UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,

Petitioner

v.

HALOZYME, INC.,

Patent Owner

Case PGR2025-00017 | U.S. Patent No. 12,110,520	Case PGR2025-00042 | U.S. Patent No. 12,037,618
Case PGR2025-00024 | U.S. Patent No. 12,060,590	Case PGR2025-00046 | U.S. Patent No. 12,091,692
Case PGR2025-00030 | U.S. Patent No. 12,054,758	Case PGR2025-00050 | U.S. Patent No. 12,077,791
Case PGR2025-00033 | U.S. Patent No. 12,049,652	Case PGR2025-00052 | U.S. Patent No. 12,264,345
Case PGR2025-00039 | U.S. Patent No. 12,104,185	Case PGR2025-00053 | U.S. Patent No. 12,195,773

quinn emanuel
quinn emanuel urquhart & sullivan, llp

Halozyme

Sterne Kessler
STERNE KESSLER GOLDSTEIN & FOX

Halozyme EX2500
Merck v. Halozyme
PGR2025-00053

Halozyme Patents

Case PGR2025-00017	U.S. Patent No. 12,110,520
Case PGR2025-00024	U.S. Patent No. 12,060,590
Case PGR2025-00030	U.S. Patent No. 12,054,758
Case PGR2025-00033	U.S. Patent No. 12,049,652
Case PGR2025-00039	U.S. Patent No. 12,104,185
Case PGR2025-00042	U.S. Patent No. 12,037,618
Case PGR2025-00046	U.S. Patent No. 12,091,692
Case PGR2025-00050	U.S. Patent No. 12,077,791
Case PGR2025-00052	U.S. Patent No. 12,264,345
Case PGR2025-00053	U.S. Patent No. 12,195,773

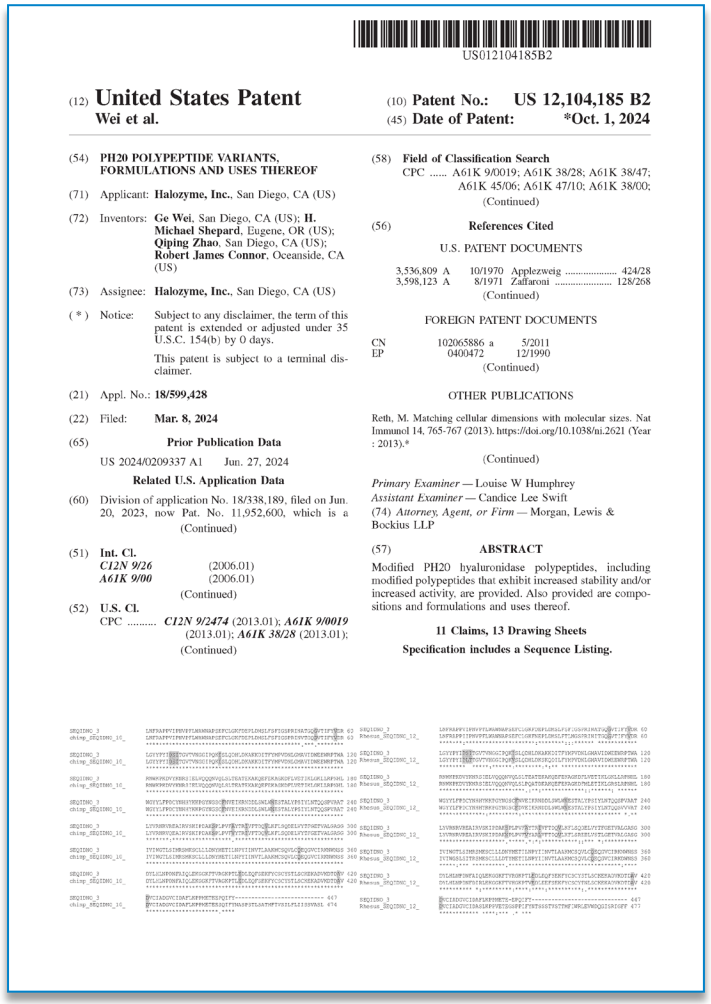
Halozyme

Halozyme Patents

PGR No.	Patent No.	Patent Category
PGR2025-00039	12,104,185	Method For Increasing Delivery Of A Therapeutic Agent
PGR2025-00053	12,195,773	Soluble Human PH20 Polypeptide
PGR2025-00042	12,037,618	Petitioner: Enzymatic Activity Not Necessarily Required
PGR2025-00046	12,091,692	Petitioner: Enzymatic Activity Not Necessarily Required
PGR2025-00017	12,110,520	Modified PH20 Polypeptide
PGR2025-00024	12,060,590	Modified PH20 Polypeptide
PGR2025-00030	12,054,758	Modified PH20 Polypeptide
PGR2025-00033	12,049,652	Modified PH20 Polypeptide
PGR2025-00050	12,077,791	Increased Hyaluronidase Activity
PGR2025-00052	12,264,345	Hyaluronidase Domain

Halozyme Patents Category I
Method For Increasing Delivery

’185 Patent



US012104185B2

(12) **United States Patent**
Wei et al.

(10) **Patent No.: US 12,104,185 B2**
(45) **Date of Patent: *Oct. 1, 2024**

(54) **PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF**

(71) Applicant: **Halozyme, Inc.**, San Diego, CA (US)

(72) Inventors: **Ge Wei**, San Diego, CA (US); **H. Michael Shepard**, Eugene, OR (US); **Qiping Zhao**, San Diego, CA (US); **Robert James Connor**, Oceanside, CA (US)

(73) Assignee: **Halozyme, Inc.**, San Diego, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.
This patent is subject to a terminal disclaimer.

(21) Appl. No.: **18/599,428**

(22) Filed: **Mar. 8, 2024**

(65) **Prior Publication Data**
US 2024/0209337 A1 Jun. 27, 2024

Related U.S. Application Data

(60) Division of application No. 18/338,189, filed on Jun. 20, 2023, now Pat. No. 11,952,600, which is a
(Continued)

(51) **Int. Cl.**
C12N 9/26 (2006.01)
A61K 9/00 (2006.01)
(Continued)

(52) **U.S. Cl.**
CPC ***C12N 9/2474*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 38/28*** (2013.01);
(Continued)

(58) **Field of Classification Search**
CPC A61K 9/0019; A61K 38/28; A61K 38/47; A61K 45/06; A61K 47/10; A61K 38/00;
(Continued)

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,536,809 A 10/1970 Applezweig 424/28
3,598,123 A 8/1971 Zaffaroni 128/268
(Continued)

FOREIGN PATENT DOCUMENTS

CN 102065886 a 5/2011
EP 0400472 12/1990
(Continued)

OTHER PUBLICATIONS

Reth, M. Matching cellular dimensions with molecular sizes. Nat Immunol 14, 765-767 (2013). https://doi.org/10.1038/ni.2621 (Year : 2013).*
(Continued)

Primary Examiner — Louise W Humphrey
Assistant Examiner — Candice Lee Swift
(74) *Attorney, Agent, or Firm* — Morgan, Lewis & Bockius LLP

(57) **ABSTRACT**

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

11 Claims, 13 Drawing Sheets

Specification includes a Sequence Listing.

PGR2025-00039

Claim 1

1. A method for increasing delivery of a therapeutic agent to a subject, comprising administering to a subject a pharmaceutical composition comprising:

(a) a therapeutic agent; and

(b) a modified PH20 polypeptide comprising an amino acid sequence, wherein:

i. 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 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

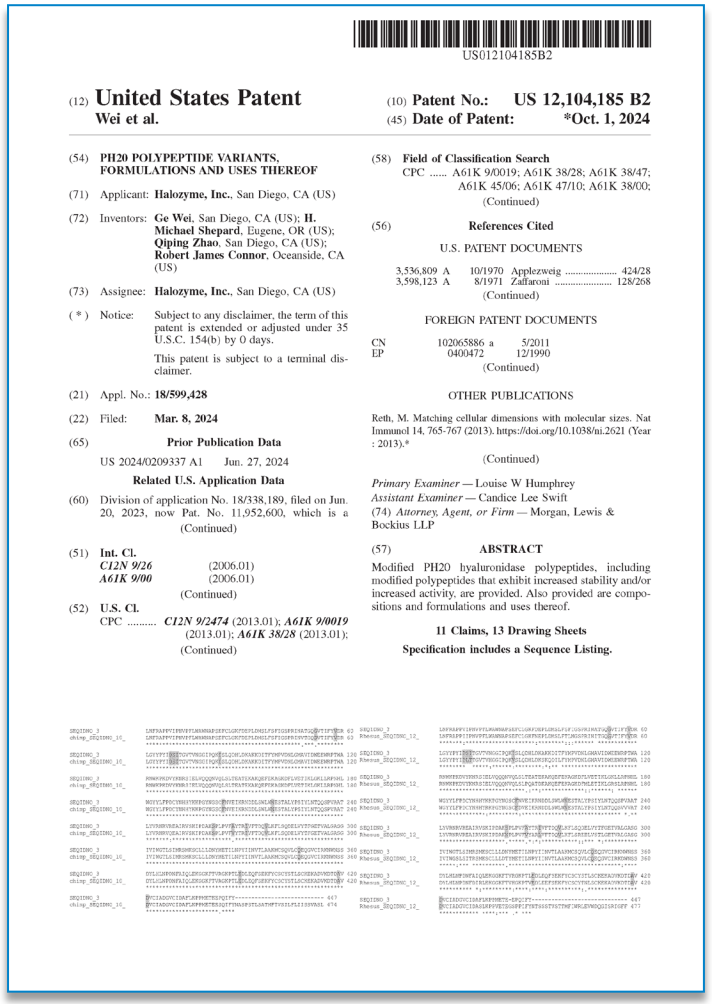
ii. the amino acid sequence of the modified PH20 polypeptide comprises an amino acid modification at a position corresponding to position 320 with reference to amino acid positions set forth in SEQ ID NO: 3; and

iii. the modification at **position 320** is a replacement selected from the group consisting of H, K, R and S.

