKLLRPNH 180
SEQ ID NO:35     121  RNNKFDVYKNNRSIELVQQQNVQLSLTEATEKAKQEFKAGKDFLVETIKLSKLLRPNH 180
SEQ ID NO:32     121  RNNKFDVYKNNRSIELVQQQNVQLSLTEATEKAKQEFKAGKDFLVETIKLSKLLRPNH 180

SEQ ID NO:3      181  WGYLFFDCYNHHYKPGYNGSCFNVEIKENDLSWLWNESTALYPSIYINTQQSPVAAT 240
SEQ ID NO:35     181  WGYLFFDCYNHHYKPGYNGSCFNVEIKENDLSWLWNESTALYPSIYINTQQSPVAAT 240
SEQ ID NO:32     181  WGYLFFDCYNHHYKPGYNGSCFNVEIKENDLSWLWNESTALYPSIYINTQQSPVAAT 240

SEQ ID NO:3      241  LYVNMVREAIRVSKIEDAKSELPVFAYTRIVETDQVLKFLSQDELVYTFGETVALGASG 300
SEQ ID NO:35     241  LYVNMVREAIRVSKIEDAKSELPVFAYTRIVETDQVLKFLSQDELVYTFGETVALGASG 300
SEQ ID NO:32     241  LYVNMVREAIRVSKIEDAKSELPVFAYTRIVETDQVLKFLSQDELVYTFGETVALGASG 300

SEQ ID NO:3      301  IYVNGTLSIMRSMKSCLLIDNYMETIINFYIINVTLAAIMCSQVLCQEGGVCIRKNNSS 360
SEQ ID NO:35     301  IYVNGTLSIMRSMKSCLLIDNYMETIINFYIINVTLAAIMCSQVLCQEGGVCIRKNNSS 360
SEQ ID NO:32     301  IYVNGTLSIMRSMKSCLLIDNYMETIINFYIINVTLAAIMCSQVLCQEGGVCIRKNNSS 360

SEQ ID NO:3      361  DYHLNFDNFAIQLEKGGKFTVRSKPTLEDLEQSEKTYCSCYETLSCKEKADVKDIDAY 420
SEQ ID NO:35     361  DYHLNFDNFAIQLEKGGKFTVRSKPTLEDLEQSEKTYCSCYETLSCKEKADVKDIDAY 420
SEQ ID NO:32     361  DYHLNFDNFAIQLEKGGKFTVRSKPTLEDLEQSEKTYCSCYETLSCKEKADVKDIDAY 420

SEQ ID NO:3      421  DVCIADGVCIIDAEFLKPPMETEEPQIFY 447
SEQ ID NO:35     421  DVCIADGVCIIDAE----- 433
SEQ ID NO:32     421  DVCIADGVCI----- 430
```

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Baker et al. (WO2009111066) teach a modified PH20 polypeptide having 99.8% identity to the amino acid sequence of SEQ ID NO:3 or instant SEQ ID NO:623 (E324N) and comprising a residue of E at position 324 (see the sequence alignment below).

SEQ ID NO:3-E324D

AXQ70926

(NOTE: this sequence has 59 duplicates in the database searched.

See complete list at the end of this report)

ID AXQ70926 standard; protein; 447 AA.

XX

AC AXQ70926;

XX

DT 12-NOV-2009 (first entry)

XX

DE Human mature hyaluronidase PH20 (1-447), SEQ ID 4.

XX

KW EC 3.2.1.35; Hyaluronidase; Sperm surface protein PH20; cell culture;
KW endo beta N acetylhexosaminidase; enzyme production.

XX

OS Homo sapiens.

Query Match 99.8%; Score 2400; Length 447;
Best Local Similarity 99.8%;
Matches 446; Conservative 1; Mismatches 0; Indels 0; Gaps 0;

SEQ ID NO:623

Petitioner Merck, Ex. 1002, p. 596