EX. 1001

Patent Disclosure

’185 Patent



US012104185B2

(12) **United States Patent**
Wei et al.

(10) **Patent No.: US 12,104,185 B2**
(45) **Date of Patent: *Oct. 1, 2024**

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(72) Inventors: **Ge Wei**, San Diego, CA (US); **H. Michael Shepard**, Eugene, OR (US); **Qiping Zhao**, San Diego, CA (US); **Robert James Connor**, Oceanside, CA (US)

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C12N 9/26 (2006.01)
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(Continued)

(52) **U.S. Cl.**
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(Continued)

(58) **Field of Classification Search**
CPC A61K 9/0019; A61K 38/28; A61K 38/47; A61K 45/06; A61K 47/10; A61K 38/00;
(Continued)

(56) **References Cited**

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(Continued)

FOREIGN PATENT DOCUMENTS

CN 102065886 a 5/2011
EP 0400472 12/1990
(Continued)

OTHER PUBLICATIONS

Reth, M. Matching cellular dimensions with molecular sizes. Nat Immunol 14, 765-767 (2013). https://doi.org/10.1038/ni.2621 (Year : 2013).*

(Continued)

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11 Claims, 13 Drawing Sheets

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PGR2025-00039

H. Methods of Treatment and Combination Therapy

Provided herein are methods and uses of any of the modified PH20 polypeptides provided herein that exhibit hyaluronidase activity based on its ability to degrade glycosaminoglycan(s) such as hyaluronan. Due to such activity, the modified PH20 polypeptides can be used as a spreading factor to increase the delivery and/or bioavailability of subcutaneously administered therapeutic agents. Delivery of

-39 PGR, EX. 1001, 174:19-28.

Similarity To Sequence Is A Common Structural Feature

"CJ disputes that similarity to the consensus sequence defines a common structural feature, citing several articles as indicating that a promoter closer to the consensus sequence will not always be stronger than one farther from that sequence."

Ajinomoto Co. v. Int'l Trade Comm'n, 932 F.3d 1342, 1360 (Fed. Cir. 2019).

"CJ's argument both assumes too strict a legal standard and reads too much into its cited references. 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.'"

Ajinomoto Co. v. Int'l Trade Comm'n, 932 F.3d 1342, 1360 (Fed. Cir. 2019).

under function-way-result framework;

increased activity of YddG protein at least partly contributed to enhanced resistance of later strains of accused product;

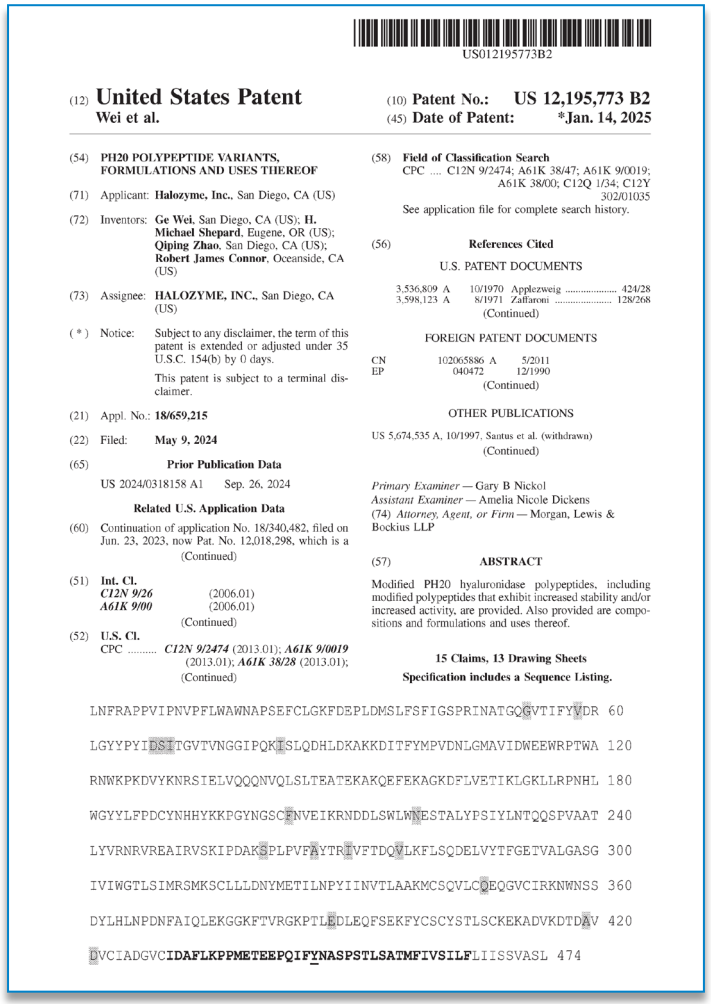
Taranto, Circuit Judge.

Ajinomoto Co., Inc. and Ajinomoto Heartland Inc. (collectively, Ajinomoto) filed a complaint against CJ

WESTLAW © 2026 Thomson Reuters. No claim to original U.S. Government Works.

Halozyme Patents Category II
Soluble Human PH20 Polypeptide

’773 Patent



US012195773B2

(12) **United States Patent**
Wei et al.

(10) **Patent No.: US 12,195,773 B2**
(45) **Date of Patent: *Jan. 14, 2025**

(54) **PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF**

(71) Applicant: **Halozyme, Inc.**, San Diego, CA (US)

(72) Inventors: **Ge Wei**, San Diego, CA (US); **H. Michael Shepard**, Eugene, OR (US); **Qiping Zhao**, San Diego, CA (US); **Robert James Connor**, Oceanside, CA (US)

(73) Assignee: **HALOZYME, INC.**, San Diego, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **18/659,215**

(22) Filed: **May 9, 2024**

(65) **Prior Publication Data**

US 2024/0318158 A1 Sep. 26, 2024

Related U.S. Application Data

(60) Continuation of application No. 18/340,482, filed on Jun. 23, 2023, now Pat. No. 12,018,298, which is a (Continued)

(51) **Int. Cl.**
C12N 9/26 (2006.01)
A61K 9/00 (2006.01)
(Continued)

(52) **U.S. Cl.**
CPC ***C12N 9/2474*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 38/28*** (2013.01);
(Continued)

(58) **Field of Classification Search**
CPC C12N 9/2474; A61K 38/47; A61K 9/0019; A61K 38/00; C12Q 1/34; C12Y 302/01035
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,536,809 A 10/1970 Applezweig 424/28
3,598,123 A 8/1971 Zaffaroni 128/268
(Continued)

FOREIGN PATENT DOCUMENTS

CN 102065886 A 5/2011
EP 040472 12/1990
(Continued)

OTHER PUBLICATIONS

US 5,674,535 A, 10/1997, Santus et al. (withdrawn)
(Continued)

Primary Examiner — Gary B Nickol
Assistant Examiner — Amelia Nicole Dickens
(74) *Attorney, Agent, or Firm* — Morgan, Lewis & Bockius LLP

(57) **ABSTRACT**

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

15 Claims, 13 Drawing Sheets
Specification includes a Sequence Listing.

LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSLFSFIGSPRINATGQGVTIFYVDR 60

LGYYPYIDSITGVTVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVIDWEEWRPTWA 120

RNWKPKDVYKNRSIELVQQQNVQLSLTEATEKAKQEFEKAGKDFLVETIKLGKLLRPNHL 180

WGYYLFPDCYNHHYKKPGYNGSCFNVEIKRNDDLSWLWNESTALYPSIYLNTQQSPVAAT 240

LYVRNRVREAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDELVYTFGETVALGASG 300

IVIWGTLSIMRSMKSCLLLDNYMETILNPYIINVTLAAKMCSQVLCQEQGVCIRKNWNSS 360

DYLHLNPDNFAIQLEKGGKFTVRGKPTLEDLEQFSEKFYCSCYSTLSCKEKADVKDTDAV 420

DVCIADGVC**IDAFLKPPMETEEPQIFYNASPSTLSATMFIVSILF**LIISSVASL 474

PGR2025-00053

Claims 1 and 15

1. **A soluble human PH20 polypeptide** comprising: a modification at a position aligned to position 320 with reference to the amino acid positions set forth in SEQ ID NO: 3, and 19 or less additional amino acid modifications, after alignment with SEQ ID NO: 3 to maximize the number of identical residues, wherein: modifications comprise insertions, deletions, and replacements, and **the modification at position 320 is a replacement selected from the group consisting of H, K, and R**.

15. A method for manufacture of the soluble human PH20 polypeptide of claim **1**, comprising:

preparing a plasmid DNA containing a cDNA encoding the soluble human PH20 polypeptide amino acid sequence,

transfecting the plasmid DNA into a host cell;

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

harvesting the protein from the culture.

-53 PGR, EX. 1001

Patent Disclosure

’773 Patent

US012195773B2

(12) **United States Patent**
Wei et al.

(10) **Patent No.: US 12,195,773 B2**
(45) **Date of Patent: *Jan. 14, 2025**

(54) **PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF**

(71) Applicant: **Halozyme, Inc.**, San Diego, CA (US)

(72) Inventors: **Ge Wei**, San Diego, CA (US); **H. Michael Shepard**, Eugene, OR (US); **Qiping Zhao**, San Diego, CA (US); **Robert James Connor**, Oceanside, CA (US)

(73) Assignee: **HALOZYME, INC.**, San Diego, CA (US)

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(22) Filed: **May 9, 2024**

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US 2024/0318158 A1 Sep. 26, 2024

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C12N 9/26 (2006.01)
A61K 9/00 (2006.01)
(Continued)

(52) **U.S. Cl.**
CPC ..... ***C12N 9/2474*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 38/28*** (2013.01); (Continued)

(58) **Field of Classification Search**
CPC C12N 9/2474; A61K 38/47; A61K 9/0019; A61K 38/00; C12Q 1/34; C12Y 302/01035
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3,598,123 A 8/1971 Zaffaroni 128/268
(Continued)

FOREIGN PATENT DOCUMENTS

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OTHER PUBLICATIONS

US 5,674,535 A, 10/1997, Santus et al. (withdrawn)
(Continued)

Primary Examiner — Gary B Nickol
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(74) *Attorney, Agent, or Firm* — Morgan, Lewis & Bockius LLP

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15 Claims, 13 Drawing Sheets

Specification includes a Sequence Listing.

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LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSLFSFIGSPRINATGQGVTIFYVDR 60
LGYYPYIDSITGVTVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVIDWEEWRPTWA 120
RNWKPKDVYKNRSIELVQQQNVQLSLTEATEKAKQEFEKAGKDFLVETIKLGKLLRPNHL 180
WGYYLFPDCYNHHYKKPGYNGSCFNVEIKRNDDLSWLWNESTALYPSIYLNTQQSPVAAT 240
LYVRNRVREAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDELVYTFGETVALGASG 300
IVIWGTLSIMRSMKSCLLLDNYMETILNPYIINVTLAAKMCSQVLCQEQGVCIRKNWNSS 360
DYLHLNPDNFAIQLEKGGKFTVRGKPTLEDLEQFSEKFYCSCYSTLSCKEKADVKDTDAV 420
DVCIADGVCIDAFLKPPMETEEPQIFYNASPSTLSATMFIVSILFLIISSVASL 474
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PGR2025-00053

As used herein, soluble human PH20 (sHuPH20) includes human PH20 polypeptides that lack a contiguous sequence of amino acids from the C-terminus of human PH20 that includes all or a portion of the glycosylphosphatidylinositol (GPI) anchor sequence (C-terminally truncated PH20 polypeptides) such that upon expression, the polypeptides are soluble under physiological conditions. For example,

-53 PGR, EX. 1001, 45:24-30

sheep or cows. Exemplary of such soluble hyaluronidases are soluble human PH20 (SEQ ID NOs: 3 or 32-66). Other soluble hyaluronidases include ovine (SEQ ID NOs:25-27) and bovine (SEQ ID NO:16 or 18) PH20.

-53 PGR, EX. 1001, 45:20-23

Petitioner's Arguments About Unclaimed Functions Are Irrelevant

Trials@uspto.gov
571-272-7822

Paper: 13
Date: March 22, 2023

UNITED STATES PATENT AND TRADEMARK OFFICE

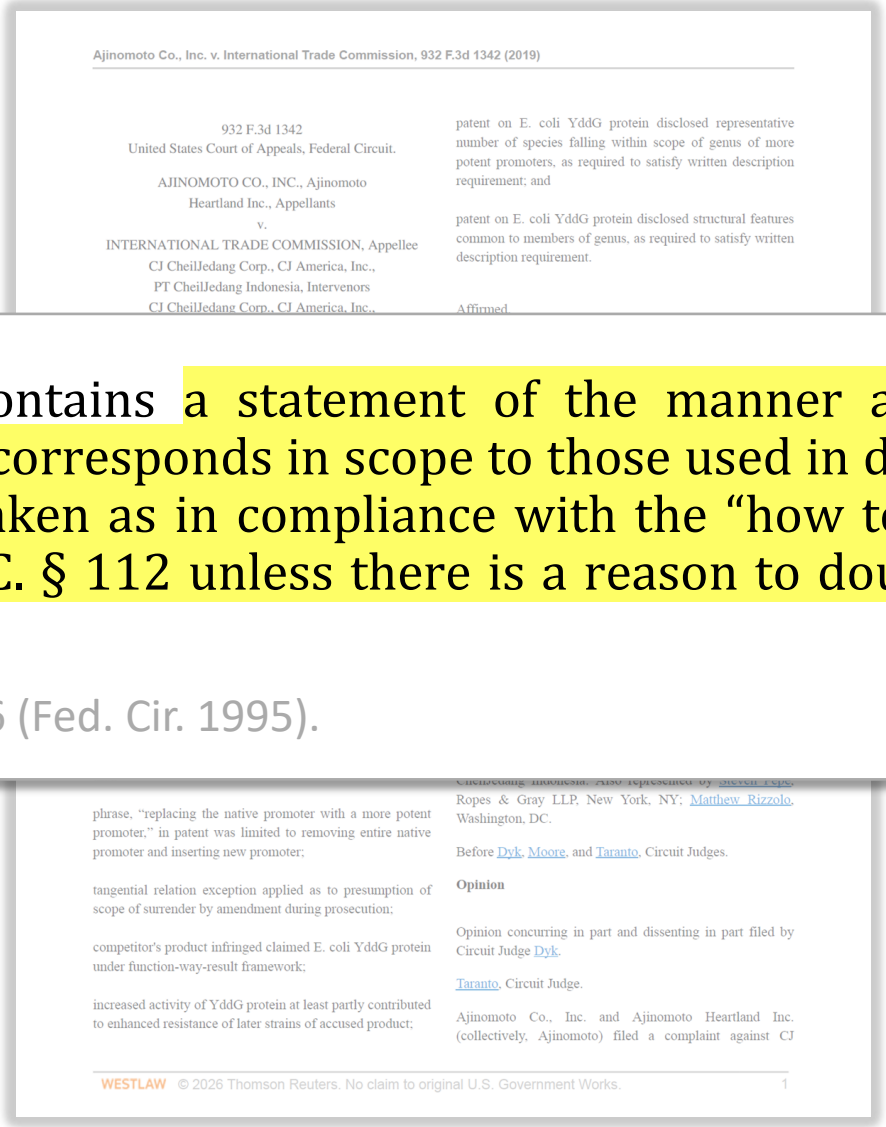
BEFORE THE PATENT TRIAL AND APPEAL BOARD

Petitioner's Section 112 argument improperly "focuses on certain functional characteristics disclosed in the Specification that are not recited in the challenged claims, and therefore, lacks sufficient merit in the context of the challenged claims."

Boehringer Ingelheim Animal Health USA Inc. v. Kansas State Univ. Res. Foundation ("Boehringer II") PGR2022-00021, Paper 13, 25-26 (P.T.A.B. Mar. 22, 2023).

35 U.S.C. § 324

Claims Are Enabled


Ajinomoto Co., Inc. v. International Trade Commission, 932 F.3d 1342 (2019)

932 F.3d 1342
United States Court of Appeals, Federal Circuit.

AJINOMOTO CO., INC., Ajinomoto Heartland Inc., Appellants
v.
INTERNATIONAL TRADE COMMISSION, Appellee
CJ CheilJedang Corp., CJ America, Inc., PT CheilJedang Indonesia, Intervenors
CJ CheilJedang Corp., CJ America, Inc.,

patent on E. coli YddG protein disclosed representative number of species falling within scope of genus of more potent promoters, as required to satisfy written description requirement; and

patent on E. coli YddG protein disclosed structural features common to members of genus, as required to satisfy written description requirement.

Affirmed.

phrase, "replacing the native promoter with a more potent promoter," in patent was limited to removing entire native promoter and inserting new promoter;

tangential relation exception applied as to presumption of scope of surrender by amendment during prosecution;

competitor's product infringed claimed E. coli YddG protein under function-way-result framework;

increased activity of YddG protein at least partly contributed to enhanced resistance of later strains of accused product;

Ropes & Gray LLP, New York, NY; Matthew Rizzolo, Washington, DC.

Before Dyk, Moore, and Taranto, Circuit Judges.

Opinion

Opinion concurring in part and dissenting in part filed by Circuit Judge Dyk.

Taranto, Circuit Judge.

Ajinomoto Co., Inc. and Ajinomoto Heartland Inc. (collectively, Ajinomoto) filed a complaint against CJ

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"A specification which contains a statement of the manner and process of using the invention in terms which corresponds in scope to those used in defining the subject sought to be patented must be taken as in compliance with the "how to use" requirement of the first paragraph of 35 U.S.C. § 112 unless there is a reason to double the objective truth of the statement."

In re Brana, 51 F.3d 1560, 1566 (Fed. Cir. 1995).

Misfolding/Aggregation From Mutation Is Rare

Halozyme Expert | **Dr. Petsko**

"That would not be the case for PH20."

EX. 1131 (Petsko), 42:6-7

"… usually not the case for most mutation." and "… it is rare."