```
Query Match          99.8%;  Score 2398;  Length 447;
Best Local Similarity 99.8%;
Matches 446; Conservative 0; Mismatches 1; Indels 0; Gaps 0;
```

Qy	1	LNFRAPVPVNPVFLWAWNAPSEFCLGKGFDEPLDMSLFSFIGSPRINATQGQVTFYFVDR	60
Db	1	LNFRAPVPVNPVFLWAWNAPSEFCLGKGFDEPLDMSLFSFIGSPRINATQGQVTFYFVDR	60
Qy	61	LGYYPIYDSITGVTVNGGIPQKISLDQHLDKAKKDITFYMPVDNLGMAVIDWEWRPTWA	120
Db	61	LGYYPIYDSITGVTVNGGIPQKISLDQHLDKAKKDITFYMPVDNLGMAVIDWEWRPTWA	120
Qy	121	RNWKPKDVYKNRSIELVQQQNVQLSLTEATEKAKQEFKAGKDFLVETIKLGLLRPNHL	180
Db	121	RNWKPKDVYKNRSIELVQQQNVQLSLTEATEKAKQEFKAGKDFLVETIKLGLLRPNHL	180
Qy	181	WGYYLPDPDCYNHHYKPGYNGSCFNVEIKRNDLSWLWNESALTALPSIYLNLTQQSPVAAT	240
Db	181	WGYYLPDPDCYNHHYKPGYNGSCFNVEIKRNDLSWLWNESALTALPSIYLNLTQQSPVAAT	240
Qy	241	LYVNRNRVRAIRVSKIPDAKSLPLVFAYTRIVFTDQVLKFLSQDELVYTFGETVALGASG	300
Db	241	LYVNRNRVRAIRVSKIPDAKSLPLVFAYTRIVFTDQVLKFLSQDELVYTFGETVALGASG	300
Qy	301	IVIWGTLSIMRSMKSCLLLDNYM N ITILNPYIINVTLAAKMCSQVLCQEQGVCIRKNWNSS	360
Db	301	IVIWGTLSIMRSMKSCLLLDNYM E ITILNPYIINVTLAAKMCSQVLCQEQGVCIRKNWNSS	360
Qy	361	DYLHLNPDNFAIQLEKGGKFTVRGKPTLEDLEQFSEKFCYSCYSTLSCKEKADVKTDAV	420
Db	361	DYLHLNPDNFAIQLEKGGKFTVRGKPTLEDLEQFSEKFCYSCYSTLSCKEKADVKTDAV	420
Qy	421	DVCIADGVCI DAF LKPPMETEPEQIFY	447

Db 421 DVCIDAGVCIDAFKPPMETEEPQIFY 447

Frost et al. (US7767429) teach a modified PH20 polypeptide having 99.8% identity to the amino acid sequence of instant SEQ ID NO:624 (E324R) and comprising a residue of E at position 324 (see the sequence alignment below).

SEQ ID NO:624

US-10-795-095-4
(NOTE: this sequence has 48 duplicates in the database searched.
See complete list at the end of this report)
Sequence 4, US/10795095
Patent No. 7767429
GENERAL INFORMATION
APPLICANT: DeliaTroph Pharmaceuticals, Inc.
APPLICANT: Frost, Gregory
APPLICANT: Kundu, Anirban
APPLICANT: Bookbinder, Louis
TITLE OF INVENTION: SOLUBLE HYLAURONIDASE GLYCOPROTEIN (SHASEGP), PROCESS FOR PREPARING THE
TITLE OF INVENTION: SAME, USES AND PHARMACEUTICAL COMPOSITIONS COMPRISING THEREOF
FILE REFERENCE: DELIA1340-1
CURRENT APPLICATION NUMBER: US/10/795,095
CURRENT FILING DATE: 2004-03-05
PRIOR APPLICATION NUMBER: US 60/452,360
PRIOR FILING DATE: 2003-03-05
NUMBER OF SEQ ID NOS: 53
SEQ ID NO 4
LENGTH: 448
TYPE: PRT
ORGANISM: Homo sapiens

Query Match 99.8%; Score 2398; Length 448;
Best Local Similarity 99.8%;
Matches 446; Conservative 0; Mismatches 1; Indels 0; Gaps 0;

Qy 1 LNFRAFPVIPNVFPLWAWNAPSEFCGLGKFDLEPLDMSLFSFIGSPRINATGQGVTFIFYVDR 60
Db 1 LNFRAFPVIPNVFPLWAWNAPSEFCGLGKFDLEPLDMSLFSFIGSPRINATGQGVTFIFYVDR 60

Qy 61 LGYYPIYDSITGVTVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVIDWEEWRPTWA 120
Db 61 LGYYPIYDSITGVTVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVIDWEEWRPTWA 120

Qy 121 RNWPKPDVYKNRSIELVQQQNVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRPNHL 180
Db 121 RNWPKPDVYKNRSIELVQQQNVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRPNHL 180

Qy 181 WGYYLFPDCYNHHYKPGYNGSCFNVEIKRNDLSQLWNESTALYPSIYLNLTQQSPVAAT 240
Db 181 WGYYLFPDCYNHHYKPGYNGSCFNVEIKRNDLSQLWNESTALYPSIYLNLTQQSPVAAT 240

Qy 241 LYVRNVRREAIRVSKIPDAKSPVPFAYTRIVFTDQVLKFLSQDELVYTFGETVALGASG 300
Db 241 LYVRNVRREAIRVSKIPDAKSPVPFAYTRIVFTDQVLKFLSQDELVYTFGETVALGASG 300

Qy 301 IVIWGTLSIMRSMKSCLLLDNYM**R**ETILNPYIINVTLAAMCSQVLCQEQGVCIRKNWNSS 360
Db 301 IVIWGTLSIMRSMKSCLLLDNYM**E**ETILNPYIINVTLAAMCSQVLCQEQGVCIRKNWNSS 360

Qy 361 DYHLNLPDNFAIQLEKGGKFTVRGKPTLEDLEQFSEKFCSCYSTLSCKEKADVKTDAV 420
Db 361 DYHLNLPDNFAIQLEKGGKFTVRGKPTLEDLEQFSEKFCSCYSTLSCKEKADVKTDAV 420

Qy 421 DVCIDAGVCIDAFKPPMETEEPQIFY 447
Db 421 DVCIDAGVCIDAFKPPMETEEPQIFY 447

Scally et al. teach a modified PH20 polypeptide having 98.7% identity to the amino acid sequence of instant SEQ ID NO:32 and comprising a residue of E at position 324 (see the sequence alignment below).

SEQ ID NO:32

G3QVL9_GORGO
(NOTE: this sequence has 1 duplicate in the database searched.
See complete list at the end of this report)
ID G3QVL9_GORGO Unreviewed; 509 AA.
AC G3QVL9;
DT 16-NOV-2011, integrated into UniProtKB/TrEMBL.
DT 16-NOV-2011, sequence version 1.
DT 13-SEP-2023, entry version 67.
DE RecName: Full=Hyaluronidase {ECO:0000256|PIRNR:PIRNR038193, ECO:0000256|RuleBase:RU610713};

DE EC=3.2.1.35 {ECO:0000256|PIRNR:PIRNR038193, ECO:0000256|RuleBase:RU610713};
GN Name=SPAM1 {ECO:0000313|Ensembl:ENSGG0P00000006796.2};
OS Gorilla gorilla gorilla (Western lowland gorilla).
OC Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia;
OC Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae;
OC Gorilla.
OX NCBI_TaxID=9595 {ECO:0000313|Ensembl:ENSGG0P00000006796.2, ECO:0000313|Proteomes:UP000001519};
RN [1] {ECO:0000313|Ensembl:ENSGG0P00000006796.2, ECO:0000313|Proteomes:UP000001519}
RP NUCLEOTIDE SEQUENCE [LARGE SCALE GENOMIC DNA].
RA Scally A.;
RT "Insights into the evolution of the great apes provided by the gorilla
RT genome.";
RL Submitted (MAY-2011) to the EMBL/GenBank/DDBJ databases.
RN [2] {ECO:0000313|Ensembl:ENSGG0P00000006796.2, ECO:0000313|Proteomes:UP000001519}
RP NUCLEOTIDE SEQUENCE [LARGE SCALE GENOMIC DNA].
RX PubMed=22398555; DOI=10.1038/nature10842;
RA Scally A., Dutheil J.Y., Hillier L.W., Jordan G.E., Goodhead I.,
RA Herrero J., Hobolth A., Lappalainen T., Mailund T., Marques-Bonet T.,
RA McCarthy S., Montgomery S.H., Schwalie P.C., Tang Y.A., Ward M.C., Xue Y.,
RA Yngvadottir B., Alkan C., Andersen L.N., Ayub Q., Ball E.V., Beal K.,
RA Bradley B.J., Chen Y., Clee C.M., Fitzgerald S., Graves T.A., Gu Y.,
RA Heath P., Heger A., Karakoc E., Kolb-Kokocinski A., Laird G.K., Lunter G.,
RA Meader S., Mort M., Mullikin J.C., Munch K., O'Connor T.D., Phillips A.D.,
RA Prado-Martinez J., Rogers A.S., Sajjadian S., Schmidt D., Shaw K.,
RA Simpson J.T., Stenson P.D., Turner D.J., Vigilant L., Vilella A.J.,
RA Whitener W., Zhu B., Cooper D.N., de Jong P., Dermitzakis E.T.,
RA Eichler E.E., Fliscek P., Goldman N., Mundy N.I., Ning Z., Odom D.T.,
RA Ponting C.P., Quail M.A., Ryder O.A., Searle S.M., Warren W.C.,
RA Wilson R.K., Schierup M.H., Rogers J., Tyler-Smith C., Durbin R.;
RT "Insights into hominid evolution from the gorilla genome sequence.";
RL Nature 483:169-175 (2012).
RN [3] {ECO:0000313|Ensembl:ENSGG0P00000006796.2}
RP IDENTIFICATION.
RG Ensembl;
RL Submitted (MAY-2023) to UniProtKB.
CC -!- CATALYTIC ACTIVITY:
CC Reaction=Random hydrolysis of (1->4)-linkages between N-acetyl-beta-D-
CC glucosamine and D-glucuronate residues in hyaluronate.; EC=3.2.1.35;
CC Evidence={ECO:0000256|ARBA:ARBA00000251,
CC ECO:0000256|PIRNR:PIRNR038193, ECO:0000256|RuleBase:RU610713};
CC -!- SUBCELLULAR LOCATION: Cell membrane {ECO:0000256|ARBA:ARBA00004609};
CC Lipid-anchor, GPI-anchor {ECO:0000256|ARBA:ARBA00004609}. Membrane
CC {ECO:0000256|ARBA:ARBA00004589}; Lipid-anchor, GPI-anchor
CC {ECO:0000256|ARBA:ARBA00004589}.
CC -!- SIMILARITY: Belongs to the glycosyl hydrolase 56 family.
CC {ECO:0000256|ARBA:ARBA00008871, ECO:0000256|PIRNR:PIRNR038193,
CC ECO:0000256|RuleBase:RU610713}.

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DR EMBL; CABD030054849; -, NOT_ANNOTATED_CDS; Genomic_DNA.
DR RefSeq; XP_018886147.1; XM_019030602.1.
DR RefSeq; XP_018886148.1; XM_019030603.1.
DR AlphaFoldDB; G3QVL9; -.
DR STRING; 9593.ENSOG0P00000006796; -.
DR GlyCosmos; G3QVL9; 1 site, No reported glycans.
DR Ensembl; ENSGG0T00000006975.3; ENSGG0P00000006796.2; ENSGG0G00000006946.3.
DR GeneID; 101150849; -.
DR CTD; 6677; -.
DR eggNOG; ENOG502R6HD; Eukaryota.
DR GeneTree; ENSGT01020000230364; -.
DR HOGENOM; CLU_036366_0_1_1; -.
DR OrthoDB; 5344684at2759; -.
DR TreeFam; TF321598; -.
DR Proteomes; UP000001519; Chromosome 7.
DR Bgee; ENSGG0G00000006946; Expressed in testis.
DR GO; GO:0005886; C:plasma membrane; IEA:UniProtKB-SubCell.
DR GO; GO:0004415; F:hyaluronoglucosaminidase activity; IEA:UniProtKB-UniRule.
DR GO; GO:0005975; P:carbohydrate metabolic process; IEA:UniProtKB-UniRule.
DR GO; GO:0007342; P:fusion of sperm to egg plasma membrane involved in single fertilization; IEA:InterPro.
DR Gene3D; 3.20.20.70; Aldolase class I; 1.
DR InterPro; IPR013785; Aldolase_TIM.
DR InterPro; IPR017853; Glycoside_hydrolase_SF.
DR InterPro; IPR018155; Hyaluronidase.
DR InterPro; IPR001439; Hyaluronidase_PH20/Hyal5.
DR PANTHER; PTHR11769; HYALURONIDASE; 1.
DR PANTHER; PTHR11769:SF20; HYALURONIDASE PH-20; 1.
DR Pfam; PF01630; Glyco_hydro_56; 1.
DR PIRSF; PIRSF038193; Hyaluronidase; 1.
DR PIRSF; PIRSF500773; Hyaluronidase_PH20_Hyal5; 1.
DR PRINTS; PR00846; GLHYDRLASE56.
DR PRINTS; PR00848; SPERMPH20.
DR SUPFAM; SSF51445; (Trans)glycosidases; 1.
PE 3: Inferred from homology;
KW Disulfide bond {ECO:0000256|PIRSR:PIRSR038193-3};
KW Glycosidase {ECO:0000256|ARBA:ARBA00023295, ECO:0000256|PIRNR:PIRNR038193};
KW Hydrolase {ECO:0000256|PIRNR:PIRNR038193, ECO:0000256|RuleBase:RU610713};

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KW Transmembrane {ECO:0000256|SAM:Phobius};
KW Transmembrane helix {ECO:0000256|SAM:Phobius}.
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FT /evidence="ECO:0000256|PIRSR:PIRSR038193-3"
FT DISULFID 224..238
FT /evidence="ECO:0000256|PIRSR:PIRSR038193-3"
FT DISULFID 376..387
FT /evidence="ECO:0000256|PIRSR:PIRSR038193-3"
FT DISULFID 381..435
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SQ SEQUENCE 509 AA; 57899 MW; 7ABD5FB44B070E72 CRC64;

Query Match 98.7%; Score 2279; Length 509;
Best Local Similarity 98.1%;
Matches 422; Conservative 5; Mismatches 3; Indels 0; Gaps 0;

Qy 1 LNFRAFPVIPNVFPLWAWNAPSEFC LGKFDEPLDMSLFSFIGSPRINATGQGVTFIFYVDR 60
Db 36 LNFRAFPVIPNVFPLWAWNAPSKFCLGKFDEPLDMSLFSLIGSPRINTGQGVTFIFYVDR 95

Qy 61 LGYYPYIDSI TGVTVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVIDWEEWRPTWA 120
Db 96 LGYYPYIDSI TGVTVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVIDWEEWRPTWA 155

Qy 121 RNWKP KDVKYKNSIELVQQQNVQLSLTEATEKAKQEF EKAGKDFLVETIKLGKLLRPNHL 180
Db 156 RNWKP KDVKYKNSIELVQQQNVQLSLTEATEKAKQEF EKAGKDFMVTIKLGKLLRPNHL 215

Qy 181 WGYLFPDCYNHYYKKPGYNGSCFNVEIKRNDLSWLWNES TALYPSIYLTQQSPVAAT 240
Db 216 WGYLFPDCYNHYYKKPGYNGSCFNVEIKRNDLSWLWNES TALYPSIYLTQQSPVAAT 275

Qy 241 LYVRNRVREAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDELVYTFGETVALGASG 300
Db 276 LYVRNRVREAIRVSKIPDAKSPLPVFVYTRIVFTDQVLKFLSQDELVYTFGETVALGASG 335

Qy 301 IVIWGTL SIMRSMKSCLLLDNYM E TILNPHYIINVT LAARMCSQVLCQEQGVCIRKNWNSS 360
Db 336 IVIWGTL SIMRSMKSCLLLDNYM E TILNPHYIINVT LAARMCSQVLCQEQGVCIRKDNWSS 395

Qy 361 DYHLHLPDNFAIQLEKGGKFTVRGKPTLEDLEQFSEKFCYSCYSTLSCKEKADVKTDAV 420
Db 396 DYHLHLPDNFAIQLEKGGKFTVRGKPTLEDLEQFSEKFCYSCYSTLSCKEKADIKDTDAV 455

Qy 421 DVCIADGVCI 430
Db 456 DVCIADGVCI 465
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Ensembl teaches a modified PH20 polypeptide having 97.2% identity to the amino acid sequence of instant SEQ ID NO:32 and comprising a residue of E at position 324 (see the sequence alignment below).

SEQ ID NO:32

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GIRNI7_NOMLE
ID GIRNI7_NOMLE Unreviewed; 511 AA.
AC GIRNI7;
DT 19-OCT-2011, integrated into UniProtKB/TrEMBL.
DT 19-OCT-2011, sequence version 1.
DT 13-SEP-2023, entry version 54.
DE RecName: Full=Hyaluronidase {ECO:0000256|PIRNR:PIRNR038193, ECO:0000256|RuleBase:RU610713};
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GN Name=SPAM1 {ECO:0000313|Ensembl:ENSNLEP00000014801.1};
OS Nomascus leucogenys (Northern white-cheeked gibbon) (Hylobates leucogenys).
OC Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia;
OC Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hylobatidae;
OC Nomascus.
OX NCBI_TaxID=61853 {ECO:0000313|Ensembl:ENSNLEP00000014801.1, ECO:0000313|Proteomes:UP000001073};
RN [1] {ECO:0000313|Ensembl:ENSNLEP00000014801.1, ECO:0000313|Proteomes:UP000001073}
RP NUCLEOTIDE SEQUENCE [LARGE SCALE GENOMIC DNA].
RG Gibbon Genome Sequencing Consortium;
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RL Submitted (OCT-2012) to the EMBL/GenBank/DDBJ databases.
RN [2] (ECO:0000313|Ensembl:ENSNLEP00000014801.1)
RP IDENTIFICATION.
RG Ensembl;
RL Submitted (MAY-2023) to UniProtKB.
CC
CC -|- CATALYTIC ACTIVITY:
CC Reaction=Random hydrolysis of (1->4)-linkages between N-acetyl-beta-D-
CC glucosamine and D-glucuronate residues in hyaluronate.; EC=3.2.1.35;
CC Evidence={ECO:0000256|ARBA:ARBA00000251,
CC ECO:0000256|PIRNR:PIRNR038193, ECO:0000256|RuleBase:RU610713};
CC -|- SUBCELLULAR LOCATION: Cell membrane (ECO:0000256|ARBA:ARBA00004609);
CC Lipid-anchor, GPI-anchor (ECO:0000256|ARBA:ARBA00004609). Membrane
CC {ECO:0000256|ARBA:ARBA00004589}; Lipid-anchor, GPI-anchor
CC {ECO:0000256|ARBA:ARBA00004589}.
CC -|- SIMILARITY: Belongs to the glycosyl hydrolase 56 family.
CC {ECO:0000256|ARBA:ARBA00008871, ECO:0000256|PIRNR:PIRNR038193,
CC ECO:0000256|RuleBase:RU610713}.
CC -----
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CC Distributed under the Creative Commons Attribution (CC BY 4.0) License
CC -----
DR EMBL; ADFV01195880; -; NOT_ANNOTATED_CDS; Genomic_DNA.
DR EMBL; ADFV01195881; -; NOT_ANNOTATED_CDS; Genomic_DNA.
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DR RefSeq; XP_003261319.1; XM_003261271.1.
DR AlphaFoldDB; G1RNI7; -.
DR STRING; 61853.ENSNLEP00000014801; -.
DR GlyCosmos; G1RNI7; 1 site, No reported glycans.
DR Ensembl; ENSNLET00000015545.2; ENSNLEP00000014801.1; ENSNLEG00000012189.2.
DR eggNOG; ENOG502R6HD; Eukaryota.
DR GeneTree; ENSGT01020000230364; -.
DR InParanoid; G1RNI7; -.
DR OMA; RAKIVFE; -.
DR TreeFam; TF321598; -.
DR Proteomes; UP000001073; Chromosome 13.
DR GO; GO:0005886; C:plasma membrane; IEA:UniProtKB-SubCell.
DR GO; GO:0004415; F:hyaluronoglucosaminidase activity; IEA:UniProtKB-UniRule.
DR GO; GO:0005975; P:carbohydrate metabolic process; IEA:UniProtKB-UniRule.
DR GO; GO:0007342; P:fusion of sperm to egg plasma membrane involved in single fertilization; IEA:InterPro.
DR Gene3D; 3.20.20.70; Aldolase class I; 1.
DR InterPro; IPR013785; Aldolase_TIM.
DR InterPro; IPR017853; Glycoside_hydrolase_SF.
DR InterPro; IPR018155; Hyaluronidase.
DR InterPro; IPR001439; Hyaluronidase_PH20/Hyal5.
DR PANTHER; PTHR11769; HYALURONIDASE; 1.
DR PANTHER; PTHR11769:SF20; HYALURONIDASE PH-20; 1.
DR Pfam; PF01630; Glyco_hydro_56; 1.
DR PIRSF; PIRSF038193; Hyaluronidase; 1.
DR PIRSF; PIRSF500773; Hyaluronidase_PH20_Hyal5; 1.
DR PRINTS; PR00846; GLHYDRLASE56.
DR PRINTS; PR00848; SPERMMPH20.
DR SUPFAM; SSF51445; (Trans)glycosidases; 1.
PE 3: Inferred from homology;
KW Disulfide bond (ECO:0000256|PIRSR:PIRSR038193-3);
KW Glycosidase (ECO:0000256|ARBA:ARBA00023295, ECO:0000256|PIRNR:PIRNR038193);
KW Hydrolase (ECO:0000256|PIRNR:PIRNR038193, ECO:0000256|RuleBase:RU610713);
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KW Signal (ECO:0000256|ARBA:ARBA00022729).
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FT /evidence="ECO:0000256|PIRSR:PIRSR038193-3"
FT DISULFID 376..387
FT /evidence="ECO:0000256|PIRSR:PIRSR038193-3"
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Query Match 97.2%; Score 2245; Length 511;
Best Local Similarity 96.7%;
Matches 416; Conservative 6; Mismatches 8; Indels 0; Gaps 0;

QY 1 LNFRAAPPVIPNVFPLWAWNAPSEFCLGKFDEPLDMSLSEFISGSPRINATGQGVTIFYVDR 60
Db 36 LNFRAAPPVIPNVFPLWAWNAPSEFCLGKFDEPLDMSLSELTGSPRINVTGQGVTIFYVDR 95

QY 61 LGYYPYIDSITGVTVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVIDWEEWRPTWA 120
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         |||
Db      216  WGYLLFPDCYNHHYKKPGYNGSCFNVEIKRNDLSQLWNESTALYPSIYLNLTQQSPVAAT 275

Qy      241  LYVRNRVREAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDELVYTFGETVALGASG 300
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Db      276  LYVRNRVREAIRVSKIPDAKSPLPVFVYARIVFTDQVLKFLSRDELVYTLGETVALGASG 335

Qy      301  IVIWGTLSIMRSMKSCLLLDNYMETILNPYIINVTLAAMCSQVLCQEQGVCIRKNWNSS 360
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Db      336  IVIWGSLSIVRSMKSCLLLDNYMETILNPYIINVTLAAMCSQVLCQEQGVCIRKDWNSS 395

Qy      361  DYHLNLPDNFAIQLEKGGKFTVRGKPTLEDLEQFSEKFCSCYSTLSCKEKADVKTDAV 420
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Db      396  DYHLNLPDNFAIQLEKGGKFTVRGKPTLEDLEQFSEKFCSCYSTLSCKEKADVKTDAV 455

Qy      421  DVCIADGVCI 430
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Db      456  DVCIADGVCI 465
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Lin et al. (PNAS, 1993; 90:10071-10075) teach a modified PH20 polypeptide having 91.9% identity to the amino acid sequence of instant SEQ ID NO:32 and comprising a residue of E at position 324 (see the sequence alignment below).

SEQ ID NO:32

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AC      P38568; G7P0K2;
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DT      01-OCT-1994, sequence version 1.
DT      13-SEP-2023, entry version 103.
DE      RecName: Full=Hyaluronidase PH-20;
DE          Short=Hyal-PH20;
DE          EC=3.2.1.35;
DE      AltName: Full=Hyaluronoglucosaminidase PH-20;
DE      AltName: Full=Sperm adhesion molecule 1;
DE      AltName: Full=Sperm surface protein PH-20;
DE      Flags: Precursor;
GN      Name=SPAM1; Synonyms=PH20; ORFNames=EGM_12920;
OS      Macaca fascicularis (Crab-eating macaque) (Cynomolgus monkey).
OC      Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia;
OC      Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini;
OC      Cercopithecoidea; Cercopithecinae; Macaca.
OX      NCBI_TaxID=9541;
RN      [1]
RP      NUCLEOTIDE SEQUENCE [MRNA] (ISOFORM 1).
RC      TISSUE=Testis;
RX      PubMed=8234258; DOI=10.1073/pnas.90.21.10071;
RA      Lin Y., Kimmel L.H., Myles D.G., Primakoff P.;
RT      "Molecular cloning of the human and monkey sperm surface protein PH-20.";
RL      Proc. Natl. Acad. Sci. U.S.A. 90:10071-10075(1993).
RN      [2]
RP      NUCLEOTIDE SEQUENCE [LARGE SCALE GENOMIC DNA].
RX      PubMed=22002653; DOI=10.1038/nbt.1992;
RA      Yan G., Zhang G., Fang X., Zhang Y., Li C., Ling F., Cooper D.N., Li Q.,
RA      Li Y., van Gool A.J., Du H., Chen J., Chen R., Zhang P., Huang Z.,
RA      Thompson J.R., Meng Y., Bai Y., Wang J., Zhuo M., Wang T., Huang Y.,
RA      Wei L., Li J., Wang Z., Hu H., Yang P., Le L., Stenson P.D., Li B., Liu X.,
RA      Ball E.V., An N., Huang Q., Zhang Y., Fan W., Zhang X., Li Y., Wang W.,
RA      Katze M.G., Su B., Nielsen R., Yang H., Wang J., Wang X., Wang J.;
RT      "Genome sequencing and comparison of two nonhuman primate animal models,
RT      the cynomolgus and Chinese rhesus macaques.";
RL      Nat. Biotechnol. 29:1019-1023(2011).
CC      -!- FUNCTION: Involved in sperm-egg adhesion. Upon fertilization sperm must
CC      first penetrate a layer of cumulus cells that surrounds the egg before
CC      reaching the zona pellucida. The cumulus cells are embedded in a matrix
CC      containing hyaluronic acid which is formed prior to ovulation. This
CC      protein aids in penetrating the layer of cumulus cells by digesting
CC      hyaluronic acid.
CC      -!- CATALYTIC ACTIVITY:
CC          Reaction=Random hydrolysis of (1->4)-linkages between N-acetyl-beta-D-
CC          glucosamine and D-glucuronate residues in hyaluronate.; EC=3.2.1.35;
CC      -!- SUBCELLULAR LOCATION: Cell membrane; Lipid-anchor, GPI-anchor.
CC      -!- ALTERNATIVE PRODUCTS:
CC          Event=Alternative splicing; Named isoforms=2;
CC          Name=1;
CC              IsoId=P38568-1; Sequence=Displayed;
CC          Name=2;
CC              IsoId=P38568-2; Sequence=VSP_046430;
CC      -!- TISSUE SPECIFICITY: Testis.
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CC      -!- SIMILARITY: Belongs to the glycosyl hydrolase 56 family. (ECO:0000305).
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CC      Copyrighted by the UniProt Consortium, see https://www.uniprot.org/terms
CC      Distributed under the Creative Commons Attribution (CC BY 4.0) License
CC      -----
DR      EMBL; L13780; -; NOT_ANNOTATED_CDS; mRNA.
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DR      AlphaFoldDB; P38568; -.
DR      SMR; P38568; -.
DR      STRING; 9541.XP_005550707.1; -.
DR      CAZy; GH56; Glycoside Hydrolase Family 56.
DR      GlyCosmos; P38568; 8 sites, No reported glycans.
DR      eggNOG; ENOG502R6HD; Eukaryota.
DR      Proteomes; UP000009130; Chromosome 3.
DR      Proteomes; UP000233100; Unplaced.
DR      GO; GO:0002079; C:inner acrosomal membrane; IDA:UniProtKB.
DR      GO; GO:0005886; C:plasma membrane; IEA:UniProtKB-SubCell.
DR      GO; GO:0098552; C:side of membrane; IEA:UniProtKB-KW.
DR      GO; GO:0004415; F:hyaluronoglucosaminidase activity; IEA:UniProtKB-EC.
DR      GO; GO:0005975; P:carbohydrate metabolic process; IEA:InterPro.
DR      GO; GO:0007155; P:cell adhesion; IEA:UniProtKB-KW.
DR      GO; GO:0007342; P:fusion of sperm to egg plasma membrane involved in single fertilization; IEA:InterPro.
DR      GO; GO:0007341; P:penetration of zona pellucida; IMP:UniProtKB.
DR      Gene3D; 3.20.20.70; Aldolase class I; 1.
DR      InterPro; IPR013785; Aldolase_TIM.
DR      InterPro; IPR017853; Glycoside_hydrolase_SF.
DR      InterPro; IPR018155; Hyaluronidase.
DR      InterPro; IPR001439; Hyaluronidase_PH20/Hyal5.
DR      PANTHER; PTHR11769; HYALURONIDASE; 1.
DR      PANTHER; PTHR11769:SF20; HYALURONIDASE PH-20; 1.
DR      Pfam; PF01630; Glyco_hydro_56; 1.
DR      PIRSF; PIRSF038193; Hyaluronidase; 1.
DR      PIRSF; PIRSF500773; Hyaluronidase_PH20_Hyal5; 1.
DR      PRINTS; PR00846; GLHYDRLASE56.
DR      PRINTS; PR00848; SPERMPH20.
DR      SUPFAM; SSF51445; (Trans)glycosidases; 1.
PE      2: Evidence at transcript level;
KW      Alternative splicing; Cell adhesion; Cell membrane; Disulfide bond;
KW      Glycoprotein; Glycosidase; GPI-anchor; Hydrolase; Lipoprotein; Membrane;
KW      Reference proteome; Signal.
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FT      PROPEP          492..510
FT                      /note="Removed in mature form"
FT                      /evidence="ECO:0000255"
FT                      /id="PRO_0000012092"
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FT                      /evidence="ECO:0000255"
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FT                      /note="N-linked (GlcNAc...) asparagine"
FT                      /evidence="ECO:0000255"
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FT                      /evidence="ECO:0000255"
FT      DISULFID        60..351
FT                      /evidence="ECO:0000250"
FT      DISULFID        224..238
FT                      /evidence="ECO:0000250"
FT      DISULFID        376..387
FT                      /evidence="ECO:0000250"
FT      DISULFID        381..435
FT                      /evidence="ECO:0000250"
FT      DISULFID        437..464
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Gibbs et al. (Science, 2007; 316:222-234) teach a modified PH20 polypeptide having 91.9% identity to the amino acid sequence of instant SEQ ID NO:32 and comprising a residue of E at position 324 (see the sequence alignment below).

F6TY69 MACMU

(NOTE: this sequence has 1 duplicate in the database searched.)

(NOTE: this sequence has 1 duplicate in the database
See complete list at the end of this report)

ID F6TY69 MACMU Unreviewed; 510 AA.

AC F6TY69;

DT 27-JUL-2011, integrated into Uni

DT 27-JUL-2011, sequence version

DT 13-SEP-2023, entry version 57.

DE RecName: Full=Hyaluronidase {ECO:0000256|PIRNR:PIRNR038193, ECO:0000256|RuleBase:RU610713};

DE EC=3.2.1.35 {ECO:0000256|PIRNR:PIRNR038193, ECO:0000256|RuleBase:RU610713};

GN Name=SPAM1 {ECO:0000313|Ensembl:ENSMMUP00000007543.2,

GN ECO:0000313|VGNC:VGNC:77853};

OS *Macaca mulatta* (Rhesus macaque).

OC Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia;

OC Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini;

OC Cercopithecidae; Cercopithecinae; Macaca.

OX NCBI TaxID=9544 {ECO:0000313|Ensembl:ENSMMUP00000007543.2, ECO:0000313|Proteomes:UP000006718};

RN [1] (ECO:0000313|Ensembl:ENSMUP00000007543.2, ECO:0000313|Proteomes:UP000006718)

RP NUCLEOTIDE SEQUENCE [LARGE SCALE GENOMIC DNA].

RC STRAIN=17573 {ECO:0000313|Ensembl:ENSMMUP00000007543.2,

RC ECO:0000313|Proteomes:UP000006718};

RX PubMed=17431167; DOI=10.1126/science.1139247;

RA Gibbs R.A., Rogers J., Katze M.G., Bumgarner R., Weinstock G.M.,

RA Mardis E.R., Remington K.A., Strausberg R.L., Venter J.C., Wilson R.K.,

RA Batzer M.A., Bustamante C.D., Eichler E.E., Hahn M.W., Hardison R.C.,

RA Makova K.D., Miller W., Milosavljevic A., Palermo R.E., Siepel A.,

BA Sikela J.M., Attaway T., Bell S., Bernard K.E., Buhay C.J.,

RA Chandrabose M.N., Dao M., Davis C., Delehaunty K.D., Ding Y., Dinh H.H.,

RA Dugan-Rocha S., Fulton L.A., Gabisi R.A., Garner T.T., Godfrey J.,

BA Hawes A.C., Hernandez J., Hines S., Holder M., Hume J., Jhangiani S.N.

RA Joshi V., Khan Z.M., Kirkness E.F., Cree A., Fowler B.G., Lee S.,

BA Lewis L.B., Li Z., Liu Y.-S., Moore S.M., Muzny D., Nazareth L.V.,

BA Ngo D.N., Okwuonu G.O., Pai G., Parker D., Paul H.A., Pfannkoch C.,

BA Pohl C.S., Rogers Y.-H.C., Ruiz S.J., Sabo A., Santibanez J.,

RA Schneider B.W., Smith S.M., Sodergren E., Svatek A.F., Utterback T.B.,

RA Vattathil S., Warren W., White C.S., Chinwalla A.T., Feng Y., Halpern A.L.

RA Vaccanti S., Varlen W., White C.S., Chinwalla A.T., Feng T., Halpern A.E.,

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RA Hillier L.W., Huang X., Minx P., Nelson J.O., Pepin K.H., Qin X.,
RA Sutton G.G., Venter E., Walenz B.P., Wallis J.W., Worley K.C., Yang S.-P.,
RA Jones S.M., Marra M.A., Rocchi M., Schein J.E., Baertsch R., Clarke L.,
RA Csuros M., Glasscock J., Harris R.A., Havlak P., Jackson A.R., Jiang H.,
RA Liu Y., Messina D.N., Shen Y., Song H.X.-Z., Wylie T., Zhang L., Birney E.,
RA Han K., Konkel M.K., Lee J., Smit A.F.A., Ullmer B., Wang H., Xing J.,
RA Burhans R., Cheng Z., Karro J.E., Ma J., Raney B., She X., Cox M.J.,
RA Demuth J.P., Dumas L.J., Han S.-G., Hopkins J., Karimpour-Fard A.,
RA Kim Y.H., Pollack J.R., Vinar T., Addo-Quaye C., Degenhardt J., Denby A.,
RA Hubisz M.J., Indap A., Kosiol C., Lahn B.T., Lawson H.A., Marklein A.,
RA Nielsen R., Vallender E.J., Clark A.G., Ferguson B., Hernandez R.D.,
RA Hirani K., Kehrner-Sawatzki H., Kolb J., Patil S., Pu L.-L., Ren Y.,
RA Smith D.G., Wheeler D.A., Schenck I., Ball E.V., Chen R., Cooper D.N.,
RA Giardine B., Hsu F., Kent W.J., Lesk A., Nelson D.L., O'Brien W.E.,
RA Pruefer K., Stenson P.D., Wallace J.C., Ke H., Liu X.-M., Wang P.,
RA Xiang A.P., Yang F., Barber G.P., Haussler D., Karolchik D., Kern A.D.,
RA Kuhn R.M., Smith K.E., Zwing A.S.;
RT "Evolutionary and biomedical insights from the rhesus macaque genome.";
RL Science 316:222-234(2007).
RN [2] (ECO:0000313|Ensembl:ENSMMUP00000007543.2)
RP IDENTIFICATION.
RC STRAIN=17573 (ECO:0000313|Ensembl:ENSMMUP00000007543.2);
RG Ensembl;
RL Submitted (MAY-2023) to UniProtKB.
CC -!- CATALYTIC ACTIVITY:
CC Reaction=Random hydrolysis of (1->4)-linkages between N-acetyl-beta-D-
CC glucosamine and D-glucuronate residues in hyaluronate.; EC=3.2.1.35;
CC Evidence={ECO:0000256|ARBA:ARBA00000251,
CC ECO:0000256|PIRNR:PIRNR038193, ECO:0000256|RuleBase:RU610713};
CC -!- SUBCELLULAR LOCATION: Cell membrane (ECO:0000256|ARBA:ARBA00004609);
CC Lipid-anchor, GPI-anchor (ECO:0000256|ARBA:ARBA00004609). Membrane
CC {ECO:0000256|ARBA:ARBA00004589}; Lipid-anchor, GPI-anchor
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CC -!- SIMILARITY: Belongs to the glycosyl hydrolase 56 family.
CC {ECO:0000256|ARBA:ARBA00008871, ECO:0000256|PIRNR:PIRNR038193,
CC ECO:0000256|RuleBase:RU610713}.
CC -----
CC Copyrighted by the UniProt Consortium, see https://www.uniprot.org/terms
CC Distributed under the Creative Commons Attribution (CC BY 4.0) License
CC -----
DR RefSeq; XP_001086882.2; XM_001086882.3.
DR RefSeq; XP_014990320.1; XM_015134834.1.
DR AlphaFoldDB; F6TY69; -.
DR GlyCosmos; F6TY69; 1 site, No reported glycans.
DR Ensembl; ENSMMUT00000008024.4; ENSMMUP00000007543.2; ENSMMUG00000005719.4.
DR GeneID; 696249; -.
DR KEGG; mcc:696249; -.
DR CTD; 6677; -.
DR VEuPathDB; HostDB:ENSMUG00000005719; -.
DR VGNC; VGNC:77853; SPAM1.
DR GeneTree; ENSGT01020000230364; -.
DR HOGENOM; CLU_036366_0_1_1; -.
DR OrthoDB; 5344684at2759; -.
DR Proteomes; UP000006718; Chromosome 3.
DR Bgee; ENSMMUG00000005719; Expressed in spermatid and 4 other tissues.
DR ExpressionAtlas; F6TY69; baseline.
DR GO; GO:0005886; C:plasma membrane; IEA:UniProtKB-SubCell.
DR GO; GO:0004415; F:hyaluronoglucosaminidase activity; IEA:UniProtKB-UniRule.
DR GO; GO:0005975; P:carbohydrate metabolic process; IEA:UniProtKB-UniRule.
DR GO; GO:0007342; P:fusion of sperm to egg plasma membrane involved in single fertilization; IEA:InterPro.
DR Gene3D; 3.20.20.70; Aldolase class I; 1.
DR InterPro; IPR013785; Aldolase_TIM.
DR InterPro; IPR017853; Glycoside_hydrolase_SF.
DR InterPro; IPR018155; Hyaluronidase.
DR InterPro; IPR001439; Hyaluronidase_PH20/Hyal5.
DR PANTHER; PTHR11769; HYALURONIDASE; 1.
DR PANTHER; PTHR11769:SF20; HYALURONIDASE PH-20; 1.
DR Pfam; PF01630; Glyco_hydro_56; 1.
DR PIRSF; PIRSF038193; Hyaluronidase; 1.
DR PIRSF; PIRSF500773; Hyaluronidase_PH20_Hyal5; 1.
DR PRINTS; PR00846; GLHYDRLASE56.
DR PRINTS; PR00848; SPERMPH20.
DR SUPFAM; SSF51445; (Trans)glycosidases; 1.
PE 3: Inferred from homology;
KW Disulfide bond (ECO:0000256|PIRSR:PIRSR038193-3);
KW Glycosidase (ECO:0000256|ARBA:ARBA00023295, ECO:0000256|PIRNR:PIRNR038193);
KW Hydrolase (ECO:0000256|PIRNR:PIRNR038193, ECO:0000256|RuleBase:RU610713);
KW Membrane (ECO:0000256|SAM:Phobius);
KW Reference proteome (ECO:0000313|Proteomes:UP000006718);
KW Signal (ECO:0000256|ARBA:ARBA00022729);
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KW Transmembrane helix (ECO:0000256|SAM:Phobius).
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SQ SEQUENCE 510 AA; 57976 MW; 1131D2BD42D8973B CRC64;

Query Match 91.9%; Score 2123; Length 510;
Best Local Similarity 90.0%;
Matches 387; Conservative 25; Mismatches 18; Indels 0; Gaps 0;

Qy 1 LNFRAFPVPIPNVFLWAWNAPSEFC LGKFDEPLDMSLFSGSPRINATGQGVITIFYVDR 60
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Qy 61 LGYYPYIDTSITGVTVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVIDWEEWRPTWA 120
Db 96 LGYYPYIDLTGVTVHGGIPQKISLQDHLDKSKQDILFYMPVDNLGMAVIDWEEWRPTWA 155

Qy 121 RNWKPDKVYKNRSIELVQQQNVQLSLTEATEKAKQEFKAGKDFLVETIKLGLLRPNHL 180
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Db 216 WGYLFLPDCYNHHYKPGYNGSCFDVEIKRNDLSWLWNES TALYPSIYLTQQSVVAT 275

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Db 276 LYVRNRVREAIRVSKIPDAKNPLPVFVYARLVFTDQVLKFLSREELVSTLGETVALGASG 335

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Qy 361 DYLHLNPNDFAIQLEKGGKFTVRGKPTLEDLEQFSEKFCSCYTLSCKEKADV KDTDAV 420
Db 396 DYLHLNPNDFIRLEKGGKFTVHGKPTVEDLEEFSEKFCSCYTLNLSCKEADV KDTDAV 455

Qy 421 DVCIADGVCI 430
Db 456 DVCIADGVCI 465
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Frost et al. (WO2009128917) teach a modified PH20 polypeptide having 100% identity to the amino acid sequence of instant SEQ ID NO:35 (see the sequence alignment below) and a modified PH20 polypeptide having 99.6% identity to the amino acid sequence of instant SEQ ID NO:3 and comprising a residue of E at position 324 (see the sequence alignment below).

SEQ ID NO:35