EX. 1131 (Petsko), 40:18-24; 197:6-15

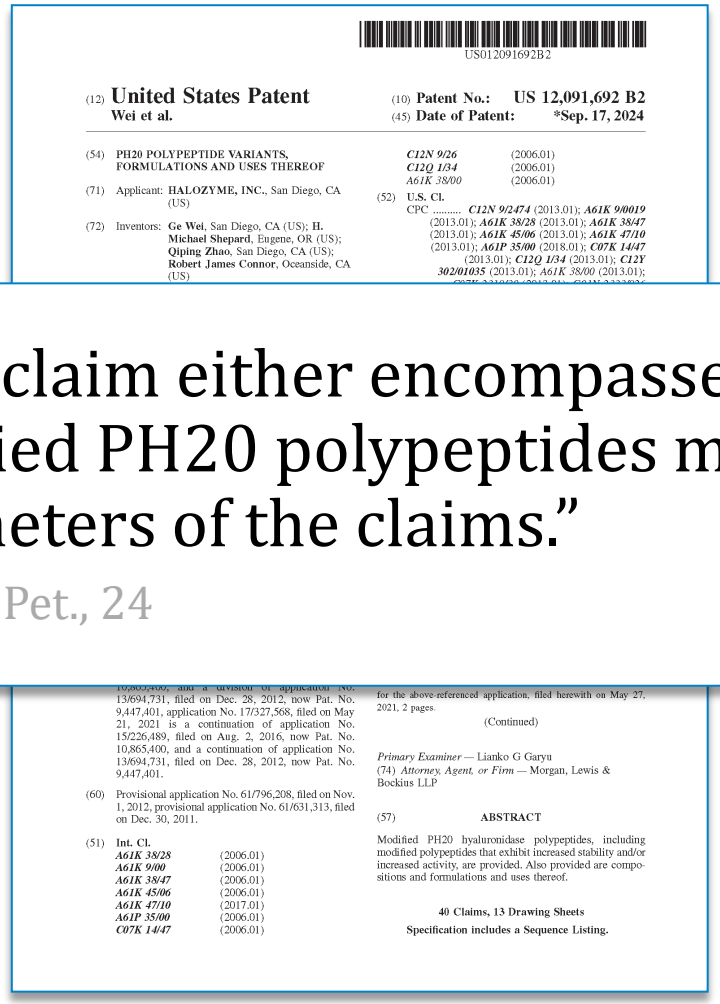
"… not a common consequence"; "If I make, typically, 100 mutations in a protein, okay, one or two might do that. None of them might do that."

EX. 1131 (Petsko), 48:23-49:8

Halozyme Patents Category III

Petitioner Agrees Enzymatic Activity Not Necessarily Required

’692 Patent



US012091692B2

(12) **United States Patent**
Wei et al.

(10) **Patent No.: US 12,091,692 B2**
(45) **Date of Patent: *Sep. 17, 2024**

(54) **PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF**

(71) Applicant: **HALOZYME, INC.**, San Diego, CA (US)

(72) Inventors: **Ge Wei**, San Diego, CA (US); **H. Michael Shepard**, Eugene, OR (US); **Qiping Zhao**, San Diego, CA (US); **Robert James Connor**, Oceanside, CA (US)

C12N 9/26 (2006.01)
C12Q 1/34 (2006.01)
A61K 38/00 (2006.01)

(52) **U.S. Cl.**
CPC ***C12N 9/2474*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 38/28*** (2013.01); ***A61K 38/47*** (2013.01); ***A61K 45/06*** (2013.01); ***A61K 47/10*** (2013.01); ***A61P 35/00*** (2018.01); ***C07K 14/47*** (2013.01); ***C12Q 1/34*** (2013.01); ***C12Y 302/01035*** (2013.01); *A61K 38/00* (2013.01);

13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, application No. 17/327,568, filed on May 21, 2021 is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, and a continuation of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401.

(60) Provisional application No. 61/796,208, filed on Nov. 1, 2012, provisional application No. 61/631,313, filed on Dec. 30, 2011.

(51) **Int. Cl.**
A61K 38/28 (2006.01)
A61K 9/00 (2006.01)
A61K 38/47 (2006.01)
A61K 45/06 (2006.01)
A61K 47/10 (2017.01)
A61P 35/00 (2006.01)
C07K 14/47 (2006.01)

for the above-referenced application, filed herewith on May 27, 2021, 2 pages.

(Continued)

Primary Examiner — Lianko G Garyu
(74) *Attorney, Agent, or Firm* — Morgan, Lewis & Bockius LLP

(57) **ABSTRACT**

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40 Claims, 13 Drawing Sheets
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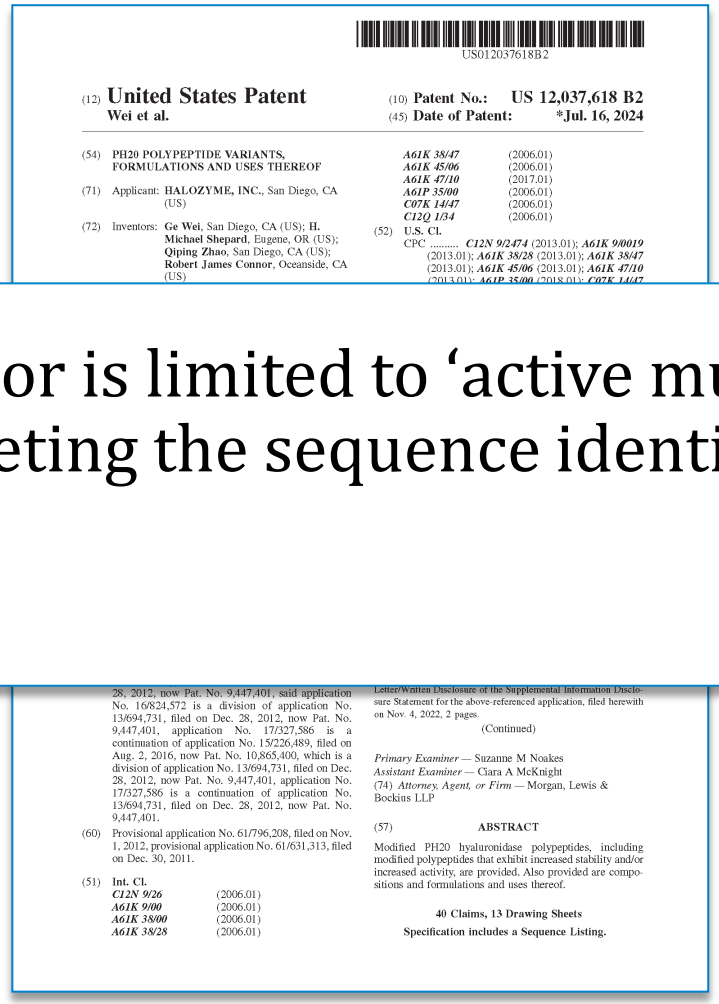
PGR2025-00046

’618 Patent



US012037618B2

(12) **United States Patent**
Wei et al.

(10) **Patent No.: US 12,037,618 B2**
(45) **Date of Patent: *Jul. 16, 2024**

(54) **PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF**

(71) Applicant: **HALOZYME, INC.**, San Diego, CA (US)

(72) Inventors: **Ge Wei**, San Diego, CA (US); **H. Michael Shepard**, Eugene, OR (US); **Qiping Zhao**, San Diego, CA (US); **Robert James Connor**, Oceanside, CA (US)

A61K 38/47 (2006.01)
A61K 45/06 (2006.01)
A61K 47/10 (2017.01)
A61P 35/00 (2006.01)
C07K 14/47 (2006.01)
C12Q 1/34 (2006.01)

(52) **U.S. Cl.**
CPC ***C12N 9/2474*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 38/28*** (2013.01); ***A61K 38/47*** (2013.01); ***A61K 45/06*** (2013.01); ***A61K 47/10***

28, 2012, now Pat. No. 9,447,401, said application No. 16/824,572 is a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, application No. 17/327,586 is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, which is a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, application No. 17/327,586 is a continuation of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401.

(60) Provisional application No. 61/796,208, filed on Nov. 1, 2012, provisional application No. 61/631,313, filed on Dec. 30, 2011.

(51) **Int. Cl.**
C12N 9/26 (2006.01)
A61K 9/00 (2006.01)
A61K 38/00 (2006.01)
A61K 38/28 (2006.01)

Letter/Written Disclosure of the Supplemental Information Disclosure Statement for the above-referenced application, filed herewith on Nov. 4, 2022, 2 pages.

(Continued)

Primary Examiner — Suzanne M Noakes
Assistant Examiner — Ciara A McKnight
(74) *Attorney, Agent, or Firm* — Morgan, Lewis & Bockius LLP

(57) **ABSTRACT**

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

40 Claims, 13 Drawing Sheets
Specification includes a Sequence Listing.

PGR2025-00042

> “Each claim either encompasses or is limited to ‘active mutant’ modified PH20 polypeptides meeting the sequence identity parameters of the claims.”
>
> -46 PGR, Pet., 24

’692 Patent Exemplary Claim
Petitioner Agrees Enzymatic Activity Not Necessarily Required

’692 Patent

US012091692B2

(12) **United States Patent**
Wei et al.

(10) **Patent No.: US 12,091,692 B2**
(45) **Date of Patent: *Sep. 17, 2024**

(54) **PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF**

(71) Applicant: **HALOZYME, INC.**, San Diego, CA (US)

(72) Inventors: **Ge Wei**, San Diego, CA (US); **H. Michael Shepard**, Eugene, OR (US); **Qiping Zhao**, San Diego, CA (US); **Robert James Connor**, Oceanside, CA (US)

(73) Assignee: **HALOZYME, INC.**, San Diego, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 700 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **17/327,568**

(22) Filed: **May 21, 2021**

(65) **Prior Publication Data**

US 2021/0284985 A1 Sep. 16, 2021

Related U.S. Application Data

(60) Continuation of application No. 16/912,590, filed on Jun. 25, 2020, now Pat. No. 11,066,656, which is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, which is a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, said application No. 16/912,590 is a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, application No. 17/327,568, filed on May 21, 2021 is a continuation of application No. 16/824,572, filed on Mar. 19, 2020, now Pat. No. 11,041,149, which is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, and a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, application No. 17/327,568, filed on May 21, 2021 is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, and a continuation of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401.