```
AKR76101
(NOTE: this sequence has 25 duplicates in the database searched.
See complete list at the end of this report)
ID AKR76101 standard; protein; 433 AA.
XX
AC AKR76101;
XX
DT 10-DEC-2009 (first entry)
XX
DE Soluble hyaluronidase mature protein PH20 sequence SEQ ID NO:168.
XX
KW Hyaluronidase; brain tumor; breast tumor; cancer; cerebroprotective;
KW cerebrovascular ischemia; colon tumor; cytostatic; dermatological;
KW diuretic; edema; endocrine-gen.; gastrointestinal-gen.; gynecological;
KW injury; neuroprotective; non-small-cell lung cancer;
KW organ transplantation; ovary tumor; pancreas tumor; prostate tumor;
KW protein therapy; respiratory-gen.; solid tumor; squamous cell carcinoma;
KW surgical-gen.; therapeutic; uropathic; vasotropic; vulnery.
XX
OS Homo sapiens.
XX
CC PN WO2009128917-A2.
XX
CC PD 22-OCT-2009.
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XX
CC PF 14-APR-2009; 2009WO-US002352.
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PR 14-APR-2009; 2008US-0124278P.
PR 29-MAY-2008; 2008US-0130357P.
PR 08-OCT-2008; 2008US-0195624P.
XX
CC PA (HALO-) HALOZYME INC.
XX
CC PI Frost GI, Jiang P, Thompson CB;
XX
DR WPI; 2009-Q23044/73.
XX
CC PT Use of soluble hyaluronidase composition formulated as a medicament for
CC PT maintaining a plasma level of hyaluronidase enzyme in plasma for treating
CC PT a disease or condition where a hyaluronidase substrate accumulates.
XX
CC PS Disclosure; SEQ ID NO 168; 292pp; English.
XX
CC The present invention relates to use of soluble hyaluronidase composition
CC formulated as a medicament for maintaining a plasma level of
CC hyaluronidase enzyme in plasma for treating a disease or condition where
CC a hyaluronidase substrate accumulates, where the composition comprises a
CC soluble hyaluronidase conjugated to a polymer in an amount sufficient to
CC maintain the level. The composition is useful for maintaining plasma
CC level of the hyaluronidase enzyme in plasma at level of at least 3 U/ml
CC for at least week for treating disease or condition where hyaluronidase
CC substrate accumulates; and for treating a hyaluronan-associated disease
CC or condition in a subject, where the disease or condition where
CC hyaluronidase substrate accumulates is associated with high interstitial
CC fluid pressure. The disease or condition is selected from disc pressure,
CC cancer (e.g. tumor, preferably solid tumor), and edema, where edema is
CC caused by organ transplant, stroke or brain trauma, and where tumor has
CC increased cellular and/or stromal expression of a hyaluronan, compared to
CC a non-cancerous tissue of the same tissue type or compared to a non-
CC metastatic tumor of the same tumor-type. Preferably, the disease or
CC condition is selected from a late-stage cancer, a metastatic cancer and
CC an undifferentiated cancer, e.g. ovarian cancer, in situ carcinoma (ISC),
CC squamous cell carcinoma (SCC), prostate cancer, pancreatic cancer, non-
CC small cell lung cancer, breast cancer, brain cancer and colon cancer. The
CC present sequence represents a soluble hyaluronidase protein sequence used
CC in the therapeutic purpose mentioned in the current invention.
XX
SQ Sequence 433 AA;

Query Match 100.0%; Score 2326; Length 433;
Best Local Similarity 100.0%;
Matches 433; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 LNFRAAPPVPIPNVPFLWAWNAPSEFCGLGKFEPLDMSLFSFIGSPRINATGQGVTFIFYVDR 60
|
Db 1 LNFRAAPPVPIPNVPFLWAWNAPSEFCGLGKFEPLDMSLFSFIGSPRINATGQGVTFIFYVDR 60

Qy 61 LGYYPYIDSITGTVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVIDWEEWRPTWA 120
|
Db 61 LGYYPYIDSITGTVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVIDWEEWRPTWA 120

Qy 121 RNWPKPKDVYKNRSIELVQQQNVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRPNHL 180
|
Db 121 RNWPKPKDVYKNRSIELVQQQNVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRPNHL 180

Qy 181 WGYLLFPDCYNHHYKPKGYNGSCFNVEIKRNDLSWLWNESTALYPSIYLNQQSPVAAT 240
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Db 181 WGYLLFPDCYNHHYKPKGYNGSCFNVEIKRNDLSWLWNESTALYPSIYLNQQSPVAAT 240

Qy 241 LYVRNRVREAIRVSKIPDAKSPVPFAYTRIVFTDQVLKFLSQDELVYTFGETVALGASG 300
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Db 241 LYVRNRVREAIRVSKIPDAKSPVPFAYTRIVFTDQVLKFLSQDELVYTFGETVALGASG 300

Qy 301 IVIWGTLSIMRSMKSCLLLDNYM~~E~~TILNPYIINVTLAAKMCSQVLCQEQGVCIKKNWNSS 360
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Db 301 IVIWGTLSIMRSMKSCLLLDNYM~~E~~TILNPYIINVTLAAKMCSQVLCQEQGVCIKKNWNSS 360

Qy 361 DYHLNPDNFAIQLEKGGKFTVRGKPTLEDLEQFSEKFCYSCYSTLSCKEKADVKTDAV 420
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Db 361 DYHLNPDNFAIQLEKGGKFTVRGKPTLEDLEQFSEKFCYSCYSTLSCKEKADVKTDAV 420

Qy 421 DVCIADGVCI DAF 433
|
Db 421 DVCIADGVCI DAF 433

Baker et al. (WO2009111066) teach a modified PH20 polypeptide having 100% identity to the amino acid sequence of instant SEQ ID NO:35 and comprising a residue of E at position 324 (see the sequence alignment below).


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Db      301  IVIWGTLSIMRSMKSCLLLDNYMETILNPYIINVTLAAKMCSQVLCQEQQGVCIRKNWNSS 360
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Db      361  DYHLNPNDFAIQLEKGGKFTVRGKPTLEDLEQFSEKFCSCYSTLSCKEKADVKTDAV 420
Qy      421  DVCIDAGVCIDAF 433
          |||
Db      421  DVCIDAGVCIDAF 433
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10. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571)272-4521. The examiner can normally be reached on Monday-Thursday, 7:00am-5:30pm EST.

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, Jeffrey Stucker, can be reached on 571-272-0911. 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.

Chang-Yu Wang
April 22, 2024

/CHANG-YU WANG/
Primary Examiner, Art Unit 1649



UNITED STATES
PATENT AND TRADEMARK OFFICE

Page 1 of 2
P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
18/340,786

RECEIPT DATE / TIME
06/18/2024 03:13:18 PM Z ET

ATTORNEY DOCKET #
63995-01-5105-US-17

Title of Invention

PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 6432

FILED BY Collins Mba-Jonas

PATENT CENTER # 66018159

FILING DATE 06/23/2023

CUSTOMER # 28977

FIRST NAMED
INVENTOR Ge WEI

CORRESPONDENCE
ADDRESS -

AUTHORIZED BY Kalpesh Upadhye

Documents

TOTAL DOCUMENTS: 3

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
20240618__ResponseFOA.pdf		11	-	198 KB
20240618__ResponseFOA-A.NE.pdf	(1-1)	1	Response After Final Action	114 KB
20240618__ResponseFOA-CLM.pdf	(2-3)	2	Claims	100 KB
20240618__ResponseFOA-REM.pdf	(4-11)	8	Applicant Arguments/Remarks Made in an Amendment	168 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
20240618_ResponseFOA.pdf	DC251D56EFC07BE8592CA936A73B7DB1E85A65F2B583F973E 0DF6CA3E0F3AA1A651162CF4BA8D807CE57DCCFE3BF94334 3FD17C842E890E777C1E4E15A74734D
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20240618_ResponseFOA- REM.pdf	2230D7C8E54C89D0F9F3F5E5A4EF417CCECA06BEE16B7DB6 FE6830F2D5A16FF7850EB5AFBBD56A0000BD329EE6CB1D2D 19CB2FB9755933BC9794DC2E344D0936

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 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

In re Application of Ge Wei <i>et al.</i>	)	
	)	Confirmation No. 6432
U.S. Application No. 18/340,786	)	
	)	Group Art Unit: 1649
Filing Date: 6/23/2023	)	
	)	Examiner: Chang Yu Wang
For: PH20 Polypeptide Variants, Formulations	)	
and Uses Thereof	)	

AMENDMENT UNDER 37 C.F.R. § 1.111

In response to the Final Office Action dated 04/26/2024, having a three-month shortened statutory period for response set to expire 07/26/2024, Applicant requests entry of the following amendments and remarks in the above patent application. To the extent necessary, a petition for an extension of time under 37 C.F.R. § 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 50-0310 and please credit any excess fees to such deposit account.

The Listing of claims begins on page 2.

Remarks begin on page 4.

The Conclusion is on page 11.

LISTING OF THE CLAIMS

This listing of the claims will replace all previous versions.

1. (Currently Amended) A modified PH20 polypeptide comprising an amino acid sequence, wherein:
 - (a) at least 95% of the residues of the amino acid sequence of the modified PH20 polypeptide are identical to the residues in an amino acid sequence set forth in SEQ ID NO: 35 when the sequence of the modified PH20 polypeptide is aligned at positions corresponding to the sequence set forth in SEQ ID NO: 35 to maximize identical residues, and wherein, ~~when aligned, gaps at the N-terminus and C-terminus of the aligned sequences are~~ terminal gaps are treated as non-identical; and
 - (b) the amino acid sequence of the modified PH20 polypeptide comprises an amino acid modification at a position corresponding to position 324 with reference to amino acid positions set forth in SEQ ID NO: 3; and
 - (c) the modification at position 324 is a replacement selected from among D, N, and R, and wherein the modified PH20 polypeptide exhibits increased hyaluronidase activity compared to the hyaluronidase activity of the polypeptide set forth in SEQ ID NO: 3, measured under identical conditions.
2. (Original) The modified PH20 polypeptide of claim 1, wherein the amino acid modification is at a position corresponding to position 324 with reference to amino acid positions set forth in SEQ ID NO: 3 is D.
3. (Previously presented) The modified PH20 polypeptide of claim 2, wherein at least 96% of the residues of the amino acid sequence of the modified PH20 polypeptide are identical to the residues in the amino acid sequence set forth in SEQ ID NO: 35.
- 4-5. (Cancelled)
6. (Original) The modified PH20 polypeptide of claim 1, wherein the hyaluronidase activity of the modified PH20 polypeptide is at least 120% of the hyaluronidase activity of the PH20 polypeptide of SEQ ID NO: 3, measured under identical conditions.
7. (Original) The modified PH20 polypeptide of claim 1 that is a soluble PH20 polypeptide.
8. (Original) The modified PH20 polypeptide of claim 1 that comprises one or more modifications of the polypeptide selected from among glycosylation, sialylation, albumination, farnesylation, carboxylation, hydroxylation, and phosphorylation.
9. (Original) The modified PH20 polypeptide of claim 8 that is glycosylated.
10. (Original) The modified PH20 polypeptide of claim 9, wherein the polypeptide is a glycoprotein that comprises an N-acetylglucosamine moiety linked to each of at least three asparagine (N) residues.
- 11-13. (Cancelled)
14. (Original) A pharmaceutical composition, comprising the modified PH20 polypeptide of claim 1.
- 15-17. (Cancelled)

18. (Original) The pharmaceutical composition of claim 16, wherein the therapeutically active agent is a small molecule drug.

19-22. (Cancelled)

23. (Withdrawn-Currently amended) A method for manufacture of the modified PH20 polypeptide of claim 1, comprising preparing a plasmid DNA containing ~~[[a]]~~ cDNA encoding the modified PH20 protein comprising an amino acid sequence, ~~wherein:~~

~~(a) at least 95% of the residues of the amino acid sequence of the encoded modified PH20 polypeptide, excluding any signal sequence, are identical to the residues an amino acid sequence selected from the group consisting of SEQ ID NOs: 3 and 32-66 when the sequence of the modified PH20 polypeptide is aligned at positions corresponding to the sequence selected from the group consisting of SEQ ID NOs: 3 and 32-66 to maximize identical residues, and wherein terminal gaps are treated as non-identical; and~~

~~(b) the amino acid sequence of the modified PH20 polypeptide comprises an amino acid modification at a position corresponding to position 324 with reference to amino acid positions set forth in SEQ ID NO: 3, and the modification at position 324 is selected from among D, N, and R; and~~

~~wherein the method comprises:~~

~~transfecting the plasmid into a host cell;~~

~~culturing the cell under conditions for expression of the cDNA as a protein; and~~

~~harvesting the protein from the culture.~~

REMARKS

Claims 1-3, 6-10, 14, 18, and 23 are pending; claims 1-10, 12 and 15-18 have been examined on the merits. Claims 1-3 and 23 are amended herein; claims 5 and 15-17 have been cancelled without disclaimer of subject matter or prejudice thereto. By this response, claim 1 is amended for clarity. Claim 23, which is withdrawn from consideration, was previously amended to depend on claim 1 and is retained for possible rejoinder upon allowance of the base claim.

As a preliminary matter, it is unclear why the Final Office Action indicates that claim 18 is withdrawn when the previous Office Action indicates that it was under examination on the merits. The Examiner provides no reasoning or discussion regarding the withdrawal of claim 18. For the purposes of expediting prosecution, Applicant assumes that the indication that claim 18 has been withdrawn was in error and assumes that claim 18 stands rejected under 35 U.S.C. § 112 (pre-AIA), second paragraph. Should these assumptions be incorrect, a new Office Action clarifying this issue is requested.

I. Rejection under 35 U.S.C. § 112 (second paragraph)

Claims 1-3, 6-10 and 14 are rejected under 35 U.S.C. § 112 (pre-AIA), second paragraph, as being indefinite. *See* Final Office Action at Section No. 6. Reconsideration of the grounds for this rejection is requested in view of the amendments herein and the following remarks.

Claim 1 and claims dependent thereon are rejected as indefinite in the recitation of “when aligned, gaps at the N-terminus and C-terminus of the aligned sequences are non-identical” recited in claim 1 because it is unclear whether the limitation “terminal gaps” refers to the “C-terminus or N-terminus or both termini of the modified PH20 polypeptide or refers to the N-and C-termini of the 5% mismatches of the amino acid sequence of SEQ ID NO: 35” (*see* Final Office Action at Section No. 6).

While Applicant disagrees with the reasoning in the Final Office Action, solely in an effort to expedite prosecution, Applicant has amended claim 1 herein to render it clear that “terminal gaps are treated as non-identical” (*see* amended claim 1 at line 6). Withdrawal of the rejection is requested in view of the amendment.

II. Rejections under 35 U.S.C. § 112 (first paragraph)

Claims 1-3, 6-10 and 14 are rejected under 35 U.S.C. § 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. *See* Final Office Action at Section No. 7. Reconsideration of the grounds for this rejection is requested in view of the following remarks.

The Rejected Claims

Independent claim 1 recites:

1. A modified PH20 polypeptide, comprising an amino acid sequence, wherein:

(a) at least 95% of the residues of the amino acid sequence of the modified PH20 polypeptide are identical to the residues in an amino acid sequence set forth in SEQ ID NO:35 when the sequence of the modified PH20 polypeptide is aligned at positions corresponding to the sequence set forth in SEQ ID NO:35 to maximize identical residues, and wherein terminal gaps are treated as non-identical;

(b) the amino acid sequence of the modified PH20 polypeptide comprises an amino acid modification at a position corresponding to position 324 with reference to amino acid positions set forth in SEQ ID NO: 3; and

(c) the modification at position 324 is a replacement selected from among D, N, and R, and

wherein the modified PH20 polypeptide exhibits increased hyaluronidase activity compared to the hyaluronidase activity of the polypeptide set forth in SEQ ID NO: 3, measured under identical conditions.

Dependent claims recite particulars of modified PH20 and compositions comprising the PH20. All claims require a replacement at the residue corresponding to E324, with reference to SEQ ID NO: 3, and encompass modified PH20 polypeptides comprising a modification at residue 324 and having at least 95% (or 96%) identical residues to SEQ ID NO: 35, including any deletions or insertions, including any gaps at the termini.

Rebuttal to Comments of the Examiner

1. In rejecting claim 1-3, 6-10 and 14, the Examiner states that “the specification fails to teach the structural and functional relationship or correlation between the claimed genus and the PH20 variants described in the specification. See Final Office Action at Section No. 7. Applicant disagrees and traverses as follows.

There is no requirement in the “Guidelines for the Examination of Patent Applications Under the 35 U.S.C. §112 (first paragraph) “Written Description” Requirement (the “Guidelines”) cited by the Examiner (see Final Office Action at p. 11) or elsewhere in case law that a structural and functional relationship is necessary to show possession of the invention. The Guidelines explain that “[t]he written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the inventor was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1559, 1568 (Fed. Cir. 1997). See also MPEP § 2163(II)(3)(a)(ii) (internal citations omitted, emphasis added).

In other words, the written description requirement for a claimed genus can be satisfied by disclosure of relevant structure. In the instant case, claim 1 recites the structure of the claimed modified PH20 polypeptide. Thus, the scope of the claims includes three of the modifications that result in active polypeptides. The specification discloses the structure of large number (around 7000) of variants of the

modified PH20 polypeptide, including those recited in claim 1, as well as details of the effects of each of those variants on properties of the PH20, as has been discussed earlier in prosecution.

Further, the claims here are not solely functionally defined as the Examiner suggests. Indeed, claim 1 is defined structurally: a PH20 polypeptide with a mutation from glutamic acid to aspartic acid, asparagine, or arginine at position 324 with 95% amino acid sequence similarity to the sequence set forth in SEQ ID NO:35. Dependent claims 2-3, 7-10 and 14-17 are also structural claims. The dependent claims directed to increased hyaluronidase activity, claims 5 and 6, add specific function to the aforementioned structure, but there is still additional supporting structure disclosed in the specification in the form of the activity data in Table 9 for all mutations that showed 20% or more of wild type hyaluronidase activity.

The specification further describes methods for creating mutated versions of PH20 polypeptides (e.g., Example 2), and hyaluronidase activity assays developed by the inventors (e.g., Example 3). The specification also shows the genus was “well explored” by the inventors with 6,753 modified PH20 polypeptides and hyaluronidase activity assays demonstrating the correlation between structure and function – hyaluronidase activity.

“Adequate written description does not require a perfect correspondence between the members of the genus and the asserted common structural feature; for a functionally defined genus like the one at issue here, we have spoken more modestly of a 'correlation between structure and function" (see *Ajinomoto v. International Trade Commission*, 932 F.3d 1342, 1358-61 (Fed. Cir. 2019) (affirming Commission's decision that genus claims of a biological invention claim "more potent promoters" were not proven invalid for an inadequate written description of the "more potent promoters" since under the circumstances, the disclosure of 4 representative examples of species in the specification, references in the specification to prior art articles, and evidence that the genus was "well explored" showed that four examples was adequate description of the claimed genus. (emphasis added))).

Providing a well-defined structural aspect to the claims, as is done here, only strengthens the support for the claimed genus. See *Ex Parte Tibor Keler*, Appeal No. 2019-006094, 2020 WL 3265323, at 6 (P.T.A.B. 2020) (holding that “claim 10 recites a sufficiently precise definition and structural formula that would allow the ordinary artisan to identify anti-CD27 antibodies that fall within the scope of claim 10 from those antibodies that do not fall within the scope of claim 10” and that “[c]laim 10 establishes this boundary both by providing specific amino acid sequences of SEQ ID Nos: 37 and 43 and by requiring other antibodies to retain 95% identity with those amino acid sequences” (emphasis added); *Ex parte H. Phillip Koeffler*, Appeal No. 2016-004476, 2018 BL 59276 at *3 (P.T.A.B. 2018) (holding that “[t]he Specification contains examples disclosing use of the polypeptides to create an expression vector that encodes the klotho polypeptide, along with methods to express and subsequently isolate the soluble klotho protein. See, e.g., pages 23-26 of Specification. Methods of using the proteins to perform the claimed method of treatment are disclosed in subsequent examples on pages 26-33 of the Specification.

Given the required homology of over 80% to the claimed (disclosed) sequences, we find that the detailed information in the Specification would have reasonably conveyed to the skilled artisan that the inventor possessed the claimed subject matter as of the filing date” (emphasis added); Ex Parte German Spangenberg, Appeal No. 2015-006408, 2017 WL 1330248, at 3 (P.T.A.B. 2017) (holding that “one of ordinary skill in the art would recognize that the description of cis-acting elements in Tables 1 and 4, together with the 98% sequence identity requirement, fulfill an adequate written description of the claimed genus of promoters because they constitute a description of “structural features commonly possessed by members of the genus that distinguish them from others” (emphasis added); Ex Parte Jamie Campbell, Appeal No. 2021-000865, 2021 WL 3124601, at 8 (P.T.A.B. 2021) (holding that “[t]he Examiner’s findings to the contrary notwithstanding, the claimed antibodies are not exclusively claimed functionally, but are also claimed structurally, i.e., by requiring that the light and heavy chains have a structure corresponding to 90-95% of the recited SEQ ID NO: . . . [w]e find that a comparison of the SEQ ID NO: of the 2D10 and 10A07 antibody CDRs provides guidance to a person of ordinary skill in the art as to where in the amino acid sequence changes could be made without significantly impairing antigen-binding functionality. Furthermore, Appellant’s Specification provides additional guidance for a person of ordinary skill to understand the amino acid loci that can be substituted without impairing functionality”).

In the instant case, the specification discloses far more than representative examples deemed sufficient by the courts and the Board. Moreover, like in many of these cases, the Specification here also provides guidance to a person of ordinary skill in the art to understand how to determine which mutants are active/inactive or increase/decrease activity. A person of ordinary skill in the art can use the hyaluronidase activity assays developed by Applicants and described in the specification to confirm modified PH20 polypeptides have increased hyaluronidase activity as claimed in the dependent claims.

2. The Examiner contends that Applicant “admits” that single point mutations or mismatches at the N-terminus and C-terminus result in inactive mutants and it is not known whether 5% mismatches would result in an inactive mutant. *See* Final Office Action at pages 7-8. Applicant disagrees and traverses as follows.

First, this argument only applies to claims 5 and 6, which claim increased hyaluronidase activity. Contrary to the Examiner’s arguments, this “admission” guides one of ordinary skill in the art, and the claim is allowed to encompass inoperative embodiments. The guidance provided by these inactive mutants applies to the Examiner’s other points as well. The disclosure relating to which point mutations are inactive or decrease activity in fact reduces unpredictability for a person of ordinary skill in the art far beyond that usually provided in other cases. Identification of the inactive or reduced activity mutants are part of the teaching of the specification supporting possession of the invention.

Furthermore, with respect to the residue corresponding to 324 of SEQ ID NO: 3, the specification discloses the effect of 15 amino acid replacements (*see* Table 8): E324A, C, D, F, G, H, L, M, N, P, R, S, V, W,

Y and shows that polypeptides with the replacement A, D, H, M, N, R, and S are active (see Table 9). Thus, the scope of the claims includes three of the modifications that result in active polypeptides. This includes teaching all of the mutations in the polypeptide that inactivate the polypeptide (see Table 8), and the effects of thousands of mutations that have no effect on or increase activity, thereby providing a structure/function map. Unlike the examples of mutations in other unrelated polypeptides (*i.e.*, FGF) mentioned in the Final Office Action, the instant application demonstrates all of the mutations in the catalytically active portion of the polypeptide that alter activity and/or a property. Applicant had possession of modifications that result in active and result in inactive polypeptides.

As to the Examiner's argument regarding inactive mutants, the disclosure includes inactive mutants as part of the written description (see Final Office Action at page 7), which was discovered as a result of extensive testing and actual examples, which is also explicitly disclosed in the written description. Further, a person of ordinary skill in the art can use the hyaluronidase activity assays described in the specification to confirm whether modified PH20 polypeptides have increased hyaluronidase activity and determine the inoperative embodiments.

Moreover, it has been consistently held that claims are permitted to encompass inoperative embodiments:

To the extent that there would be some unpredictability in any particular altered antibody sequence, it is almost always possible to so construe a claim as to have it read on inoperative embodiments. . . ., but the alternative of requiring an applicant to be so specific in his claims "as to exclude materials known to be inoperative and [which] even those not skilled in the art would not try" would result in claims which would fail to comply with 35 U.S.C. § 112, second paragraph, because they would be so detailed as to obscure, rather than to particularly point out and distinctly claim, the invention. *In re Smythe*, 480 F.2d 1376, 1385 (CCPA 1973). In this case, while claim 10 excluding inoperative embodiments might not be indefinite, it would be narrower than the scope supported by the disclosure in the Specification. Thus, Appellant has demonstrated descriptive support for the embodiments encompassed by claim 10.

Ex Parte Tibor Keler, Appeal No. 2019-006094, 2020 WL 3265323, at 7 (P.T.A.B. 2020).

Here, the specification includes extensive disclosure of the structure of active and inactive mutants. Further, the description teaches a person of ordinary skill in the art how to determine whether a particular mutant is active or inactive. As a result, one of ordinary skill in the art would readily understand that the inventor was in possession of the claimed genus. Moreover, in the instant case, requiring Applicant to be so specific as to exclude every inactive mutant would render the claims substantially narrower than what Applicant is entitled to, in view of the disclosure of the specification.

As discussed earlier, the inventors disclosed inactive mutants as part of their written description, which was discovered as a result of their extensive testing and actual examples. In other cases, such as *Ex Parte Keler*, inoperative embodiments were encompassed but not described and claims were still found to have written description. Here, the disclosure in the specification is further evidence

of the inventors' possession of the claimed subject matter. It cannot be that claims can encompass inoperative embodiments while still having written description as a general matter, but that if one identifies them via testing and discloses them in the specification, the claims lack it.

Excluding inoperative embodiments would be narrower than the scope supported by the express disclosures in the specification. A person of ordinary skill in the art can use the hyaluronidase activity assays developed by Applicants and described in the specification to confirm whether modified PH20 polypeptides have increased hyaluronidase activity, and readily determine the inoperative embodiments.

3. The Examiner argues that the specification fails to provide what other common structures and sequences and features for the claimed variants are and what 5% of amino acids and/or gaps can or cannot be changed to reach increased activity. *See* Final Office Action at page 8. Applicant disagrees and traverses as follows.

As has been discussed in detail earlier, there is no requirement that the written description requirement be met by providing common structures, sequences and features for claimed variants in the specification. Moreover, Applicant further cites *Ex Parte Philippe Duchateau*, Appeal No. 2021-000639, 2021 WL 2495261, 14, 17 (P.T.A.B. 2021) (holding that “a person of ordinary skill in this highly-refined art would have well understood what was meant by the [contended] claim terms” based on the teachings in the “specification, together with the teachings of the prior art at the time of the invention”) to support this premise.

4. The Examiner cites to *Vas-Cath* to argue that the specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed” (*see* Final Office Action at page 10). The Examiner contends that the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of other structurally and functionally undefined variants (as claimed), and that “[a]dequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The compound itself is required” (citing *Fiers v. Revel*). The Examiner cites several other cases to contend that “one cannot describe what one has not conceived” (*Id.*). Applicant disagrees and traverses as follows.

Complete structures of every embodiment are not required, and reduction to practice of every one of the individual embodiments need not be complete. *See e.g. Ex Parte Olga Bandman*, Appeal No. 2004-2319, 2005 WL 4773698, at 2-3 (B.P.A.I. 2005) (holding that “the written description requirement of 35 U.S.C. § 112, first paragraph, does not require a description of the complete structure of every species within a chemical genus (citing *Utter v. Hiraga*, 845 F.2d 993, 998, (Fed. Cir. 1988)).

The courts have also consistently held that “the written description requirement can be met by showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, functional

characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of characteristics” (see *Enzo Biochem v. Gen-Probe*, 296 F.3d 1316, 1324 (citations omitted)). Indeed, MPEP § 2163(II)(3)(a)(ii) adopts its guidance from *Enzo Biochem*.

In *Ex parte Bandman*, the specification described the complete structure of the polynucleotide of SEQ ID NO: 2, and the genus was limited to a polynucleotide comprising a naturally occurring polynucleotide sequence at least 95% identical to the polynucleotide sequence of SEQ ID NO: 2. In addition, the complete structure of the polypeptide of SEQ ID NO: 1 was described, and the genus limited to polypeptides comprising a naturally occurring amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 1.

Here, as in *Ex parte Bandman*, the Specification describes the complete structure of the PH20 polynucleotide of SEQ ID NO: 35, and the claimed genus is limited to polynucleotides comprising at least 95% identical to the polynucleotide of SEQ ID NO: 35. Moreover, like in *Ex parte Bandman*, the Examiner here fails to adequately explain and/or provide evidence to support the assertion that the specification provides no disclosure of any particular structure to function/activity relationship in the single disclosed species. Indeed, as discussed extensively herein, the present application not only discloses a list of a large number of active/inactive variants and mutations that increase/decrease activity, it also describes, with experimental data, examples of how activity is measured to arrive at the list of variants. The present application also describes a method for arriving at these variants.

The Board has also held that “[i]t is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention” (see *Ex Parte Abad*, Appeal No. 2007-4356, 2008 WL 904457 (B.P.A.I. 2008) (citing *Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005)). In *Ex parte Abad*, the Board found that “significant information to characterize the generic invention, ranging from the capacity to generate, identify and screen members of the genus, to large numbers of different mutations which characterize structure/function relationships, to both information on the primary, secondary and tertiary physical structure of the δ e-endotoxins” *Id.* at 12.

Here, as discussed extensively above and during prosecution, the specification discloses a large number of active/inactive mutations as well as mutations which increase/decrease activity so as to characterize the structure/function relationships. The specification also discloses methods of identifying and screening mutants for activity/inactivity as well as for increase/decrease in activity.

Applicant, therefore, submits that the specification provides sufficient information for one of ordinary skill in the art to understand that the Applicant had possession of the claimed genus. This position is supported by ample case law as discussed in detail herein. For at least these reasons, withdrawal of the rejection under 35 U.S.C. § 112 (first paragraph) is requested.

Conclusion

In view of the foregoing, Applicant awaits a favorable action on the merits. Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact the undersigned representative to expedite prosecution.

Date: June 18, 2024

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18/340,786	06/23/2023	Ge WEI	63995-01-5105-US-17	6432
28977 7590 07/12/2024 Morgan, Lewis & Bockius LLP (PH) 2222 Market Street Philadelphia, PA 19103			EXAMINER WANG, CHANG YU	
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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):

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Advisory Action Before the Filing of an Appeal Brief	Application No. 18/340,786	Applicant(s) WEI et al.	
	Examiner CHANG-YU WANG	Art Unit 1649	AIA (FITF) Status No

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

THE REPLY FILED 18 June 2024 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

NO NOTICE OF APPEAL FILED

1. ☒ The reply was filed after a final rejection. No Notice of Appeal has been filed. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114 if this is a utility or plant application. Note that RCEs are not permitted in design applications. The reply must be filed within one of the following time periods:

a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.

b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action; or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

c) ☐ A prior Advisory Action was mailed more than 3 months after the mailing date of the final rejection in response to a first after-final reply filed within 2 months of the mailing date of the final rejection. The current period for reply expires _____ months from the mailing date of the prior Advisory Action or SIX MONTHS from the mailing date of the final rejection, whichever is earlier.

Examiner Note: If box 1 is checked, check either box (a), (b) or (c). ONLY CHECK BOX (b) WHEN THIS ADVISORY ACTION IS THE FIRST RESPONSE TO APPLICANTS FIRST AFTER-FINAL REPLY WHICH WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. ONLY CHECK BOX (c) IN THE LIMITED SITUATION SET FORTH UNDER BOX (c). See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) or (c) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendments filed after a final rejection, but prior to the date of filing a brief, will not be entered because

a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);

b) ☐ They raise the issue of new matter (see NOTE below);

c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: See Continuation Sheet (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): (a) ☒ will not be entered; or (b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____

9. ☐ The affidavit or other evidence filed after final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

10. ☐ The affidavit or other evidence filed after the date of filing the Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

11. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

12. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See Continuation Sheet.

13. ☐ Note the attached Information *Disclosure Statement(s)*. (PTO/SB/08) Paper No(s). _____

14. ☐ Other: _____

STATUS OF CLAIMS

15. The status of the claim(s) is (or will be) as follows:
 Claim(s) allowed: _____
 Claim(s) objected to: _____
 Claim(s) rejected: 1-3, 5-10 and 14-17.
 Claim(s) withdrawn from consideration: 18 and 23.

/CHANG-YU WANG/ Primary Examiner, Art Unit 1649	
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Continuation of 3. NOTE:

The claims, if amended as proposed, would not avoid any of the rejections set forth in the last Office action, and thus the amendment would not place the case in condition for allowance or in better condition for appeal. The claims as amended present new issues requiring further consideration or search, for example, "...identical to the residues in an amino acid set forth in SEQ ID NO:35.... wherein the modified PH20 polypeptide exhibits increased hyaluronidase active.....under identical conditions" in claim 1 or "the modified PH20 polypeptide of claim 2, wherein at least 96%. Set forth in the amino acid sequence set forth in SEQ ID NO:35" in claim 3. The claims if amended as proposed, would change the scope of the invention, and the claims encompass new limitations, which would raise potential new grounds of rejection, so further search and/or consideration is required. Thus, the amendment does not simplify the issues of the rejections and further does not place the application in better condition for appeal or allowance. Accordingly, the proposed amendment will not be entered.

Continuation of REQUEST FOR RECONSIDERATION/OTHER 12. The request for reconsideration has been considered but does NOT place the application in condition for allowance because: Applicant's arguments have been fully considered but they are insufficient to overcome the rejection under 112(a), lack of written description requirement and the rejection under 112(b). The rejections are maintained for the reasons made of record in final office action dated 04/26/2024 as directed to the previously presented claim limitations. Applicant's amendment filed on 06/18/2024 has not been entered. Thus, the arguments directed to claim amendments not entered are currently moot.