(60) Provisional application No. 61/796,208, filed on Nov. 1, 2012, provisional application No. 61/631,313, filed on Dec. 30, 2011.

(51) **Int. Cl.**

A61K 38/28	(2006.01)
A61K 9/00	(2006.01)
A61K 38/47	(2006.01)
A61K 45/06	(2006.01)
A61K 47/10	(2017.01)
A61P 35/00	(2006.01)
C07K 14/47	(2006.01)
C12N 9/26	(2006.01)
C12Q 1/34	(2006.01)
A61K 38/00	(2006.01)

(52) **U.S. Cl.**
CPC ***C12N 9/2474*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 38/28*** (2013.01); ***A61K 38/47*** (2013.01); ***A61K 45/06*** (2013.01); ***A61K 47/10*** (2013.01); ***A61P 35/00*** (2018.01); ***C07K 14/47*** (2013.01); ***C12Q 1/34*** (2013.01); ***C12Y 302/01035*** (2013.01); *A61K 38/00* (2013.01); *C07K 2319/30* (2013.01); *G01N 2333/926* (2013.01); *G01N 2333/928* (2013.01); *Y02A 50/30* (2018.01)

(58) **Field of Classification Search**
CPC C12N 9/2474; C12Y 302/01035
See application file for complete search history.

(56) **References Cited**

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Letter/Written Disclosure of the Information Disclosure Statement for the above-referenced application, filed herewith on May 27, 2021, 2 pages.

(Continued)

Primary Examiner — Lianko G Garyu
(74) *Attorney, Agent, or Firm* — Morgan, Lewis & Bockius LLP

(57) **ABSTRACT**

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

40 Claims, 13 Drawing Sheets

Specification includes a Sequence Listing.

PGR2025-00046

Claim 1

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

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NO: 3, 7 and 32-66;

amino acid modifications are selected from the group consisting of amino acid replacements(s), deletion(s), and/or insertion(s);

the modified PH20 polypeptide comprises **a modification at a position corresponding to position 313 with reference to amino acid positions of SEQ ID NO:**3;

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

the modified PH20 polypeptide has **at least 91% sequence identity** to the amino acid sequence selected from the group consisting of SEQ ID NO: 3, 7 and 32-66.

-46 PGR, EX. 1001

Halozyme Patents Category IV

’520 Patent

US012110520B2

(12) **United States Patent**
Wei et al.

(10) **Patent No.: US 12,110,520 B2**
(45) **Date of Patent: *Oct. 8, 2024**

(54) **PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF**

(71) Applicant: **HALOZYME, INC.**, San Diego, CA (US)

(72) Inventors: **Ge Wei**, San Diego, CA (US); **H. Michael Shepard**, Eugene, OR (US); **Qiping Zhao**, San Diego, CA (US); **Robert James Connor**, Oceanside, CA (US)

(73) Assignee: **Halozyme, Inc.**, San Diego, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1 day.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **18/068,418**

(22) Filed: **Dec. 19, 2022**

(65) **Prior Publication Data**

US 2023/0250409 A1 Aug. 10, 2023

Related U.S. Application Data

(60) Division of application No. 17/327,568, filed on May 21, 2021, which is a continuation of application No. 16/912,590, filed on Jun. 25, 2020, now Pat. No. 11,066,656, which is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, which is a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, said application No. 17/327,568 is a continuation of application No. 16/824,572, filed on Mar. 19, 2020, now Pat. No. 11,041,149, which is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, which is a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, said application No. 17/327,568 is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, which is a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, application No. 18/068,418 is a division of application No. 17/327,586, filed on May 21, 2021, now Pat. No. 12,037,618, which is a continuation of application No. 16/912,590, filed on Jun. 25, 2020, now Pat. No. 11,066,656, which is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, which is a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, said application No. 17/327,586 is a continuation of application No. 16/824,572, filed on Mar. 19, 2020, now Pat. No. 11,041,149, which is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, which is a continuation of application No. 13/694,731, filed on (Continued)

(51) **Int. Cl.**
C12N 9/26 (2006.01)
A61K 9/00 (2006.01)
A61K 38/00 (2006.01)
A61K 38/28 (2006.01)
A61K 38/47 (2006.01)
A61K 45/06 (2006.01)
A61K 47/10 (2017.01)
A61P 35/00 (2006.01)
C07K 14/47 (2006.01)
C12Q 1/34 (2006.01)

(52) **U.S. Cl.**
CPC ***C12N 9/2474*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 38/28*** (2013.01); ***A61K 38/47*** (2013.01); ***A61K 45/06*** (2013.01); ***A61K 47/10*** (2013.01); ***A61P 35/00*** (2018.01); ***C07K 14/47*** (2013.01); ***C12Q 1/34*** (2013.01); ***C12Y 302/01035*** (2013.01); *A61K 38/00* (2013.01); *C07K 2319/30* (2013.01); *G01N 2333/926* (2013.01); *G01N 2333/928* (2013.01); *Y02A 50/30* (2018.01)

(58) **Field of Classification Search**
CPC C12N 9/2474; A61P 35/00; A61K 9/0019; A61K 38/28; A61K 38/47; A61K 47/10; A61K 38/00; C07K 14/47; C07K 2319/30; C12Q 1/34; C12Y 302/01035; Y02A 50/30; G01N 2333/926; G01N 2333/928
See application file for complete search history.

(56) **References Cited**

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U.S. Appl. No. 16/930,766, filed Jul. 16, 2020, 2020/0368330, Nov. 26, 2020.
(Continued)

Primary Examiner — Suzanne M Noakes
Assistant Examiner — Ciara A McKnight
(74) *Attorney, Agent, or Firm* — Morgan, Lewis & Bockius LLP

(57) **ABSTRACT**

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

35 Claims, 13 Drawing Sheets

Specification includes a Sequence Listing.

PGR2025-00019

’758 Patent

US012054758B2

(12) **United States Patent**
Wei et al.

(10) **Patent No.: US 12,054,758 B2**
(45) **Date of Patent: *Aug. 6, 2024**

(54) **PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF**

(71) Applicant: **HALOZYME, INC.**, San Diego, CA (US)

(72) Inventors: **Ge Wei**, San Diego, CA (US); **H. Michael Shepard**, Eugene, OR (US); **Qiping Zhao**, San Diego, CA (US); **Robert James Connor**, Oceanside, CA (US)

(73) Assignee: **HALOZYME, INC.**, San Diego, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **18/066,960**

(22) Filed: **Dec. 15, 2022**

(65) **Prior Publication Data**

US 2023/0151346 A1 May 18, 2023

Related U.S. Application Data

(60) Division of application No. 17/327,568, filed on May 21, 2021, which is a continuation of application No. 16/912,590, filed on Jun. 25, 2020, now Pat. No. 11,066,656, which is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, which is a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, said application No. 17/327,568 is a continuation of application No. 16/824,572, filed on Mar. 19, 2020, now Pat. No. 11,041,149, which is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, said application No. 17/327,568 is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, and a continuation of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, application No. 18/066,960, filed on Dec. 15, 2022 is a division of application No. 17/327,568, filed on May 21, 2021, which is a continuation of application No. 16/912,590, filed on Jun. 25, 2020, now Pat. No. 11,066,656, and a continuation of application No. 16/824,572, filed on Mar. 19, 2020, now Pat. No. 11,041,149, and a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, and a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, application No. 18/066,960, filed on Dec. 15, 2022 is a division
(Continued)

(51) **Int. Cl.**
C12N 9/26 (2006.01)
A61K 9/00 (2006.01)
A61K 38/00 (2006.01)
A61K 38/28 (2006.01)
A61K 38/47 (2006.01)
A61K 45/06 (2006.01)
A61K 47/10 (2017.01)
A61P 3/04 (2006.01)
A61P 3/10 (2006.01)
A61P 11/00 (2006.01)
A61P 27/02 (2006.01)
A61P 29/00 (2006.01)
A61P 35/00 (2006.01)
A61P 43/00 (2006.01)
C07K 14/47 (2006.01)
C12Q 1/34 (2006.01)

(52) **U.S. Cl.**
CPC ***C12N 9/2474*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 38/28*** (2013.01); ***A61K 38/47*** (2013.01); ***A61K 45/06*** (2013.01); ***A61K 47/10*** (2013.01); ***A61P 35/00*** (2018.01); ***C07K 14/47*** (2013.01); ***C12Q 1/34*** (2013.01); ***C12Y 302/01035*** (2013.01); *A61K 38/00* (2013.01); *C07K 2319/30* (2013.01); *G01N 2333/926* (2013.01); *G01N 2333/928* (2013.01); *Y02A 50/30* (2018.01)

(58) **Field of Classification Search**
CPC combination set(s) only.
See application file for complete search history.

(56) **References Cited**

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3,598,123 A 8/1971 Zaffaroni 128/268
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Letter/Written Disclosure of the Information Disclosure Statement for the above-referenced application, filed herewith on Mar. 13, 2023, 2 pages.
(Continued)

Primary Examiner — Manjunath N Rao
Assistant Examiner — Ciara A McKnight
(74) *Attorney, Agent, or Firm* — Morgan, Lewis & Bockius LLP

(57) **ABSTRACT**

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

40 Claims, 13 Drawing Sheets

Specification includes a Sequence Listing.

PGR2025-00030

’590 Patent

US012060590B2

(12) **United States Patent**
Wei et al.

(10) **Patent No.: US 12,060,590 B2**
(45) **Date of Patent: Aug. 13, 2024**

(54) **PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF**

(71) Applicant: **HALOZYME, INC.**, San Diego, CA (US)

(72) Inventors: **Ge Wei**, San Diego, CA (US); **H. Michael Shepard**, Eugene, OR (US); **Qiping Zhao**, San Diego, CA (US); **Robert James Connor**, Oceanside, CA (US)

(73) Assignee: **HALOZYME, INC.**, San Diego, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **18/068,218**

(22) Filed: **Dec. 19, 2022**

(65) **Prior Publication Data**

US 2023/0295593 A1 Sep. 21, 2023

Related U.S. Application Data

(60) Division of application No. 17/327,568, filed on May 21, 2021, which is a continuation of application No. 16/912,590, filed on Jun. 25, 2020, now Pat. No. 11,066,656, and a continuation of application No. 16/824,572, filed on Mar. 19, 2020, now Pat. No. 11,041,149, and a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, and a continuation of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, application No. 18/068,218, filed on Dec. 19, 2022 is a division of application No. 16/912,590, filed on Jun. 25, 2020, now Pat. No. 11,066,656, and a division of application No. 16/824,572, filed on Mar. 19, 2020, now Pat. No. 11,041,149, and a division of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, and a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, and a division of application No. 17/327,586, filed on May 21, 2021, which is a continuation of application No. 16/912,590, filed on Jun. 25, 2020, now Pat. No. 11,066,656, which is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, which is a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, said application No. 16/912,590 is a division of application No.
(Continued)

(51) **Int. Cl.**
C12N 9/26 (2006.01)
A61K 9/00 (2006.01)
A61K 38/00 (2006.01)
A61K 38/28 (2006.01)
A61K 38/47 (2006.01)
A61K 45/06 (2006.01)
A61K 47/10 (2017.01)
A61P 3/04 (2006.01)
A61P 3/10 (2006.01)
A61P 11/00 (2006.01)
A61P 27/02 (2006.01)
A61P 29/00 (2006.01)
A61P 35/00 (2006.01)
A61P 43/00 (2006.01)
C07K 14/47 (2006.01)
C12Q 1/34 (2006.01)

(52) **U.S. Cl.**
CPC ***C12N 9/2474*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 38/28*** (2013.01); ***A61K 38/47*** (2013.01); ***A61K 45/06*** (2013.01); ***A61K 47/10*** (2013.01); ***A61P 35/00*** (2018.01); ***C07K 14/47*** (2013.01); ***C12Q 1/34*** (2013.01); ***C12Y 302/01035*** (2013.01); *A61K 38/00* (2013.01); *C07K 2319/30* (2013.01); *G01N 2333/926* (2013.01); *G01N 2333/928* (2013.01); *Y02A 50/30* (2018.01)

(58) **Field of Classification Search**
CPC C12N 9/2474; A61P 35/00; A61K 9/0019; A61K 38/28; A61K 38/47; A61K 45/06; A61K 47/10; A61K 38/00; C07K 14/47; C07K 2319/30; C12Q 1/34; C12Y 302/01035; Y02A 50/30; G01N 2333/926; G01N 2333/928
See application file for complete search history.

(56) **References Cited**

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3,598,123 A 8/1971 Zaffaroni 128/268
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(Continued)

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Letter/Written Disclosure of the Information Disclosure Statement for the above-referenced application, filed herewith on Mar. 15, 2023, 2 pages.
(Continued)

Primary Examiner — Suzanne M Noakes
Assistant Examiner — Ciara A McKnight
(74) *Attorney, Agent, or Firm* — Morgan, Lewis & Bockius LLP

(57) **ABSTRACT**

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

35 Claims, 13 Drawing Sheets

Specification includes a Sequence Listing.

PGR2025-00024

’652 Patent

US012049652B2

(12) **United States Patent**
Wei et al.

(10) **Patent No.: US 12,049,652 B2**
(45) **Date of Patent: *Jul. 30, 2024**

(54) **PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF**

(71) Applicant: **HALOZYME, INC.**, San Diego, CA (US)

(72) Inventors: **Ge Wei**, San Diego, CA (US); **H. Michael Shepard**, Eugene, OR (US); **Qiping Zhao**, San Diego, CA (US); **Robert James Connor**, Oceanside, CA (US)

(73) Assignee: **HALOZYME, INC.**, San Diego, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **18/064,886**

(22) Filed: **Dec. 12, 2022**

(65) **Prior Publication Data**

US 2023/0295592 A1 Sep. 21, 2023

Related U.S. Application Data

(60) Division of application No. 17/327,568, filed on May 21, 2021, which is a continuation of application No. 16/912,590, filed on Jun. 25, 2020, now Pat. No. 11,066,656, which is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, and a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, said application No. 17/327,568 is a continuation of application No. 16/824,572, filed on Mar. 19, 2020, now Pat. No. 11,041,149, which is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, which is a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, said application No. 17/327,568 is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, which is a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, said application No. 17/327,568 is a continuation of application No. 16/824,572, filed on Mar. 19, 2020, now Pat. No. 11,041,149, which is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, which is a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, said application No. 17/327,586 is a continuation of application No. 16/824,572, filed on Mar. 19, 2020, now Pat. No. 11,041,149, which is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, which is a continuation of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, said application No. 17/327,586, filed on May 21, 2021, which is a continuation of application No. 16/912,590, filed on
(Continued)

(51) **Int. Cl.**
C12N 9/26 (2006.01)
A61K 9/00 (2006.01)
A61K 38/00 (2006.01)
A61K 38/28 (2006.01)
A61K 38/47 (2006.01)
A61K 45/06 (2006.01)
A61K 47/10 (2017.01)
A61P 3/04 (2006.01)
A61P 3/10 (2006.01)
A61P 11/00 (2006.01)
A61P 27/02 (2006.01)
A61P 29/00 (2006.01)
A61P 35/00 (2006.01)
A61P 43/00 (2006.01)
C07K 14/47 (2006.01)
C12Q 1/34 (2006.01)

(52) **U.S. Cl.**
CPC ***C12N 9/2474*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 38/28*** (2013.01); ***A61K 38/47*** (2013.01); ***A61K 45/06*** (2013.01); ***A61K 47/10*** (2013.01); ***A61P 35/00*** (2018.01); ***C07K 14/47*** (2013.01); ***C12Q 1/34*** (2013.01); ***C12Y 302/01035*** (2013.01); *A61K 38/00* (2013.01); *C07K 2319/30* (2013.01); *G01N 2333/926* (2013.01); *G01N 2333/928* (2013.01); *Y02A 50/30* (2018.01)

(58) **Field of Classification Search**
CPC C12N 9/2474; A61P 35/00; A61K 9/0019; A61K 38/28; A61K 38/47; A61K 45/06; A61K 47/10; A61K 38/00; C07K 14/47; C07K 2319/30; C12Q 1/34; C12Y 302/01035; Y02A 50/30; G01N 2333/926; G01N 2333/928
See application file for complete search history.

(56) **References Cited**

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3,536,809 A 10/1970 Applezweig 424/28
3,598,123 A 8/1971 Zaffaroni 128/268
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EP 0400472 12/1990
(Continued)

OTHER PUBLICATIONS

Letter/Written Disclosure of the Information Disclosure Statement for the above-referenced application, filed herewith on Mar. 10, 2023, 2 pages.
(Continued)

Primary Examiner — Suzanne M Noakes
Assistant Examiner — Ciara A McKnight
(74) *Attorney, Agent, or Firm* — Morgan, Lewis & Bockius LLP

(57) **ABSTRACT**

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

40 Claims, 13 Drawing Sheets

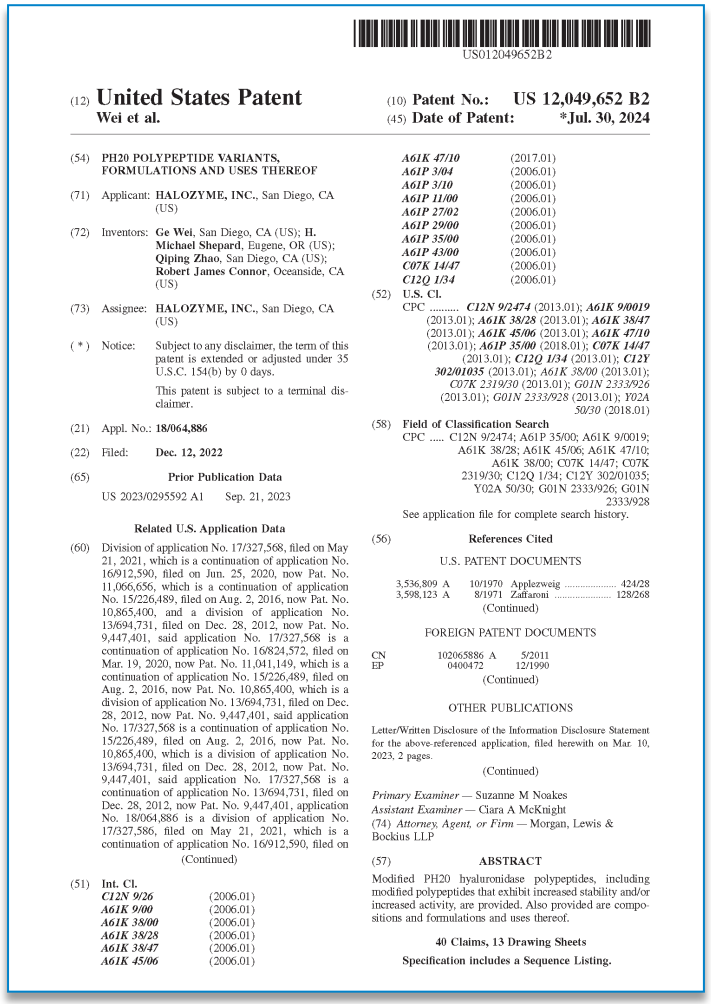
Specification includes a Sequence Listing.