<i>Examiner-Initiated Interview Summary</i>	Application No. 18/340,786	Applicant(s) WEI et al.		
	Examiner CHANG-YU WANG	Art Unit 1649	AIA (First Inventor to File) Status No	Page 1 of 1

All Participants (applicant, applicants representative, PTO personnel)	Title	Type
CHANG-YU WANG	Primary Examiner	Telephonic
Robert Smyth	Attorney of Record	

Date of Interview: 02 July 2024

Issues Discussed:

Proposed Amendment(s)

07/02/2024, Discussed possible claim amendment to place the application in condition for allowance (see the attached draft of proposed amendment).
Applicant provides no further response.

☒ Attachment

/CHANG-YU WANG/ Primary Examiner, Art Unit 1649	
<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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Ge Wei <i>et al.</i>	)	
	)	Confirmation No. 6432
U.S. Application No. 18/340,786	)	
	)	Group Art Unit: 1649
Filing Date: 6/23/2023	)	
	)	Examiner: Chang Yu Wang
For: PH20 Polypeptide Variants, Formulations	)	
and Uses Thereof	)	

AMENDMENT UNDER 37 C.F.R. § 1.111

In response to the Final Office Action dated 04/26/2024, having a three-month shortened statutory period for response set to expire 07/26/2024, Applicant requests entry of the following amendments and remarks in the above patent application. To the extent necessary, a petition for an extension of time under 37 C.F.R. § 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 50-0310 and please credit any excess fees to such deposit account.

The Listing of claims begins on page 2.

Remarks begin on page 4.

The Conclusion is on page 11.



UNITED STATES PATENT AND TRADEMARK OFFICE

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Fax Cover Sheet

Date: 07/03/2024

To: Robert Smyth, Ph.D.	From: CHANG-YU WANG
Application/Control Number: 18/340,786	Art Unit: 1649
Fax No.: 215 963 5001	Phone No.: (571)272-4521
Voice No.: 215 963 5000	Return Fax No.:
Re: Proposed amendment	CC:
☒ Urgent ☒ For Review ☒ For Comment ☒ For Reply ☐ Per Your Request	

Comments:

Number of pages 4 including this page

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Notice of Pre-AIA or AIA Status

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

Status of Application/Amendment/Claims

2. Claims 1 and 23 were amended in the response filed June 18, 2024. Claims 4-5, 11-13, 15-17 and 19-22 are canceled. Claims 1-3, 6-10, 14, 18 and 23 are currently pending in this application and the subject matter of the instant Office action.

EXAMINER'S AMENDMENT

3. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Robert Smyth, Ph.D. on July 2, 2024.

The application has been amended as follows:

In the claims:

Please cancel claim 18 without prejudice.

1. (Currently amended) A modified PH20 polypeptide comprising an amino acid sequence, wherein:(a) at least 95% of the residues of the amino acid sequence of the

modified PH20 polypeptide are identical to the residues in ~~an~~ the amino acid sequence ~~set forth in of~~ SEQ ID NO: 35 when the sequence of the modified PH20 polypeptide is aligned at positions corresponding to the sequence set forth in the amino acid sequence of SEQ ID NO: 35 to maximize identical residues, and wherein terminal gaps are treated as non-identical; (b) the amino acid sequence of the modified PH20 polypeptide comprises an amino acid modification at a position corresponding to position 324 with reference to amino acid positions set forth in the amino acid sequence of SEQ ID NO: 3; and (c) the modification at position 324 is a replacement selected from among D, N and R, and wherein the modified PH20 polypeptide exhibits increased hyaluronidase activity compared to the hyaluronidase activity of the polypeptide set forth in the amino acid sequence of SEQ ID NO: 3, measured under identical conditions.

2. (Currently amended) The modified PH20 polypeptide of claim 1, wherein the amino acid modification ~~is~~ at a position corresponding to position 324 with reference to amino acid positions set forth in the amino acid sequence of SEQ ID NO: 3 is D.

3. (Currently amended) The modified PH20 polypeptide of claim 2, wherein at least 96% of the residues of the amino acid sequence of the modified PH20 polypeptide are identical to the residues in the amino acid sequence ~~set forth in of~~ SEQ ID NO:35, and comprises D at a position corresponding to position 324 in the amino acid sequence of SEQ ID NO: 3.

7. (Currently amended) The modified PH20 polypeptide of claim 1 ~~that~~, wherein
the modified PH20 polypeptide is a soluble PH20 polypeptide.

8. (Currently amended) The modified PH20 polypeptide of claim 1, further
comprising ~~that comprises~~ one or more modifications of on the polypeptide selected
from among glycosylation, sialylation, albumination, farnesylation, carboxylation,
hydroxylation, and phosphorylation.

9. (Currently amended) The modified PH20 polypeptide of claim 8 ~~that~~, wherein
the modified PH20 polypeptide is glycosylated.

10. (Currently amended) The modified PH20 polypeptide of claim 9, wherein the
modified PH20 polypeptide is a glycoprotein that comprises an N-acetylglucosamine
moiety linked to each of at least three asparagine (N) residues.

23. (Currently amended) A method for manufacture of the modified PH20
polypeptide of claim 1, comprising preparing a plasmid DNA containing cDNA encoding
the modified PH20 polypeptide ~~protein comprising an amino acid sequence~~, wherein the
~~method comprises:~~ transfecting the plasmid into an isolated host cell; culturing the cell
under conditions for expression of the modified PH20 polypeptide cDNA as a protein;
and harvesting the ~~protein~~ modified PH20 polypeptide from the culture.

Rejoinder

4. Claims 1-3, 6-10 and 14 are directed to an allowable product. Pursuant to the procedures set forth in MPEP § 821.04(B), claim 23, directed to the process of making or using an allowable product, previously withdrawn from consideration as a result of a restriction requirement, is hereby rejoined and fully examined for patentability under 37 CFR 1.104.

Because all claims previously withdrawn from consideration under 37 CFR 1.142 have been rejoined, **the restriction requirement as set forth in the Office action mailed on 10/20/2023 is hereby withdrawn.** In view of the withdrawal of the restriction requirement as to the rejoined inventions, applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Once the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

5. Claims 1-3, 6-10, 14 and 23 are allowed. Claims 6-10, 14 and 23 were renumbered as claims 4-10 respectively.

6. The title was changed to "PH20 POLYPEPTIDE VARIANTS WITH A MODIFICATION AT POSITION 324 OF THE PH20 POLYPEPTIDE AND A METHOD OF MAKING THEREOF".

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.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875				Application or Docket Number 18/340,786		Filing Date 06/23/2023		☐ 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 \$480 =							
☐ 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	07/25/2024		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR		PRESENT EXTRA		RATE (\$)		ADDITIONAL FEE (\$)		
	Total (37 CFR 1.16(i))		* 10		Minus ** 23		= 0		x \$100 =		0		
	Independent (37 CFR 1.16(h))		* 1		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.										LIE			
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".										/CAROLYN E THOMAS/			
*** 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.**

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Page 1 of 2
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
18/340,786

RECEIPT DATE / TIME
07/25/2024 06:49:07 PM Z ET

ATTORNEY DOCKET #
63995-01-5105-US-17

Title of Invention

PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 6432

FILED BY Kalpesh Upadhye

PATENT CENTER # 66527189

FILING DATE 06/23/2023

CUSTOMER # 28977

FIRST NAMED
INVENTOR Ge WEI

CORRESPONDENCE
ADDRESS -

AUTHORIZED BY -

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
063995-5105- 17_supp_RIOA.pdf	12	Supplemental Response or Supplemental Amendment	287 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
063995-5105- 17_supp_RIOA.pdf	614051E6786F139EE1A370E3B783180DBE319FEDE1A87A78B A17CE29BA47B0F6D28EE355680A410FFDCA49212B38058BB7 4A5077B4076333BC6D66965DFA1C27

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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 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

In re Application of Ge Wei <i>et al.</i>	)	
	)	Confirmation No. 6432
U.S. Application No. 18/340,786	)	
	)	Group Art Unit: 1649
Filing Date: 6/3/2023	)	
	)	Examiner: Chung Yu Wang
For: PH20 Polypeptide Variants, Formulations	)	
and Uses Thereof	)	

AMENDMENT UNDER 37 C.F.R. § 1.116

In response to the Final Office Action dated 04/26/2024, and the Advisory Action dated July 12, 2024, having a three-month shortened statutory period for response set to expire 07/26/2024, Applicant requests entry of the following amendments and remarks in the above patent application. To the extent necessary, a petition for an extension of time under 37 C.F.R. § 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 50-0310 and please credit any excess fees to such deposit account.

The Listing of claims begins on page 2.

Remarks begin on page 4.

The Conclusion is on page 11.

LISTING OF THE CLAIMS

This listing of the claims will replace all previous versions.

1. (Currently Amended) A modified PH20 polypeptide comprising an amino acid sequence, wherein:
 - (a) at least 95% of the residues of the amino acid sequence of the modified PH20 polypeptide are identical to the residues in ~~[[an]] the amino acid sequence set forth in~~ of SEQ ID NO: 35 when the sequence of the modified PH20 polypeptide is aligned at positions corresponding to the sequence set forth in the amino acid sequence of SEQ ID NO: 35 to maximize identical residues, and wherein, ~~when aligned, gaps at the N-terminus and C-terminus of the aligned sequences are~~ terminal gaps are treated as non-identical; and
 - (b) the amino acid sequence of the modified PH20 polypeptide comprises an amino acid modification at a position corresponding to position 324 with reference to amino acid positions set forth in the amino acid sequence of SEQ ID NO: 3; and
 - (c) the modification at position 324 is a replacement selected from among D, N, and R, and wherein the modified PH20 polypeptide exhibits increased hyaluronidase activity compared to the hyaluronidase activity of the polypeptide set forth in the amino acid sequence of SEQ ID NO: 3, measured under identical conditions.
2. (Original) The modified PH20 polypeptide of claim 1, wherein the amino acid modification is at a position corresponding to position 324 with reference to amino acid positions ~~set forth in~~ the amino acid sequence of SEQ ID NO: 3 is D.
3. (Previously presented) The modified PH20 polypeptide of claim 2, wherein at least 96% of the residues of the amino acid sequence of the modified PH20 polypeptide are identical to the residues in the amino acid sequence ~~set forth in~~ of SEQ ID NO: 35, and comprises D at a position corresponding to position 324 in the amino acid sequence of SEQ ID NO: 3.
- 4-5. (Cancelled)
6. (Original) The modified PH20 polypeptide of claim 1, wherein the hyaluronidase activity of the modified PH20 polypeptide is at least 120% of the hyaluronidase activity of the PH20 polypeptide of SEQ ID NO: 3, measured under identical conditions.
7. (Original) The modified PH20 polypeptide of claim 1, wherein the modified PH20 polypeptide ~~[[that]]~~ is ~~[[a]]~~ soluble PH20 polypeptide.
8. (Original) The modified PH20 polypeptide of claim 1, further comprising ~~that comprises~~ one or more modifications ~~[[of]]~~ on the polypeptide selected from among glycosylation, sialylation, albumination, farnesylation, carboxylation, hydroxylation, and phosphorylation.
9. (Original) The modified PH20 polypeptide of claim 8, wherein the modified polypeptide ~~[[that]]~~ is glycosylated.

10. (Original) The modified PH20 polypeptide of claim 9, wherein the modified PH20 polypeptide is a glycoprotein that comprises an N-acetylglucosamine moiety linked to each of at least three asparagine (N) residues.

11-13. (Cancelled)

14. (Original) A pharmaceutical composition, comprising the modified PH20 polypeptide of claim 1.

15-22. (Cancelled)

23. (Withdrawn-Currently amended) A method for manufacture of the modified PH20 polypeptide of claim 1, comprising:

preparing a plasmid DNA containing ~~[[a]]~~ cDNA encoding the modified PH20 polypeptide; ~~protein comprising an amino acid sequence, wherein:~~

~~(a) at least 95% of the residues of the amino acid sequence of the encoded modified PH20 polypeptide, excluding any signal sequence, are identical to the residues an amino acid sequence selected from the group consisting of SEQ ID NOs: 3 and 32-66 when the sequence of the modified PH20 polypeptide is aligned at positions corresponding to the sequence selected from the group consisting of SEQ ID NOs: 3 and 32-66 to maximize identical residues, and wherein terminal gaps are treated as non-identical; and~~

~~(b) the amino acid sequence of the modified PH20 polypeptide comprises an amino acid modification at a position corresponding to position 324 with reference to amino acid positions set forth in SEQ ID NO: 3, and the modification at position 324 is selected from among D, N, and R; and~~

~~wherein the method comprises:~~

~~transfecting the plasmid into ~~[[a]]~~ an isolated host cell;~~

~~culturing the cell under conditions for expression of the ~~cDNA as a protein~~ modified PH20 polypeptide; and~~

~~harvesting the ~~protein~~ modified PH20 polypeptide from the culture.~~

REMARKS

Claims 1-3, 6-10, 14, 18, and 23 are pending; claims 1-10, 12 and 15-18 have been examined on the merits. Claims 1-3 and 23 are amended herein; claims 5 and 15-17 have been cancelled without disclaimer of subject matter or prejudice thereto. By this response, claim 1 is amended for clarity. Claim 23, which is withdrawn from consideration, was previously amended to depend on claim 1 and is retained for possible rejoinder upon allowance of the base claim.

As a preliminary matter, it is unclear why the Final Office Action indicates that claim 18 is withdrawn when the previous Office Action indicates that it was under examination on the merits. The Examiner provides no reasoning or discussion regarding the withdrawal of claim 18. For the purposes of expediting prosecution, Applicant assumes that the indication that claim 18 has been withdrawn was in error and assumes that claim 18 stands rejected under 35 U.S.C. § 112 (pre-AIA), second paragraph. Should these assumptions be incorrect, a new Office Action clarifying this issue is requested.

I. Advisory Action

The Examiner issued an Advisory Action indicating that the claim amendments and remarks included in paper filed on June 18, 2024, in response to the final Office Action dated April 26, 2024, will not be entered because the amendments do not place the claims in condition for allowance.

In addition, the Examiner proposed claim amendments to address issues outstanding following the claim amendments in the June 18, 2024, paper. Because the claims presented herein bring the application in condition for allowance, entry of the foregoing amendments and following remarks is respectfully requested.

II. Examiner Interview

Applicant and the undersigned representatives thank the Examiner for her thoughtful consideration of claims and the proposed claim amendments discussed during the telephonic interview held on July 24, 2024.

During the interview, the Examiner indicated that the amendments presented herein (and proposed in the Advisory Action, would bring the claims in condition for allowance. The Examiner further confirmed that a request for continued examination would not be necessary.

III. Rejection under 35 U.S.C. § 112 (second paragraph)

Claims 1-3, 6-10 and 14 are rejected under 35 U.S.C. § 112 (pre-AIA), second paragraph, as being indefinite. *See* Final Office Action at Section No. 6. Reconsideration of the grounds for this rejection is requested in view of the amendments herein and the following remarks.

Claim 1 and claims dependent thereon are rejected as indefinite in the recitation of “when aligned, gaps at the N-terminus and C-terminus of the aligned sequences are non-identical” recited in claim 1 because it is unclear whether the limitation “terminal gaps” refers to the “C-terminus or N-terminus or both termini of the modified PH20 polypeptide or refers to the N-and C-termini of the 5% mismatches of the amino acid sequence of SEQ ID NO: 35” (see Final Office Action at Section No. 6).

While Applicant disagrees with the reasoning in the Final Office Action, solely in an effort to expedite prosecution, Applicant has amended claim 1 herein to render it clear that “terminal gaps are treated as non-identical” (see amended claim 1 at line 6). Withdrawal of the rejection is requested in view of the amendment.

IV. Rejections under 35 U.S.C. § 112 (first paragraph)

Claims 1-3, 6-10 and 14 are rejected under 35 U.S.C. § 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. See Final Office Action at Section No. 7. Reconsideration of the grounds for this rejection is requested in view of the following remarks.

The Rejected Claims

Independent claim 1 recites:

1. A modified PH20 polypeptide, comprising an amino acid sequence, wherein:

(a) at least 95% of the residues of the amino acid sequence of the modified PH20 polypeptide are identical to the residues in an amino acid sequence set forth in SEQ ID NO:35 when the sequence of the modified PH20 polypeptide is aligned at positions corresponding to the sequence set forth in SEQ ID NO:35 to maximize identical residues, and wherein terminal gaps are treated as non-identical;

(b) the amino acid sequence of the modified PH20 polypeptide comprises an amino acid modification at a position corresponding to position 324 with reference to amino acid positions set forth in SEQ ID NO: 3; and

(c) the modification at position 324 is a replacement selected from among D, N, and R, and

wherein the modified PH20 polypeptide exhibits increased hyaluronidase activity compared to the hyaluronidase activity of the polypeptide set forth in SEQ ID NO: 3, measured under identical conditions.

Dependent claims recite particulars of modified PH20 and compositions comprising the PH20. All claims require a replacement at the residue corresponding to E324, with reference to SEQ ID NO: 3, and encompass modified PH20 polypeptides comprising a modification at residue 324 and having at least 95% (or 96%) identical residues to SEQ ID NO: 35, including any deletions or insertions, including any gaps at the termini.

Rebuttal to Comments of the Examiner

1. In rejecting claim 1-3, 6-10 and 14, the Examiner states that “the specification fails to teach the structural and functional relationship or correlation between the claimed genus and the PH20 variants

described in the specification. See Final Office Action at Section No. 7. Applicant disagrees and traverses as follows.

There is no requirement in the “Guidelines for the Examination of Patent Applications Under the 35 U.S.C. §112 (first paragraph) “Written Description” Requirement (the “Guidelines”) cited by the Examiner (see Final Office Action at p. 11) or elsewhere in case law that a structural and functional relationship is necessary to show possession of the invention. The Guidelines explain that “[t]he written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the inventor was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1559, 1568 (Fed. Cir. 1997). See also MPEP § 2163(II)(3)(a)(ii) (internal citations omitted, emphasis added).

In other words, the written description requirement for a claimed genus can be satisfied by disclosure of relevant structure. In the instant case, claim 1 recites the structure of the claimed modified PH20 polypeptide. Thus, the scope of the claims includes three of the modifications that result in active polypeptides. The specification discloses the structure of large number (around 7000) of variants of the modified PH20 polypeptide, including those recited in claim 1, as well as details of the effects of each of those variants on properties of the PH20, as has been discussed earlier in prosecution.

Further, the claims here are not solely functionally defined as the Examiner suggests. Indeed, claim 1 is defined structurally: a PH20 polypeptide with a mutation from glutamic acid to aspartic acid, asparagine, or arginine at position 324 with 95% amino acid sequence similarity to the sequence set forth in SEQ ID NO:35. Dependent claims 2-3, 7-10 and 14-17 are also structural claims. The dependent claims directed to increased hyaluronidase activity, claims 5 and 6, add specific function to the aforementioned structure, but there is still additional supporting structure disclosed in the specification in the form of the activity data in Table 9 for all mutations that showed 20% or more of wild type hyaluronidase activity.

The specification further describes methods for creating mutated versions of PH20 polypeptides (e.g., Example 2), and hyaluronidase activity assays developed by the inventors (e.g., Example 3). The specification also shows the genus was “well explored” by the inventors with 6,753 modified PH20 polypeptides and hyaluronidase activity assays demonstrating the correlation between structure and function – hyaluronidase activity.

“Adequate written description does not require a perfect correspondence between the members of the genus and the asserted common structural feature; for a functionally defined genus like the one at issue here, we have spoken more modestly of a ‘correlation between structure and function’ (see *Ajinomoto v. International Trade Commission*, 932 F.3d 1342, 1358-61 (Fed. Cir. 2019) (affirming

Commission's decision that genus claims of a biological invention claim "more potent promoters" were not proven invalid for an inadequate written description of the "more potent promoters" since under the circumstances, the disclosure of 4 representative examples of species in the specification, references in the specification to prior art articles, and evidence that the genus was "well explored" showed that four examples was adequate description of the claimed genus. (emphasis added))).

Providing a well-defined structural aspect to the claims, as is done here, only strengthens the support for the claimed genus. See *Ex Parte Tibor Keler*, Appeal No. 2019-006094, 2020 WL 3265323, at 6 (P.T.A.B. 2020) (holding that "claim 10 recites a sufficiently precise definition and structural formula that would allow the ordinary artisan to identify anti-CD27 antibodies that fall within the scope of claim 10 from those antibodies that do not fall within the scope of claim 10" and that "[c]laim 10 establishes this boundary both by providing specific amino acid sequences of SEQ ID Nos: 37 and 43 and by requiring other antibodies to retain 95% identity with those amino acid sequences" (emphasis added); *Ex parte H. Phillip Koeffler*, Appeal No. 2016-004476, 2018 BL 59276 at *3 (P.T.A.B. 2018) (holding that "[t]he Specification contains examples disclosing use of the polypeptides to create an expression vector that encodes the klotho polypeptide, along with methods to express and subsequently isolate the soluble klotho protein. See, e.g., pages 23-26 of Specification. Methods of using the proteins to perform the claimed method of treatment are disclosed in subsequent examples on pages 26-33 of the Specification. Given the required homology of over 80% to the claimed (disclosed) sequences, we find that the detailed information in the Specification would have reasonably conveyed to the skilled artisan that the inventor possessed the claimed subject matter as of the filing date" (emphasis added); *Ex Parte German Spangenberg*, Appeal No. 2015-006408, 2017 WL 1330248, at 3 (P.T.A.B. 2017) (holding that "one of ordinary skill in the art would recognize that the description of cis-acting elements in Tables 1 and 4, together with the 98% sequence identity requirement, fulfill an adequate written description of the claimed genus of promoters because they constitute a description of "structural features commonly possessed by members of the genus that distinguish them from others" (emphasis added); *Ex Parte Jamie Campbell*, Appeal No. 2021-000865, 2021 WL 3124601, at 8 (P.T.A.B. 2021) (holding that "[t]he Examiner's findings to the contrary notwithstanding, the claimed antibodies are not exclusively claimed functionally, but are also claimed structurally, i.e., by requiring that the light and heavy chains have a structure corresponding to 90-95% of the recited SEQ ID NO: . . . [w]e find that a comparison of the SEQ ID NO: of the 2D10 and 10A07 antibody CDRs provides guidance to a person of ordinary skill in the art as to where in the amino acid sequence changes could be made without significantly impairing antigen-binding functionality. Furthermore, Appellant's Specification provides additional guidance for a person of ordinary skill to understand the amino acid loci that can be substituted without impairing functionality").

In the instant case, the specification discloses far more than representative examples deemed sufficient by the courts and the Board. Moreover, like in many of these cases, the Specification here also

provides guidance to a person of ordinary skill in the art to understand how to determine which mutants are active/inactive or increase/decrease activity. A person of ordinary skill in the art can use the hyaluronidase activity assays developed by Applicants and described in the specification to confirm modified PH20 polypeptides have increased hyaluronidase activity as claimed in the dependent claims.

2. The Examiner contends that Applicant “admits” that single point mutations or mismatches at the N-terminus and C-terminus result in inactive mutants and it is not known whether 5% mismatches would result in an inactive mutant. See Final Office Action at pages 7-8. Applicant disagrees and traverses as follows.

First, this argument only applies to claims 5 and 6, which claim increased hyaluronidase activity. Contrary to the Examiner’s arguments, this “admission” guides one of ordinary skill in the art, and the claim is allowed to encompass inoperative embodiments. The guidance provided by these inactive mutants applies to the Examiner’s other points as well. The disclosure relating to which point mutations are inactive or decrease activity in fact reduces unpredictability for a person of ordinary skill in the art far beyond that usually provided in other cases. Identification of the inactive or reduced activity mutants are part of the teaching of the specification supporting possession of the invention.

Furthermore, with respect to the residue corresponding to 324 of SEQ ID NO: 3, the specification discloses the effect of 15 amino acid replacements (see Table 8): E324A, C, D, F, G, H, L, M, N, P, R, S, V, W, Y and shows that polypeptides with the replacement A, D, H, M, N, R, and S are active (see Table 9). Thus, the scope of the claims includes three of the modifications that result in active polypeptides. This includes teaching all of the mutations in the polypeptide that inactivate the polypeptide (see Table 8), and the effects of thousands of mutations that have no effect on or increase activity, thereby providing a structure/function map. Unlike the examples of mutations in other unrelated polypeptides (*i.e.*, FGF) mentioned in the Final Office Action, the instant application demonstrates all of the mutations in the catalytically active portion of the polypeptide that alter activity and/or a property. Applicant had possession of modifications that result in active and result in inactive polypeptides.

As to the Examiner’s argument regarding inactive mutants, the disclosure includes inactive mutants as part of the written description (see Final Office Action at page 7), which was discovered as a result of extensive testing and actual examples, which is also explicitly disclosed in the written description. Further, a person of ordinary skill in the art can use the hyaluronidase activity assays described in the specification to confirm whether modified PH20 polypeptides have increased hyaluronidase activity and determine the inoperative embodiments.

Moreover, it has been consistently held that claims are permitted to encompass inoperative embodiments:

To the extent that there would be some unpredictability in any particular altered antibody sequence, it is almost always possible to so construe a claim as to have it read on inoperative embodiments. . . ., but the alternative of requiring

an applicant to be so specific in his claims “as to exclude materials known to be inoperative and [which] even those not skilled in the art would not try” would result in claims which would fail to comply with 35 U.S.C. § 112, second paragraph, because they would be so detailed as to obscure, rather than to particularly point out and distinctly claim, the invention. *In re Smythe*, 480 F.2d 1376, 1385 (CCPA 1973). In this case, while claim 10 excluding inoperative embodiments might not be indefinite, it would be narrower than the scope supported by the disclosure in the Specification. Thus, Appellant has demonstrated descriptive support for the embodiments encompassed by claim 10.

Ex Parte Tibor Keler, Appeal No. 2019-006094, 2020 WL 3265323, at 7 (P.T.A.B. 2020).

Here, the specification includes extensive disclosure of the structure of active and inactive mutants. Further, the description teaches a person of ordinary skill in the art how to determine whether a particular mutant is active or inactive. As a result, one of ordinary skill in the art would readily understand that the inventor was in possession of the claimed genus. Moreover, in the instant case, requiring Applicant to be so specific as to exclude every inactive mutant would render the claims substantially narrower than what Applicant is entitled to, in view of the disclosure of the specification.

As discussed earlier, the inventors disclosed inactive mutants as part of their written description, which was discovered as a result of their extensive testing and actual examples. In other cases, such as *Ex Parte Keler*, inoperative embodiments were encompassed but not described and claims were still found to have written description. Here, the disclosure in the specification is further evidence of the inventors’ possession of the claimed subject matter. It cannot be that claims can encompass inoperative embodiments while still having written description as a general matter, but that if one identifies them via testing and discloses them in the specification, the claims lack it.

Excluding inoperative embodiments would be narrower than the scope supported by the express disclosures in the specification. A person of ordinary skill in the art can use the hyaluronidase activity assays developed by Applicants and described in the specification to confirm whether modified PH20 polypeptides have increased hyaluronidase activity, and readily determine the inoperative embodiments.

3. The Examiner argues that the specification fails to provide what other common structures and sequences and features for the claimed variants are and what 5% of amino acids and/or gaps can or cannot be changed to reach increased activity. See Final Office Action at page 8. Applicant disagrees and traverses as follows.

As has been discussed in detail earlier, there is no requirement that the written description requirement be met by providing common structures, sequences and features for claimed variants in the specification. Moreover, Applicant further cites *Ex Parte Philippe Duchateau*, Appeal No. 2021-000639, 2021 WL 2495261, 14, 17 (P.T.A.B. 2021) (holding that “a person of ordinary skill in this highly-refined art would have well understood what was meant by the [contended] claim terms” based on the

teachings in the “specification, together with the teachings of the prior art at the time of the invention”) to support this premise.

4. The Examiner cites to *Vas-Cath* to argue that the specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed” (see Final Office Action at page 10). The Examiner contends that the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of other structurally and functionally undefined variants (as claimed), and that “[a]dequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The compound itself is required” (citing *Fiers v. Revel*). The Examiner cites several other cases to contend that “one cannot describe what one has not conceived” (Id). Applicant disagrees and traverses as follows.

Complete structures of every embodiment are not required, and reduction to practice of every one of the individual embodiments need not be complete. See e.g. *Ex Parte Olga Bandman*, Appeal No. 2004-2319, 2005 WL 4773698, at 2-3 (B.P.A.I. 2005) (holding that “the written description requirement of 35 U.S.C. § 112, first paragraph, does not require a description of the complete structure of every species within a chemical genus (citing *Utter v. Hiraga*, 845 F.2d 993, 998, (Fed. Cir. 1988)).

The courts have also consistently held that “the written description requirement can be met by showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of characteristics” (see *Enzo Biochem v. Gen-Probe*, 296 F.3d 1316, 1324 (citations omitted)). Indeed, MPEP § 2163(II)(3)(a)(ii) adopts its guidance from *Enzo Biochem*.

In *Ex parte Bandman*, the specification described the complete structure of the polynucleotide of SEQ ID NO: 2, and the genus was limited to a polynucleotide comprising a naturally occurring polynucleotide sequence at least 95% identical to the polynucleotide sequence of SEQ ID NO: 2. In addition, the complete structure of the polypeptide of SEQ ID NO: 1 was described, and the genus limited to polypeptides comprising a naturally occurring amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 1.

Here, as in *Ex parte Bandman*, the Specification describes the complete structure of the PH20 polynucleotide of SEQ ID NO: 35, and the claimed genus is limited to polynucleotides comprising at least 95% identical to the polynucleotide of SEQ ID NO: 35. Moreover, like in *Ex parte Bandman*, the Examiner here fails to adequately explain and/or provide evidence to support the assertion that the specification provides no disclosure of any particular structure to function/activity relationship in the single disclosed species. Indeed, as discussed extensively herein, the present application not only discloses a list of a large number of active/inactive variants and mutations that increase/decrease activity, it also describes,

with experimental data, examples of how activity is measured to arrive at the list of variants. The present application also describes a method for arriving at these variants.

The Board has also held that “[i]t is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention” (see *Ex Parte Abad*, Appeal No. 2007-4356, 2008 WL 904457 (B.P.A.I. 2008) (citing *Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005)). In *Ex parte Abad*, the Board found that “significant information to characterize the generic invention, ranging from the capacity to generate, identify and screen members of the genus, to large numbers of different mutations which characterize structure/function relationships, to both information on the primary, secondary and tertiary physical structure of the δ e-endotoxins” *Id.* at 12.

Here, as discussed extensively above and during prosecution, the specification discloses a large number of active/inactive mutations as well as mutations which increase/decrease activity so as to characterize the structure/function relationships. The specification also discloses methods of identifying and screening mutants for activity/inactivity as well as for increase/decrease in activity.

Applicant, therefore, submits that the specification provides sufficient information for one of ordinary skill in the art to understand that the Applicant had possession of the claimed genus. This position is supported by ample case law as discussed in detail herein. For at least these reasons, withdrawal of the rejection under 35 U.S.C. § 112 (first paragraph) is requested.

Conclusion

In view of the foregoing, Applicant awaits a favorable action on the merits. Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact the undersigned representative to expedite prosecution.

Date: July 25, 2024

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Respectfully submitted,

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Registration No. 50,801

<i>Examiner-Initiated Interview Summary</i>	Application No. 18/340,786	Applicant(s) WEI et al.		
	Examiner CHANG-YU WANG	Art Unit 1649	AIA (First Inventor to File) Status No	Page 1 of 1

All Participants (applicant, applicants representative, PTO personnel)	Title	Type
CHANG-YU WANG	Primary Examiner	Telephonic
Kalpesh V. Upadhye	Attorney of Record	

Date of Interview: 02 August 2024

Issues Discussed:

Proposed Amendment(s)

- i. On 08/02/2024, discussed possible amendment to place the application in condition for allowance.
- ii. Applicant agreed to delete the limitation "PH20 polypeptide" at the end of claim 7 and agreed to amend claim 10 to "The modified PH20 polypeptide of claim 9, wherein the glycosylated modified PH20 polypeptide comprises an N-acetylglucosamine moiety linked to each of at least three asparagine (n) residues" in claim 10.

/CHANG-YU WANG/ Primary Examiner, Art Unit 1649	
<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.

Issue Classification 	Application/Control No. 18/340,786	Applicant(s)/Patent Under Reexamination WEI et al.	
	Examiner CHANG-YU WANG	Art Unit 1649	

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
A61P	/	35	/	00	I	2018-01-01
C07K	/	14	/	47	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
C07K	/	2319	/	30	A	2013-01-01
A61K	/	38	/	00	A	2013-01-01

CPC Combination Sets								
Symbol					Type	Set	Ranking	Version
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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

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	10	
/CHANG-YU WANG/	08 August 2024	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

Issue Classification 	Application/Control No. 18/340,786	Applicant(s)/Patent Under Reexamination WEI et al.
	Examiner CHANG-YU WANG	Art Unit 1649

INTERNATIONAL CLASSIFICATION				
CLAIMED				
C07K	/	14	/	47
C07K	/	14	/	00
A61K	/	38	/	00
A61K	/	38	/	47
NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS
530	350

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					
530	324					
435	183	195				

NONE (Assistant Examiner)		Total Claims Allowed: 10	
/CHANG-YU WANG/ Primary Examiner, Art Unit 1649 (Primary Examiner)		08 August 2024 (Date)	O.G. Print Claim(s) 1
			O.G. Print Figure None

Issue Classification 	Application/Control No. 18/340,786	Applicant(s)/Patent Under Reexamination WEI et al.
	Examiner CHANG-YU WANG	Art Unit 1649

☒ 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		23												
	2														
	3														
	6														
	7														
	8														
	9														
	10														
	14														

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	10	
/CHANG-YU WANG/ Primary Examiner, Art Unit 1649	08 August 2024	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

<i>Search Notes</i> 	Application/Control No. 18/340,786	Applicant(s)/Patent Under Reexamination WEI et al.
	Examiner CHANG-YU WANG	Art Unit 1649

CPC - Searched*		
Symbol	Date	Examiner
A61K38/00;38/47	08/08/2024	CYW
C07K14/47;2319/30	08/08/2024	CYW
A61P35/00;29/00;25/00;25/28	08/08/2024	CYW
C12N9/2474;9/00	08/08/2024	CYW

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.

/C.Y.W./ Primary Examiner, Art Unit 1649	
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<i>Search Notes</i> 	Application/Control No. 18/340,786	Applicant(s)/Patent Under Reexamination WEI et al.
	Examiner CHANG-YU WANG	Art Unit 1649

Search Notes		
Search Notes	Date	Examiner
Sequence search: SEQ ID NOs:3, 32, 35, 623 and 624 and SEQ ID NO:3 with a mutation E324D, E324N, or E324R. See sequence search results in SCV (01/16/2024,02/01/2024 & 07/03/2024).	08/08/2024	CYW
PE2E Search, STN: search strategy attached (updated).	08/08/2024	CYW
Inventor name search:PE2E Search, STN, PALM. See attached (updated).	08/08/2024	CYW
Similarity Search: PE2E Search. See attached.	08/08/2024	CYW
Review of Filing Receipt.	08/08/2024	CYW
PDP search-DAV continuity data map and inventor information tabs.	08/08/2024	CYW
PE2E Search for assignee/applicant. See attached (updated).	08/08/2024	CYW
Global Dossier. See attached.	08/08/2024	CYW
Google Scholar & Patents. See attached.	08/08/2024	CYW
A61K38/00;38/47	08/08/2024	CYW
C07K14/47;2319/30	08/08/2024	CYW
A61P35/00;29/00;25/00;25/28	08/08/2024	CYW
C12N9/2474;9/00	08/08/2024	CYW

/C.Y.W./ Primary Examiner, Art Unit 1649	
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<i>Search Notes</i> 	Application/Control No. 18/340,786	Applicant(s)/Patent Under Reexamination WEI et al.
	Examiner CHANG-YU WANG	Art Unit 1649

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
Sequence Interference search: SEQ ID NOs:3, 32, 35, 623 and 624 and SEQ ID NO:3 with a mutation E324D, E324N, or E324R. See sequence search results in SCV (07/03/2024).		08/08/2024	CYW
Text Interference Search: PE2E Search. See attached.		08/08/2024	CYW
Inventor name interference search: PE2E Search. See attached.		08/08/2024	CYW
CPC:A61K38/00;C07K14/47; C12N9/2474; C12Y302/01035:PE2E Search. See attached.		08/08/2024	CYW
Global Dossier. see attached.		08/08/2024	CYW

/C.Y.W./ Primary Examiner, Art Unit 1649	
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<i>Index of Claims</i> 	Application/Control No. 18/340,786	Applicant(s)/Patent Under Reexamination WEI et al.
	Examiner CHANG-YU WANG	Art Unit 1649

☒ Rejected	☐ Cancelled	☐ Non-Elected	☐ Appeal
☐ Allowed	☐ Restricted	☐ Interference	☐ Objected

CLAIMS										
☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47										
CLAIM		DATE								
Final	Original	08/08/2024								
	1	=								
	2	=								
	3	=								
	4	-								
	5	-								
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	21	-								
	22	-								
	23	=								

Web Search History

date, time	web site	search string
8/8/2024 5:33:06 PM	Google	ph20 hyaluronidase variant "324"
8/8/2024 5:33:15 PM	Google Patents	Search Term 1 (ph20 hyaluronidase variant "324")
8/8/2024 5:33:22 PM	Google Scholar	ph20 hyaluronidase variant "324"

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Ge Wei <i>et al.</i>	)	
	)	Confirmation No. 6432
U.S. Application No. 18/340,786	)	
	)	Group Art Unit: 1649
Filing Date: 6/3/2023	)	
	)	Examiner: Chung Yu Wang
For: PH20 Polypeptide Variants, Formulations	)	
and Uses Thereof	)	

AMENDMENT UNDER 37 C.F.R. § 1.116

In response to the Final Office Action dated 04/26/2024, and the Advisory Action dated July 12, 2024, having a three-month shortened statutory period for response set to expire 07/26/2024, Applicant requests entry of the following amendments and remarks in the above patent application. To the extent necessary, a petition for an extension of time under 37 C.F.R. § 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 50-0310 and please credit any excess fees to such deposit account.

The Listing of claims begins on page 2.

Remarks begin on page 4.

The Conclusion is on page 11.