PGR2025-00033

EX. 1001

’652 Patent Exemplary Claim

’652 Patent



US012049652B2

(12) **United States Patent**
Wei et al.

(10) **Patent No.: US 12,049,652 B2**
(45) **Date of Patent: *Jul. 30, 2024**

(54) **PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF**

(71) Applicant: **HALOZYME, INC.**, San Diego, CA (US)

(72) Inventors: **Ge Wei**, San Diego, CA (US); **H. Michael Shepard**, Eugene, OR (US); **Qiping Zhao**, San Diego, CA (US); **Robert James Connor**, Oceanside, CA (US)

(73) Assignee: **HALOZYME, INC.**, San Diego, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **18/064,886**

(22) Filed: **Dec. 12, 2022**

(65) **Prior Publication Data**

US 2023/0295592 A1 Sep. 21, 2023

Related U.S. Application Data

(60) Division of application No. 17/327,568, filed on May 21, 2021, which is a continuation of application No. 16/912,590, filed on Jun. 25, 2020, now Pat. No. 11,066,656, which is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, and a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, said application No. 17/327,568 is a continuation of application No. 16/824,572, filed on Mar. 19, 2020, now Pat. No. 11,041,149, which is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, which is a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, said application No. 17/327,568 is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, which is a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, said application No. 17/327,568 is a continuation of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, application No. 18/064,886 is a division of application No. 17/327,586, filed on May 21, 2021, which is a continuation of application No. 16/912,590, filed on

(Continued)

(51) **Int. Cl.**

C12N 9/26	(2006.01)
A61K 9/00	(2006.01)
A61K 38/00	(2006.01)
A61K 38/28	(2006.01)
A61K 38/47	(2006.01)
A61K 45/06	(2006.01)
A61K 47/10	(2017.01)
A61P 3/04	(2006.01)
A61P 3/10	(2006.01)
A61P 11/00	(2006.01)
A61P 27/02	(2006.01)
A61P 29/00	(2006.01)
A61P 35/00	(2006.01)
A61P 43/00	(2006.01)
C07K 14/47	(2006.01)
C12Q 1/34	(2006.01)

(52) **U.S. Cl.**

CPC ***C12N 9/2474*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 38/28*** (2013.01); ***A61K 38/47*** (2013.01); ***A61K 45/06*** (2013.01); ***A61K 47/10*** (2013.01); ***A61P 35/00*** (2018.01); ***C07K 14/47*** (2013.01); ***C12Q 1/34*** (2013.01); ***C12Y 302/01035*** (2013.01); *A61K 38/00* (2013.01); *C07K 2319/30* (2013.01); *G01N 2333/926* (2013.01); *G01N 2333/928* (2013.01); *Y02A 50/30* (2018.01)

(58) **Field of Classification Search**

CPC C12N 9/2474; A61P 35/00; A61K 9/0019; A61K 38/28; A61K 45/06; A61K 47/10; A61K 38/00; C07K 14/47; C07K 2319/30; C12Q 1/34; C12Y 302/01035; Y02A 50/30; G01N 2333/926; G01N 2333/928

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

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3,598,123	A	8/1971	Zaffaroni	128/268

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EP	0400472	12/1990

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Letter/Written Disclosure of the Information Disclosure Statement for the above-referenced application, filed herewith on Mar. 10, 2023, 2 pages.

(Continued)

Primary Examiner — Suzanne M Noakes
Assistant Examiner — Ciara A McKnight
(74) *Attorney, Agent, or Firm* — Morgan, Lewis & Bockius LLP

(57) **ABSTRACT**

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

40 Claims, 13 Drawing Sheets

Specification includes a Sequence Listing.

PGR2025-00033

Claim 1

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

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NO: 3, 7 and 32-66;

amino acid modifications are selected from the group consisting of amino acid replacements(s), deletion(s), and/or insertion(s);

the modified PH20 polypeptide comprises an amino acid replacement at a position corresponding to residue 320, with reference to amino acid positions set forth in SEQ ID NO:3;

the replacement at the position corresponding to residue 320 is selected from the group consisting of H, K, R, and S;

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

the modified PH20 polypeptide has **at least 91% sequence identity** to a polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7 and 32-66.

EX. 1001

Halozyme Patents Category V
Increased Activity

’791 Patent

US012077791B2

(12) **United States Patent**
Wei et al.

(10) **Patent No.: US 12,077,791 B2**
(45) **Date of Patent: *Sep. 3, 2024**

(54) **PH20 POLYPEPTIDE VARIANTS WITH A MODIFICATION AT POSITION 309 OF THE PH20 POLYPEPTIDE AND A METHOD OF MAKING THEREOF**

(71) Applicant: **HALOZYME, INC.**, San Diego, CA (US)

(72) Inventors: **Ge Wei**, San Diego, CA (US); **H. Michael Shepard**, Eugene, OR (US); **Qiping Zhao**, San Diego, CA (US); **Robert James Connor**, Oceanside, CA (US)

(73) Assignee: **HALOZYME, INC.**, San Diego, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **18/339,829**

(22) Filed: **Jun. 22, 2023**

(65) **Prior Publication Data**

US 2024/0026327 A1 Jan. 25, 2024

Related U.S. Application Data

(60) Continuation of application No. 17/327,586, filed on May 21, 2021, which is a continuation of application No. 16/912,590, filed on Jun. 25, 2020, now Pat. No. 11,066,656, and a continuation of application No. 16/824,572, filed on Mar. 19, 2020, now Pat. No. 11,041,149, said application No. 16/912,590 is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, said application No. 16/824,572 is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, said application No. 17/327,586 is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, and a continuation-in-part of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, said application No. 15/226,489 is a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, said application No. 16/824,572 is a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, said application No. 16/912,590 is a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401.

(60) Provisional application No. 61/796,208, filed on Nov. 1, 2012, provisional application No. 61/631,313, filed on Dec. 30, 2011.

(51) **Int. Cl.**

C07K 14/00	(2006.01)
A61K 9/00	(2006.01)
A61K 38/00	(2006.01)
A61K 38/16	(2006.01)
A61K 38/28	(2006.01)
A61K 38/43	(2006.01)
A61K 38/47	(2006.01)
A61K 45/06	(2006.01)
A61K 47/10	(2017.01)
A61P 35/00	(2006.01)
C07K 14/47	(2006.01)
C12N 9/26	(2006.01)
C12Q 1/34	(2006.01)

(52) **U.S. Cl.**
CPC ***C12N 9/2474*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 38/28*** (2013.01); ***A61K 38/47*** (2013.01); ***A61K 45/06*** (2013.01); ***A61K 47/10*** (2013.01); ***A61P 35/00*** (2018.01); ***C07K 14/47*** (2013.01); ***C12Q 1/34*** (2013.01); ***C12Y 302/01035*** (2013.01); *A61K 38/00* (2013.01); *C07K 2319/30* (2013.01); *G01N 2333/926* (2013.01); *G01N 2333/928* (2013.01); *Y02A 50/30* (2018.01)

(58) **Field of Classification Search**
CPC A61K 38/00; C07K 14/47; C07K 14/00; A61P 25/00; A61P 29/00; A61P 35/00; A61P 9/00; A61P 35/02; A61P 21/00; C12Y 302/01035; C12Y 302/01036; C12N 9/2474
See application file for complete search history.

(56) **References Cited**

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EP	0400472	12/1990

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Kim et al., Funct. Integr. Genomics, 2011; 11:507-517. DOI 10.1007/s10142-011-0220-9.*

(Continued)

Primary Examiner — Chang-Yu Wang
(74) *Attorney, Agent, or Firm* — Morgan, Lewis & Bockius LLP

(57) **ABSTRACT**

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

10 Claims, 13 Drawing Sheets

Specification includes a Sequence Listing.