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L143	118	((("HALOZYME") near3 ("INC"))).AS,AANM.	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/07 09:38 AM
L144	60	((("WEI") near3 ("Ge"))).INV.	(EPO; JPO; DERWENT)	ADJ	ON	ON	2024/08/07 09:38 AM
L145	329	((("WEI") near3 ("Ge"))).INV.	(US-PGPUB; USPAT; USOCR)	ADJ	ON	ON	2024/08/07 09:38 AM
L146	41	((("Shepard") near3 ("H") near3 ("Michael"))).INV.	(EPO; JPO; DERWENT)	ADJ	ON	ON	2024/08/07 09:38 AM
L147	115	((("Shepard") near3 ("H") near3 ("Michael"))).INV.	(US-PGPUB; USPAT; USOCR)	ADJ	ON	ON	2024/08/07 09:38 AM
L148	2	((("Zhao") near3 ("Qiping"))).INV.	(EPO; JPO; DERWENT)	ADJ	ON	ON	2024/08/07 09:38 AM
L149	29	((("Zhao") near3 ("Qiping"))).INV.	(US-PGPUB; USPAT; USOCR)	ADJ	ON	ON	2024/08/07 09:38 AM
L150	2	((("Connor") near3 ("Robert") near3 ("James"))).INV.	(EPO; JPO; DERWENT)	ADJ	ON	ON	2024/08/07 09:38 AM
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L154	273	Shepard m	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2024/08/07 09:39 AM
L155	83818	Zhao q	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2024/08/07 09:39 AM
L156	1150	Connor r	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2024/08/07 09:39 AM
L157	2030903	"324" OR E324	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2024/08/07 09:39 AM
L158	1792	position "324"	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2024/08/07 09:39 AM

L159	588	amino acid "324"	DERWENT) (US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2024/08/07 09:39 AM
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L161	35	E324N	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2024/08/07 09:39 AM
L162	33	E324R	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2024/08/07 09:39 AM
L163	41	(Artificial Intelligence) Similar to: 18/340,786 with 0 CPC Selections and 0 Text Selections Text: (AU-2012362141-A1 OR US-9447401-B2 OR AU-2012362141-B2 OR EP-2797622-B1 OR NZ-626126-A OR DK- 2797622-T3 OR EP- 2797622-A2 OR MX- 2014007966-A OR JP- 2017112999-A OR ES- 2609582-T3 OR EP- 3130347-B1 OR CA- 2861919-C OR IL- 298330-A OR NZ- 626126-B2 OR US- 20160362670-A1 OR US-20140178330-A9 OR US-20130302275- A1 OR US-10865400- B2 OR IL-280949-B2 OR WO-2013102144- A2 OR EP-3130347-A1 OR AU-2017245352-A1 OR US-11041149-B2 OR ES-2749620-T3 OR NZ-720075-A OR NZ- 720075-B2 OR JP- 2015504666-A OR US- 20200255814-A1 OR US-20210284985-A1 OR US-20210277376- A1 OR CA-2861919-A1 OR US-11066656-B2 OR AU-2017245352-B2 OR US-20200318091- A1 OR JP-6067746-B2 OR JP-6422933-B2 OR BR-112014016195-A2	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN))	ADJ	ON	ON	2024/08/07 09:39 AM

		OR CN-104244968-B OR US-20230295593-A1 OR US-20230357739-A1 OR US-20230250409-A1 OR CN-104244968-A OR US-20230295592-A1 OR US-20230287381-A1 OR US-20230151346-A1 OR US-20230212547-A1 OR EA-030252-B1 OR HR-P20192249-T1 OR WO-2015003167-A1 OR US-20150010529-A1).did.					
L164	30	L73 AND L67	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2024/08/07 09:39 AM
L165	30	L72 AND L67	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2024/08/07 09:39 AM
L166	30	L71 AND L67	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2024/08/07 09:39 AM
L167	9591	L68 AND L67	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2024/08/07 09:39 AM
L168	12	L70 AND L67	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2024/08/07 09:39 AM
L169	30	L77 AND ((A61K38/00 OR A61P35/00 OR A61P29/00 OR C12N9/2474 OR C07K14/47 OR C07K2319/30).cpc.)	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2024/08/07 09:39 AM
L170	1643	L78 AND ((A61P35/00 OR A61P29/00 OR A61P25/00 OR A61P25/28 OR A61K38/00 OR A61K38/47 OR C07K14/47 OR C12N9/2474 OR C12N9/00).cpc.)	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2024/08/07 09:39 AM
L171	2	L85 AND L67	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2024/08/07 09:39 AM
L172	14	L84 AND L67	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2024/08/07 09:39 AM
L173	14	L83 AND L67	(US-PGPUB; USPAT; USOCR; EPO; JPO;	ADJ	ON	ON	2024/08/07 09:39 AM

L174	10	L82 AND L67	DERWENT) (US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2024/08/07 09:39 AM
L175	2	("10865400").pn.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2024/08/07 09:39 AM

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N1	118	((("HALOZYME") near3 ("INC"))).AS,AANM.	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/07 09:48 AM
N2	329	((("WEI") near3 ("Ge"))).INV.	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/07 09:48 AM
N3	329	((("WEI") near3 ("Ge"))).INV.	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/07 09:48 AM
N4	115	((("Shepard") near3 ("H") near3 ("Michael"))).INV.	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/07 09:48 AM
N5	115	((("Shepard") near3 ("H") near3 ("Michael"))).INV.	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/07 09:48 AM
N6	29	((("Zhao") near3 ("Qiping"))).INV.	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/07 09:48 AM
N7	29	((("Zhao") near3 ("Qiping"))).INV.	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/07 09:49 AM
N8	30	((("Connor") near3 ("Robert") near3 ("James"))).INV.	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/07 09:49 AM
N9	30	((("Connor") near3 ("Robert") near3 ("James"))).INV.	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/07 09:49 AM
N10	52591	(PH-20) OR (SPAM1) OR (SPAM) OR (2B1) OR (sperm adhesion molecule 1) OR (hyaluronidase 1 precursor) OR (HYAL3) OR (hyaluronidase PH-20) OR (sperm PH-20)	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/07 09:49 AM
N11	1158	wei g	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/07 09:49 AM
N12	128	Shepard m	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/07 09:50 AM
N13	2011	Zhao q	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/07 09:50 AM
N14	825	Connor r	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/07 09:50 AM
N15	1618031	"324" OR E324	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/07 09:50 AM

N16	1638	position "324"	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/07 09:50 AM
N17	569	amino acid "324"	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/07 09:50 AM
N18	48	E324D	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/07 09:50 AM
N19	34	E324N	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/07 09:50 AM
N20	33	E324R	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/07 09:51 AM
N21	52617	(PH-20) OR (SPAM1) OR (SPAM) OR (2B1) OR (sperm adhesion molecule 1) OR (hyaluronidase 1 precursor) OR (HYAL3) OR (hyaluronidase PH- 20) OR (sperm PH-20)	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/08 12:33 PM
N22	30	N21 AND N20	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/08 12:33 PM
N23	30	N21 AND N19	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/08 12:33 PM
N24	30	N21 AND N18	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/08 12:33 PM
N25	12	N21 AND N17	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/08 12:33 PM
N26	53	N21 AND N16	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/08 12:33 PM
N27	9504	N21 AND N15	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/08 12:34 PM
N28	80	N27 AND N1	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/08 12:34 PM
N29	34	N27 AND N2	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/08 12:34 PM
N30	34	N27 AND N3	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/08 12:34 PM
N31	50	N27 AND N4	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/08 12:34 PM
N32	50	N27 AND N5	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/08 12:34 PM
N33	29	N27 AND N6	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/08 12:34 PM
N34	29	N27 AND N7	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/08 12:35 PM
N35	29	N27 AND N8	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/08 12:35 PM
N36	29	N27 AND N9	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/08 12:35 PM
N37	9504	N27 AND N10	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/08 12:35 PM

N38	0	N27 AND N11	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/08 12:35 PM
N39	14	N27 AND N12	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/08 12:35 PM
N40	5	N27 AND N13	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/08 12:35 PM
N41	1	N27 AND N14	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/08 12:35 PM
N42	29	N26 AND ((A61K38/00 OR C07K14/47 OR C12Y302/01035).cpc.)	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/08 12:54 PM
N43	29	N26 AND ((A61K38/00 OR C07K14/47 OR C12N9/2474 OR C12Y302/01035).cpc.)	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/08/08 01:07 PM

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FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 17:34:38 ON 08 AUG
2024
L1      4812 FILE MEDLINE
L2      3829 FILE BIOSIS
L3      18269 FILE CAPLUS
L4      5290 FILE EMBASE
TOTAL FOR ALL FILES
L5      32200 S ((WEI, G?) OR (WEI G?))/AU
L6      288 FILE MEDLINE
L7      328 FILE BIOSIS
L8      278 FILE CAPLUS
L9      345 FILE EMBASE
TOTAL FOR ALL FILES
L10     1239 S ((SHEPARD, M?) OR (SHEPARD M?))/AU
L11     19130 FILE MEDLINE
L12     14400 FILE BIOSIS
L13     59070 FILE CAPLUS
L14     20824 FILE EMBASE
TOTAL FOR ALL FILES
L15     113424 S ((ZHAO, Q?) OR (ZHAO Q?))/AU
L16     402 FILE MEDLINE
L17     1001 FILE BIOSIS
L18     408 FILE CAPLUS
L19     434 FILE EMBASE
TOTAL FOR ALL FILES
L20     2245 S ((CONNOR, R?) OR (CONNOR R?))/AU
L21     2132 FILE MEDLINE
L22     2355 FILE BIOSIS
L23     4925 FILE CAPLUS
L24     3638 FILE EMBASE
TOTAL FOR ALL FILES
L25     13050 S (PH-20) OR (SPAM1) OR (SPAM) OR (2B1) OR (SPERM
ADHESION
L26     2023971 FILE MEDLINE
L27     1552804 FILE BIOSIS
L28     3949714 FILE CAPLUS
L29     2695654 FILE EMBASE
TOTAL FOR ALL FILES
L30     10222143 S REPLAC? OR MODIF?
L31     484447 FILE MEDLINE
L32     416683 FILE BIOSIS
L33     450587 FILE CAPLUS
L34     652680 FILE EMBASE
TOTAL FOR ALL FILES
L35     2004397 S VARIANT?
L36     18339 FILE MEDLINE
L37     13946 FILE BIOSIS
L38     22682 FILE CAPLUS
L39     29318 FILE EMBASE
TOTAL FOR ALL FILES
L40     84285 S 324
L41     0 FILE MEDLINE
L42     0 FILE BIOSIS
L43     0 FILE CAPLUS
L44     0 FILE EMBASE
TOTAL FOR ALL FILES
L45     0 S L25 AND L35 AND L40
L46     2 FILE MEDLINE
L47     3 FILE BIOSIS
L48     1 FILE CAPLUS

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L49 4 FILE EMBASE
TOTAL FOR ALL FILES
L50 10 S L25 AND L40
L51 0 FILE MEDLINE
L52 1 FILE BIOSIS
L53 0 FILE CAPLUS
L54 1 FILE EMBASE
TOTAL FOR ALL FILES
L55 2 S L50 AND L30
L56 2 DUP REM L55 (0 DUPLICATES REMOVED)
L57 0 FILE MEDLINE
L58 0 FILE BIOSIS
L59 0 FILE CAPLUS
L60 0 FILE EMBASE
TOTAL FOR ALL FILES
L61 0 S L50 AND L5
L62 0 FILE MEDLINE
L63 0 FILE BIOSIS
L64 0 FILE CAPLUS
L65 0 FILE EMBASE
TOTAL FOR ALL FILES
L66 0 S L50 AND L10
L67 0 FILE MEDLINE
L68 0 FILE BIOSIS
L69 0 FILE CAPLUS
L70 0 FILE EMBASE
TOTAL FOR ALL FILES
L71 0 S L50 AND L15
L72 0 FILE MEDLINE
L73 0 FILE BIOSIS
L74 0 FILE CAPLUS
L75 0 FILE EMBASE
TOTAL FOR ALL FILES
L76 0 S L50 AND L20
L77 179 FILE MEDLINE
L78 185 FILE BIOSIS
L79 340 FILE CAPLUS
L80 306 FILE EMBASE
TOTAL FOR ALL FILES
L81 1010 S L25 AND L30
L82 0 FILE MEDLINE
L83 0 FILE BIOSIS
L84 0 FILE CAPLUS
L85 0 FILE EMBASE
TOTAL FOR ALL FILES
L86 0 S L81 AND L5
L87 0 FILE MEDLINE
L88 0 FILE BIOSIS
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L90 0 FILE EMBASE
TOTAL FOR ALL FILES
L91 0 S L81 AND L10
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L93 0 FILE BIOSIS
L94 0 FILE CAPLUS
L95 0 FILE EMBASE
TOTAL FOR ALL FILES
L96 0 S L81 AND L15
L97 0 FILE MEDLINE
L98 0 FILE BIOSIS
L99 0 FILE CAPLUS

8/8/24, 5:36 PM

STNext

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L100          0 FILE EMBASE
TOTAL FOR ALL FILES
L101          0 S L81 AND L20
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Bibliographic Data

Application No: 18/340,786

Foreign Priority claimed: ☐ Yes ☒ No

35 USC 119 (a-d) conditions met: ☐ Yes ☒ No

☐ Met After Allowance

Verified and Acknowledged: /CHANG-YU WANG/

Examiner's Signature

Initials

Title:

PH20 POLYPEPTIDE VARIANTS WITH A MODIFICATION AT
POSITION 324 OF THE PH20 POLYPEPTIDE AND A METHOD
OF MAKING THEREOF

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
06/23/2023	424	1649	
RULE			

APPLICANTS

HALOZYME, INC., San Diego, CA, UNITED STATES

INVENTORS

Ge WEI,

H. Michael Shepard,

Qiping Zhao,

Robert James Connor,

CONTINUING DATA

This application is a DIV of 17327568 05/21/2021

17327568 is a CON of 16912590 06/25/2020 PAT 11066656

17327568 is a CON of 16824572 03/19/2020 PAT 11041149

16912590 is a CON of 15226489 08/02/2016 PAT 10865400

17327568 is a CON of 15226489 08/02/2016 PAT 10865400

16824572 is a CON of 15226489 08/02/2016 PAT 10865400

15226489 is a DIV of 13694731 12/28/2012 PAT 9447401

17327568 is a CON of 13694731 12/28/2012 PAT 9447401

16912590 is a DIV of 13694731 12/28/2012 PAT 9447401

13694731 has PRO of 61796208 11/01/2012

13694731 has PRO of 61631313 12/30/2011

FOREIGN APPLICATIONS

IF REQUIRED, FOREIGN LICENSE GRANTED**

09/25/2023

STATE OR COUNTRY

ADDRESS

FILING FEE RECEIVED

\$8,140

IP Office	Application	Applicant	Title	Application Date	Priority Number	Publication Number	Publication Date
BR	112014016195			12/28/2012	US PCT/US12/72182 US 61631313 US 61796208	BR 112014016195 A2	10/27/2020
NZ	72007512			12/28/2012	US 61631313 US 61796208 NZ 62612612	NZ 720075 A	03/27/2020
DK	16189970			12/28/2012	EP 12816624 US 61631313 US 61796208	DK 3130347 T3	10/14/2019
MX	2014007966			12/28/2012	US PCT/US12/72182 US 61631313 US 61796208	MX 2014007966 A MX 361727 B	10/17/2014 12/14/2018
EP	16189970			12/28/2012	EP 12816624 US 61631313 US 61796208 US PCT/US12/72182	EP 3130347 A1 EP 3130347 B1	02/15/2017 09/18/2019
SG	10201604470T			12/28/2012	US 61631313 US 61796208	SG 10201604470T A	07/28/2016
DK	12816624			12/28/2012	US PCT/US12/72182 US 61631313 US 61796208	DK 2797622 T3	01/16/2017
EA	201400772			12/28/2012	US PCT/US12/72182 US 61631313 US 61796208	EA 201400772 A1 EA 030252 B1 EA 030252 B9	07/30/2015 07/31/2018 09/09/2021
EP	12816624			12/28/2012	US PCT/US12/72182 US 61631313 US 61796208	EP 2797622 A2 EP 2797622 B1	11/05/2014 10/12/2016
LT	16189970			12/28/2012	US 61631313 US 61796208	LT 3130347 T	10/25/2019
PL	16189970			12/28/2012	EP 12816624 US 61631313 US 61796208 EP 16189970 US PCT/US12/72182	PL 3130347 T3	04/30/2020
SI	201231709			12/28/2012	US 61631313 US 61796208 EP 16189970	SI 3130347 T1	02/28/2020

IP Office	Application	Applicant	Title	Application Date	Priority Number	Publication Number	Publication Date
ES	16189970			12/28/2012	US 61631313 US 61796208	ES 2749620 T3	03/23/2020
HU	E16189970			12/28/2012	US 61631313 US 61796208	HU E047849 T2	05/28/2020
CA	2861919			12/28/2012	US PCT/US12/72182 US 61631313 US 61796208	CA 2861919 A1 CA 2861919 C	07/04/2013 04/02/2019
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CN	201280070954			12/28/2012	US PCT/US12/72182 US 61631313 US 61796208	CN 104244968 A CN 104244968 B	12/24/2014 07/25/2017
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JP	2014550526			12/28/2012	US PCT/US12/72182 US 61631313 US 61796208	JP 2015504666 A JP 6067746 B2	02/16/2015 01/25/2017
AU	2012362141			12/28/2012	US PCT/US12/72182 US 61631313 US 61796208	AU 2012362141 A1 AU 2012362141 B2	07/10/2014 09/21/2017
ES	12816624			12/28/2012	US PCT/US12/72182 US 61631313 US 61796208	ES 2609582 T3	04/21/2017
RS	P20191613			12/28/2012	US 61631313 US 61796208 EP 16189970	RS 59703 B1	01/31/2020
SG	11201403714T			12/28/2012	US PCT/US12/72182 US 61631313 US 61796208	SG 11201403714T A	07/30/2014

IP Office	Application	Applicant	Title	Application Date	Priority Number	Publication Number	Publication Date
US	13694731			12/28/2012	US 61631313 US 61796208 US 13694731	US 20130302275 A1 US 20140178330 A9 US 9447401 B2	11/14/2013 06/26/2014 09/20/2016
NZ	62612612			12/28/2012	US PCT/US12/72182 US 61631313 US 61796208	NZ 626126 A	06/24/2016
IL	23319214			06/17/2014	US PCT/US12/72182 US 61631313 US 61796208	IL 233192 B	06/30/2020
MX	2018012394			06/27/2014	US 61631313 US 61796208	MX 2018012394 A	09/02/2020
HK	15103502			04/09/2015	US PCT/US12/72182 US 61631313 US 61796208	HK 1202814 A1	10/09/2015
US	15226489			08/02/2016	US 61631313 US 61796208 US 15226489 US 13694731	US 20160362670 A1 US 10865400 B2	12/15/2016 12/15/2020
JP	2016247708			12/21/2016	US 61631313 US 61796208	JP 2017112999 A JP 6422933 B2	06/29/2017 11/14/2018
AU	2017245352			10/11/2017	US 61631313 US 61796208 AU 2012362141 US PCT/US12/72182 AU 2017245352	AU 2017245352 A1 AU 2017245352 B2	11/02/2017 08/01/2019
CY	191101301			12/10/2019	EP 12816624 US 61631313 US 61796208 US PCT/US12/72182	CY 1122532 T1	01/27/2021
HR	P20192249			12/13/2019	US 61631313 US 61796208 EP 16189970	HR P20192249 T1	03/06/2020
US	16824572			03/19/2020	US 16824572 US 61631313 US 61796208 US 15226489 US 13694731	US 20200255814 A1 US 11041149 B2	08/13/2020 06/22/2021

IP Office	Application	Applicant	Title	Application Date	Priority Number	Publication Number	Publication Date
IL	27479820			05/20/2020	US PCT/US12/72182 US 61631313 US 61796208	IL 274798 A 274798 B IL	07/30/2020 03/25/2021
US	16912590			06/25/2020	US 61631313 US 61796208 US 15226489 US 16912590 US 13694731	US 20200318091 A1 US 11066656 B2	10/08/2020 07/20/2021
IL	28094921			02/18/2021	US PCT/US12/72182 US 61631313 US 61796208	IL 280949 A 280949 B IL 280949 B2	04/29/2021 12/01/2022 04/01/2023
US	17327568			05/21/2021	US 16824572 US 61631313 US 61796208 US 16912590 US 13694731 US 17327568 US 15226489	US 20210284985 A1	09/16/2021
US	17327586			05/21/2021	US 16824572 US 61631313 US 61796208 US 16912590 US 13694731 US 15226489 US 17327586	US 20210277376 A1 US 12037618 B2	09/09/2021 07/16/2024
IL	29833022			11/17/2022	US PCT/US12/72182 US 61631313 US 61796208	IL 298330 A	01/01/2023
US	18064886			12/12/2022	US 16824572 US 61631313 US 61796208 US 16912590 US 18064886 US 13694731 US 17327568 US 15226489 US 17327586	US 20230295592 A1 US 12049652 B2	09/21/2023 07/30/2024
US	18066960			12/15/2022	US 16824572 US 61631313 US 61796208 US 18066960 US 16912590 US 13694731 US 17327568 US 15226489 US 17327586	US 20230151346 A1	05/18/2023

IP Office	Application	Applicant	Title	Application Date	Priority Number	Publication Number	Publication Date
US	18068327			12/19/2022	US 16824572 US 18068327 US 61631313 US 61796208 US 16912590 US 13694731 US 17327568 US 15226489 US 17327586	US 20230357739 A1	11/09/2023
US	18068443			12/19/2022	US 16824572 US 61631313 US 61796208 US 16912590 US 13694731 US 17327568 US 18068443 US 15226489	US 20230212547 A1	07/06/2023
US	18068218			12/19/2022	US 16824572 US 61631313 US 61796208 US 16912590 US 13694731 US 17327568 US 15226489 US 17327586 US 18068218	US 20230295593 A1	09/21/2023
US	18068418			12/19/2022	US 16824572 US 61631313 US 61796208 US 16912590 US 13694731 US 18068418 US 17327568 US 15226489 US 17327586	US 20230250409 A1	08/10/2023
US	18069651			12/21/2022	US 16824572 US 18069651 US 61631313 US 61796208 US 16912590 US 13694731 US 17327568 US 15226489	US 20230287381 A1	09/14/2023
US	18338189			06/20/2023	US 16824572 US 61631313 US 61796208 US 16912590 US 13694731 US 17327568 US 18338189 US 15226489	US 20240011008 A1 US 11952600 B2	01/11/2024 04/09/2024
US	18339829			06/22/2023	US 16824572 US 61631313 US 61796208 US 16912590 US 13694731 US 15226489 US 17327586 US 18339829	US 20240026327 A1	01/25/2024

IP Office	Application	Applicant	Title	Application Date	Priority Number	Publication Number	Publication Date
US	18340786	1)WEI, Ge, 2)Shopard, H. Michael, 3)Zhao, Qiping, 4)Connor, Robert James	PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF	06/23/2023	US 16824572 US 61631313 US 61796208 US 16912590 US 18340796 US 13694731 US 17327568 US 15226489	US 20240002826 A1	01/04/2024
US	18340802			06/23/2023	US 16824572 US 61631313 US 61796208 US 16912590 US 13694731 US 17327568 US 18340802 US 15226489	US 20240026328 A1	01/25/2024
US	18340482			06/23/2023	US 16824572 US 61631313 US 61796208 US 16912590 US 18340482 US 13694731 US 17327568 US 15226489	US 20240002825 A1 US 12018298 B2	01/04/2024 06/25/2024
US	18599428			03/08/2024	US 16824572 US 61631313 US 61796208 US 16912590 US 18599428 US 13694731 US 17327568 US 18338189 US 15226489 US 17327596	US 20240209337 A1	06/27/2024



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UNITED STATES DEPARTMENT OF COMMERCE
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NOTICE OF ALLOWANCE AND FEE(S) DUE

28977 7590 08/14/2024
Morgan, Lewis & Bockius LLP (PH)
2222 Market Street
Philadelphia, PA 19103

EXAMINER

WANG, CHANG YU

ART UNIT

PAPER NUMBER

1649

DATE MAILED: 08/14/2024

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/340,786	06/23/2023	Ge WEI	63995-01-5105-US-17	6432

TITLE OF INVENTION: PH20 POLYPEPTIDE VARIANTS WITH A MODIFICATION AT POSITION 324 OF THE PH20 POLYPEPTIDE AND A METHOD OF MAKING 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	11/14/2024

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 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted 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. 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 the USPTO patent electronic filing system.

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 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. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

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

28977 7590 08/14/2024
Morgan, Lewis & Bockius LLP (PH)
2222 Market Street
Philadelphia, PA 19103

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 the USPTO patent electronic filing system 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.
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18/340,786

06/23/2023

Ge WEI

63995-01-5105-US-17

6432

TITLE OF INVENTION: PH20 POLYPEPTIDE VARIANTS WITH A MODIFICATION AT POSITION 324 OF THE PH20 POLYPEPTIDE AND A METHOD OF MAKING 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	11/14/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
WANG, CHANG YU	1649	424-094620

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/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or 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,

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 ☐ Government4a. Fees submitted: ☐ Issue Fee ☐ Publication Fee (if required)

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

☐ Electronic Payment via the USPTO patent electronic filing system ☐ 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. _____



UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/340,786	06/23/2023	Ge WEI	63995-01-5105-US-17	6432
28977	7590	08/14/2024	EXAMINER	
Morgan, Lewis & Bockius LLP (PH)			WANG, CHANG YU	
2222 Market Street			ART UNIT	
Philadelphia, PA 19103			PAPER NUMBER	
			1649	
DATE MAILED: 08/14/2024				

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. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).

<https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf>

Routine uses of the information in this record may include disclosure to:

- 1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
- 2) a federal, state, local, or international agency, in response to its request;
- 3) a contractor of the USPTO having need for the information in order to perform a contract;
- 4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
- 5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
- 6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
- 7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
- 8) 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));
- 9) the Office of Personnel Management (OPM) for personnel research purposes; and
- 10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	Application No. 18/340,786	Applicant(s) WEI et al.	
	Examiner CHANG-YU WANG	Art Unit 1649	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 July 25, 2024.
☐ 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 1-3,6-10,14 and 23. 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)	5. ☒ Examiner's Amendment/Comment
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.	6. ☒ Examiner's Statement of Reasons for Allowance
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.	7. ☐ Other _____.
4. ☒ Interview Summary (PTO-413), Paper No./Mail Date. <u>20240628</u> .	

/CHANG-YU WANG/ Primary Examiner, Art Unit 1649	
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Notice of Pre-AIA or AIA Status

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

Status of Application/Amendment/Claims

2. Claims 1-3, 7-10 and 23 were amended in the response filed July 25, 2024. Claims 4-5, 11-13 and 15-22 are canceled. Claims 1-3, 6-10, 14 and 23 are currently pending in this application and the subject matter of the instant Office action.

EXAMINER'S AMENDMENT

3. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Kalpesh V. Upadhye, Ph.D. on August 2, 2024.

The application has been amended as follows:

In the claims:

7. (Currently amended) The modified PH20 polypeptide of claim 1, wherein the modified PH20 polypeptide is soluble PH20 polypeptide.

10. (Currently amended) The modified PH20 polypeptide of claim 9, wherein the glycosylated modified PH20 polypeptide ~~is a glycoprotein that~~ comprises an N-acetylglucosamine moiety linked to each of at least three asparagine (N) residues.

Rejoinder

4. Claims 1-3, 6-10 and 14 are directed to an allowable product. Pursuant to the procedures set forth in MPEP § 821.04(B), claim 23, directed to the process of making or using an allowable product, previously withdrawn from consideration as a result of a restriction requirement, is hereby rejoined and fully examined for patentability under 37 CFR 1.104.

Because all claims previously withdrawn from consideration under 37 CFR 1.142 have been rejoined, **the restriction requirement as set forth in the Office action mailed on 10/20/2023 is hereby withdrawn.** In view of the withdrawal of the restriction requirement as to the rejoined inventions, applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Once the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

5. Claims 1-3, 6-10, 14 and 23 are allowed. Claims 6-10, 14 and 23 were renumbered as claims 4-10 respectively.

6. The title was changed to "PH20 POLYPEPTIDE VARIANTS WITH A MODIFICATION AT POSITION 324 OF THE PH20 POLYPEPTIDE AND A METHOD OF MAKING THEREOF".

Reasons for Allowance

7. The following is an examiner's statement of reasons for allowance: Claims 1-3, 6-10, 14 and 23 are allowed because the recited modified PH20 polypeptide comprising the claimed sequence with specific modifications sets forth a specific claim limitation clearly present in the allowed claim which is neither taught nor suggested by the prior art as a whole, either alone or in combination. The double patenting is withdrawn in response to Applicant's approved terminal disclaimer.

8. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571)272-4521. The examiner can normally be reached on Monday-Thursday, 7:00am-5:30pm EST.

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, Jeffrey Stucker, can be reached on 571-272-0911. 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.

Chang-Yu Wang
August 6, 2024

/CHANG-YU WANG/
Primary Examiner, Art Unit 1649



UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #
18/340,786

RECEIPT DATE / TIME
08/16/2024 09:17:43 PM Z ET

ATTORNEY DOCKET #
63995-01-5105-US-17

Title of Invention

PH20 POLYPEPTIDE VARIANTS WITH A MODIFICATION AT POSITION 324 OF THE PH20 POLYPEPTIDE AND A METHOD OF MAKING THEREOF

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6432	FILED BY	Collins Mba-Jonas
PATENT CENTER #	66821587	AUTHORIZED BY	Kalpesh Upadhye
CUSTOMER #	28977	FILING DATE	06/23/2023
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Ge WEI

Payment Information

PAYMENT METHOD CARD / 5344	PAYMENT TRANSACTION ID E20248FL18098302	PAYMENT AUTHORIZED BY Kalpesh Upadhye
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FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1501	UTILITY ISSUE FEE	1200.00	1	1200.00
TOTAL AMOUNT:				\$1,200.00

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 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.



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PATENT AND TRADEMARK OFFICE

Page 1 of 2
P.O. Box 1450
Alexandria, VA 22313 - 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
18/340,786

RECEIPT DATE / TIME
08/16/2024 09:17:43 PM Z ET

ATTORNEY DOCKET #
63995-01-5105-US-17

Title of Invention

PH20 POLYPEPTIDE VARIANTS WITH A MODIFICATION AT POSITION 324 OF THE PH20 POLYPEPTIDE AND A METHOD OF MAKING THEREOF

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
 under 35 USC 111(a)

PATENT # -

CONFIRMATION # 6432

FILED BY Collins Mba-Jonas

PATENT CENTER # 66821587

FILING DATE 06/23/2023

CUSTOMER # 28977

FIRST NAMED
INVENTOR Ge WEI

CORRESPONDENCE
ADDRESS -

AUTHORIZED BY Kalpesh Upadhye

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
20240816_Issuefeepayment.pdf	1	Issue Fee Payment (PTO-85B)	125 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
20240816_Issuefeepayment.pdf	3DE1C1FED756BD08339687BCF47CC5D24AEBAA66280B481C C9C26E9077CC576D829287CEE91998B29AD41609CAF7BD36 8A640B99506860509E3BB2BDFF8147F8

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 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
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
18/340,786	06/23/2023	1649	3380	63995-01-5105-US-17	23	2

28977

Morgan, Lewis & Bockius LLP (PH)
2222 Market Street
Philadelphia, PA 19103

CONFIRMATION NO. 6432
REPLACEMENT FILING RECEIPT



0C000000076844297

Date Mailed: 08/22/2024

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, Eugene, OR;
Qiping Zhao, San Diego, CA;
Robert James Connor, Oceanside, CA;

Applicant(s)

HALOZYME, INC., San Diego, CA;

Power of Attorney: The patent practitioners associated with Customer Number 28977

Domestic Priority data as claimed by applicant

This application is a DIV of 17/327,568 05/21/2021
which is a CON of 16/912,590 06/25/2020 PAT 11,066,656
which is a CON of 15/226,489 08/02/2016 PAT 10,865,400
which is a DIV of 13/694,731 12/28/2012 PAT 9,447,401
which claims benefit of 61/796,208 11/01/2012
and claims benefit of 61/631,313 12/30/2011
and said 17/327,568 05/21/2021 is a CON of 16/824,572 03/19/2020 PAT 11,041,149
which is a CON of 15/226,489 08/02/2016 PAT 10,865,400
and said 17/327,568 05/21/2021 is a CON of 15/226,489 08/02/2016 PAT 10,865,400
and is a CON of 13/694,731 12/28/2012 PAT 9,447,401
This application is a DIV of 17/327,586 05/21/2021 PAT 12,037,618
and is a DIV of 16/912,590 06/25/2020 PAT 11,066,656
and is a DIV of 16/824,572 03/19/2020 PAT 11,041,149

page 1 of 4

which is a DIV of 13/694,731 12/28/2012 PAT 9,447,401
This application is a CON of 15/226,489 08/02/2016 PAT 10,865,400
and is a DIV of 13/694,731 12/28/2012 PAT 9,447,401

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: 09/25/2023

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 18/340,786**

Projected Publication Date: 01/04/2024

Non-Publication Request: No

Early Publication Request: No

Title

PH20 POLYPEPTIDE VARIANTS WITH A MODIFICATION AT POSITION 324 OF THE PH20
POLYPEPTIDE AND A METHOD OF MAKING THEREOF

Preliminary Class

424

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

page 2 of 4

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.

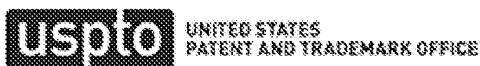
The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise 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.



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FEE ADDRESS CHANGE

APPLICATION #	FILING OR 371(C) DATE	REQUEST ID
18/340,786	06/23/2023	326253

The following fields have been changed to Customer Number 203235 on 12/12/2024 via Patent Center in view of the certification copied below that authorized the change.

- Maintenance Fee Address

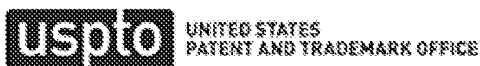
The address for Customer Number 203235 is:

203235 - Morgan, Lewis & Bockius LLP (Antares/Halozyme))
2222 Market Street
Philadelphia, PA 19103

I certify, in accordance with 37 CFR 1.4(d)(4), that I am :

An attorney or Agent of Record registered to practice before the Patent and Trademark Office who has been given power of attorney in this application

Signature	Name	Registration #
/John L. Hemmer/	John Hemmer	58752



P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

CORRESPONDENCE ADDRESS CHANGE

APPLICATION #	FILING OR 371(C) DATE	REQUEST ID
18/340,786	06/23/2023	326253

The following fields have been changed to Customer Number 203235 on 12/12/2024 via Patent Center in view of the certification copied below that authorized the change.

- Correspondence Address

The address for Customer Number 203235 is:

203235 - Morgan, Lewis & Bockius LLP (Antares/Halozyme))
2222 Market Street
Philadelphia , PA 19103

I certify, in accordance with 37 CFR 1.4(d)(4), that I am :

An attorney or Agent of Record registered to practice before the Patent and Trademark Office who has been given power of attorney in this application

Signature	Name	Registration #
/John L. Hemmer/	John Hemmer	58752



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.
18/340,786	06/23/2023	Ge WEI	63995-01-5105-US-17	6432
203235 7590 03/17/2025 Morgan, Lewis & Bockius LLP (Antares/Halozyne)) 2222 Market Street Philadelphia, PA 19103			EXAMINER WANG, CHANG YU	
			ART UNIT 1675	PAPER NUMBER
			NOTIFICATION DATE 03/17/2025	DELIVERY MODE 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):

judith.troilo@morganlewis.com
phpatentcorrespondence@morganlewis.com



United States Patent and Trademark Office

Office of the Commissioner for Patents

Morgan, Lewis & Bockius LLP (Antares/Halozyme))
2222 Market Street
Philadelphia, PA 19103

Ge WEI, et al.
San Diego, CA

In re: Application Serial No. 18340786

NOTICE OF FAILURE TO FILE PART B – FEE(S) TRANSMITTAL, FORM PTOL-85 PART B, OR EQUIVALENT

On August 14, 2024, a notice of allowance was mailed in the present application, 18/340786, notifying the applicant that an issue fee payment was required to be timely submitted in order for the patent to issue. The notice stated, in part (emphasis in underlining added):

HOW TO REPLY TO THIS NOTICE:

*

*

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 PUBLICATIONS FEE (if required).

An issue fee payment for the present application was received on August 16, 2024. The Office, however, has not received a properly signed Part B – Fee(s) Transmittal, Form PTOL-85 Part B, or its equivalent.

A properly signed and completed Part B – Fee(s) Transmittal, Form PTOL-85 Part B, or its equivalent, is required to be filed in response to this notice. A properly signed and completed, Part B – Fee(s) Transmittal, Form PTOL-85 Part B, or its equivalent, may be filed via the Office's electronic filing system EFS-Web, or via first class mail with the United States Postal Service, per the instructions detailed on the Part B – Fee(s) Transmittal, Form PTOL-85 Part B.

37 CFR 1.33(b) requires that correspondence with the Office concerning a patent application must be signed in accordance with 37 CFR 1.33(b)(1)-(3). **To be proper, a Part B Fee(s) Transmittal, Form PTOL-85 Part B, or its equivalent, must be signed by one of the parties identified in 37 CFR 1.33(b)(1)-(3).**

THE ISSUANCE OF THE PATENT WILL BE DELAYED UNTIL A PROPER RESPONSE TO THIS NOTICE IS RECEIVED.

If you have any questions or concerns, I can be reached by telephone at (703)756-1607, or by email at GERALD.CARTER@USPTO.GOV

/GERALD V. CARTER/

P.O. Box 1450, Alexandria, VA 22313-1450 • www.uspto.gov

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

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 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. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

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

28977 7590 08/14/2024
Morgan, Lewis & Bockius LLP (PH)
2222 Market Street
Philadelphia, PA 19103

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 the USPTO patent electronic filing system 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.
-----------------	-------------	----------------------	---------------------	------------------

18/340,786 06/23/2023 Ge WEI 63995-01-5105-US-17 6432

TITLE OF INVENTION: PH20 POLYPEPTIDE VARIANTS WITH A MODIFICATION AT POSITION 324 OF THE PH20 POLYPEPTIDE AND A METHOD OF MAKING 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	11/14/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
WANG, CHANG YU	1649	424-094620

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/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or 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,

1 Morgan, Lewis & Bockius LLP

(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
HALOZYME, INC.

(B) RESIDENCE: (CITY and STATE OR COUNTRY)
San Diego, CA

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government4a. Fees submitted: ☒ Issue Fee ☐ Publication Fee (if required)

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

☒ Electronic Payment via the USPTO patent electronic filing system ☐ 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. 50-0310

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 /Robert Smyth

Date March 19, 2025

Typed or printed name Robert Smyth

Registration No. 50801



UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
18/340,786

RECEIPT DATE / TIME
03/19/2025 02:45:37 PM Z ET

ATTORNEY DOCKET #
63995-01-5105-US-17

Title of Invention

PH20 POLYPEPTIDE VARIANTS WITH A MODIFICATION AT POSITION 324 OF THE PH20 POLYPEPTIDE AND A METHOD OF MAKING THEREOF

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 6432

FILED BY Robert Smyth

PATENT CENTER # 69641757

FILING DATE 06/23/2023

CUSTOMER # 203235

FIRST NAMED
INVENTOR Ge WEI

CORRESPONDENCE
ADDRESS -

AUTHORIZED BY Robert Smyth

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
20250319_02Issuefeepayment.pdf	1	Issue Fee Payment (PTO-85B)	126 KB
20250319_01Transmittal.pdf	2	Transmittal Letter	79 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
20250319_02Issuefeepayment.pdf	F05C42F38C21354B7F9145398F7366C432901523DA6C91CFE0 2DA7ECDA35407E2398F2AEB70E880A8A5DCC22EDBF3B607 D7ED7BE72A5290888CDF19DF8DC94A3
20250319_01Transmittal.pdf	4498CADF85CCA6109E1445FC88DD52BC7C23A5C55221DA32

2E425D6EC443FA505D2FB1CD74F71C36AC077119472A63BA2
32E15F93E2E5831B01B0EB750EAB851

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 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.



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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/340,786	07/29/2025	12371685	63995-01-5105-US-17	6432

203235 7590 07/16/2025

Morgan, Lewis & Bockius LLP (Antares/Halozyme))
2222 Market Street
Philadelphia, PA 19103

ISSUE NOTIFICATION

The projected patent number and issue date are specified above. The patent will issue electronically. The electronically issued patent is the official patent grant pursuant to 35 U.S.C. § 153. The patent may be accessed on or after the issue date through Patent Center at <https://patentcenter.uspto.gov/>. The patent will be available in both the public and the private sides of Patent Center. Further assistance in electronically accessing the patent, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-888-217-9197.

The USPTO is implementing electronic patent issuance with a transition period, during which period the USPTO will mail a ceremonial paper copy of the electronic patent grant to the correspondence address of record. Additional copies of the patent (i.e., certified and presentation copies) may be ordered for a fee from the USPTO's Certified Copy Center at <https://certifiedcopycenter.uspto.gov/index.html>. The Certified Copy Center may be reached at (800)972-6382.

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 225 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 Center (<https://patentcenter.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 Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

INVENTOR(s) (Please see PATENT CENTER site <https://patentcenter.uspto.gov> for additional inventors):

Ge WEI, San Diego, CA;
H. Michael Shepard, Eugene, OR;
Qiping Zhao, San Diego, CA;
Robert James Connor, Oceanside, CA;

APPLICANT(s) (Please see PATENT CENTER site <https://patentcenter.uspto.gov> for additional applicants):

HALOZYME, INC., San Diego, CA;

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/340,786	06/23/2023	Ge WEI	63995-01-5105-US-17	6432
203235 7590 07/29/2025 Morgan, Lewis & Bockius LLP (Antares/Halozyne)) 2222 Market Street Philadelphia, PA 19103			EXAMINER WANG, CHANG YU	
			ART UNIT	PAPER NUMBER
			1675	
			NOTIFICATION DATE	DELIVERY MODE
			07/29/2025	ELECTRONIC

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