PGR2025-00050

Claims 1 and 10

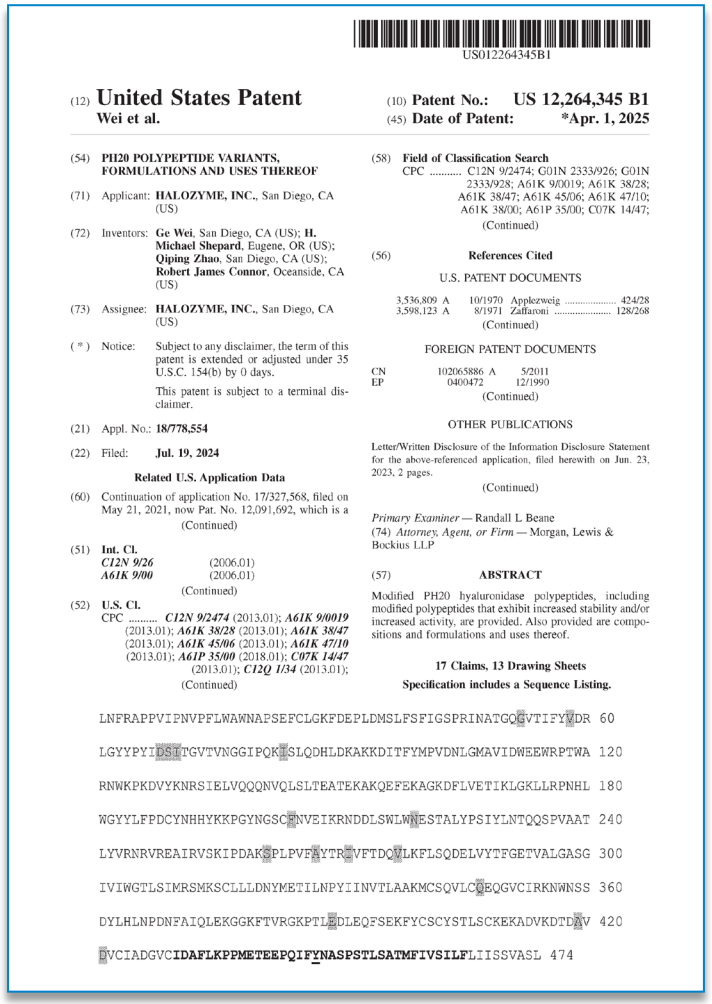
1. **A modified PH20 polypeptide** comprising an amino acid sequence, wherein: (a) at least 95% of the residues of the amino acid sequence of the modified PH20 polypeptide are identical to the residues in the amino acid sequence of SEQ ID NO: 35 when the sequence of the modified PH20 polypeptide is aligned at positions corresponding to the sequence set forth in the amino acid sequence of SEQ ID NO: 35 to maximize identical residues, and 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 309 with reference to amino acid positions set forth in the amino acid sequence of SEQ ID NO: 3; and (c) the modification at position 309 is a replacement selected from among E, G, H, L, M, N, Q, R, S, and T, and wherein **the modified PH20 polypeptide exhibits increased hyaluronidase activity compared to the hyaluronidase activity of the polypeptide of SEQ ID NO: 3**, measured under identical conditions.

10. 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; transfecting the plasmid into an isolated host cell; culturing the cell under conditions for expression of the modified PH20 polypeptide; and harvesting the modified PH20 polypeptide from the culture.

-50 PGR, EX. 1001

Halozyme Patents Category VI
Hyaluronidase Domain

’345 Patent



US012264345B1

(12) **United States Patent**
Wei et al.

(10) **Patent No.: US 12,264,345 B1**
(45) **Date of Patent: *Apr. 1, 2025**

(54) **PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF**

(71) Applicant: **HALOZYME, INC.**, San Diego, CA (US)

(72) Inventors: **Ge Wei**, San Diego, CA (US); **H. Michael Shepard**, Eugene, OR (US); **Qiping Zhao**, San Diego, CA (US); **Robert James Connor**, Oceanside, CA (US)

(73) Assignee: **HALOZYME, INC.**, San Diego, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **18/778,554**

(22) Filed: **Jul. 19, 2024**

Related U.S. Application Data

(60) Continuation of application No. 17/327,568, filed on May 21, 2021, now Pat. No. 12,091,692, which is a
(Continued)

(51) **Int. Cl.**
C12N 9/26 (2006.01)
A61K 9/00 (2006.01)
(Continued)

(52) **U.S. Cl.**
CPC ***C12N 9/2474*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 38/28*** (2013.01); ***A61K 38/47*** (2013.01); ***A61K 45/06*** (2013.01); ***A61K 47/10*** (2013.01); ***A61P 35/00*** (2018.01); ***C07K 14/47*** (2013.01); ***C12Q 1/34*** (2013.01);
(Continued)

(58) **Field of Classification Search**
CPC C12N 9/2474; G01N 2333/926; G01N 2333/928; A61K 9/0019; A61K 38/28; A61K 38/47; A61K 45/06; A61K 47/10; A61K 38/00; A61P 35/00; C07K 14/47;
(Continued)

(56) **References Cited**

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EP 0400472 12/1990
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Letter/Written Disclosure of the Information Disclosure Statement for the above-referenced application, filed herewith on Jun. 23, 2023, 2 pages.
(Continued)

Primary Examiner — Randall L Beane
(74) *Attorney, Agent, or Firm* — Morgan, Lewis & Bockius LLP

(57) **ABSTRACT**

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

17 Claims, 13 Drawing Sheets
Specification includes a Sequence Listing.

```
LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSLFSFIGSPRINATGQGVTIFYVDR 60
LGYYPYIDSITGVTVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVIDWEEWRPTWA 120
RNWKPKDVYKNRSIELVQQQNVQLSLTEATEKAKQEFEKAGKDFLVETIKLGKLLRPNHL 180
WGYYLFPDCYNHHYKKPGYNGSCFNVEIKRNDDLSWLWNESTALYPSIYLNTQQSPVAAT 240
LYVRNRVREAIRVSKIPDAKSPLPVFAYTRMVFTDQVLKFLSQDELVYTFGETVALGASG 300
IVIWGTLSIMRSMKSCLLLDNYMETILNPYIINVTLAAKMCSQVLCQEQGVCIRKNWNSS 360
DYLHLNPDNFAIQLEKGGKFTVRGKPTLEDLEQFSEKFYCSCYSTLSCKEKADVKDTDAV 420
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```

PGR2025-00052

Claim 1

1. A modified PH20 polypeptide, comprising:

(i) **a hyaluronidase domain** that corresponds to amino acid residues 3-339 with reference to numbering in SEQ ID NO:7; and

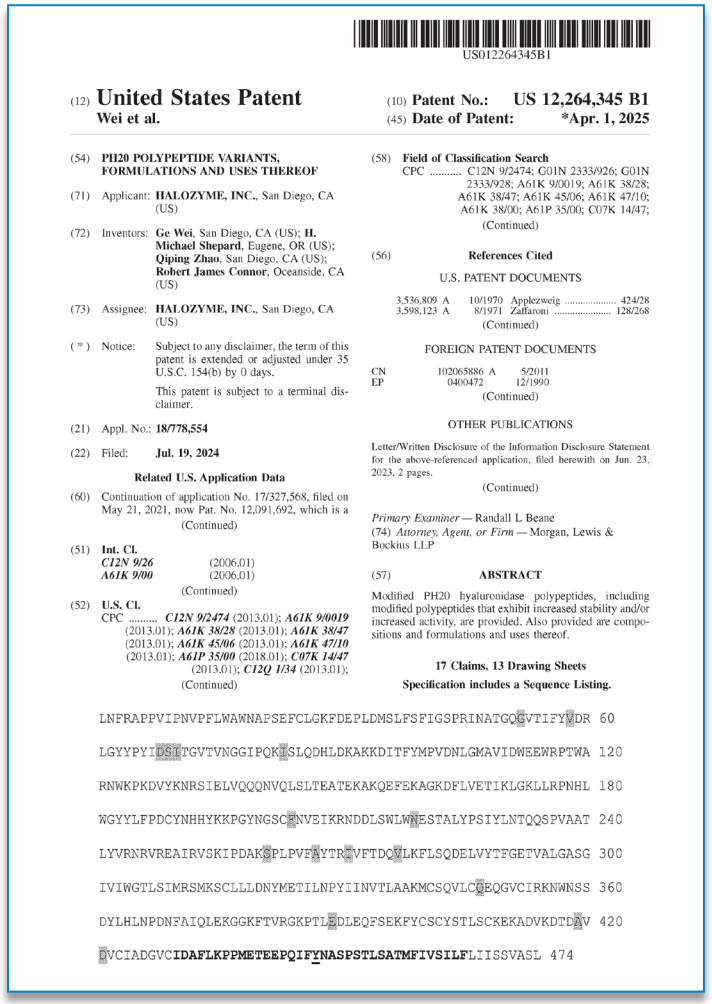
(ii) **an amino acid replacement at the residue corresponding to M313** with reference to numbering in SEQ ID NO:7,

wherein the hyaluronidase domain contains **up to 20 modifications**.

-52 PGR, EX. 1001

Patent Disclosure

’345 Patent



US012264345B1

(12) **United States Patent**
Wei et al.

(10) **Patent No.: US 12,264,345 B1**
(45) **Date of Patent: *Apr. 1, 2025**

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(71) Applicant: **HALOZYME, INC.**, San Diego, CA (US)

(72) Inventors: **Ge Wei**, San Diego, CA (US); **H. Michael Shepard**, Eugene, OR (US); **Qiping Zhao**, San Diego, CA (US); **Robert James Connor**, Oceanside, CA (US)

(73) Assignee: **HALOZYME, INC.**, San Diego, CA (US)

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(21) Appl. No.: **18/778,554**

(22) Filed: **Jul. 19, 2024**

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(51) **Int. Cl.**
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A61K 9/00 (2006.01)
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(52) **U.S. Cl.**
CPC ***C12N 9/2474*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 38/28*** (2013.01); ***A61K 38/47*** (2013.01); ***A61K 45/06*** (2013.01); ***A61K 47/10*** (2013.01); ***A61P 35/00*** (2018.01); ***C07K 14/47*** (2013.01); ***C12Q 1/34*** (2013.01);
(Continued)

(58) **Field of Classification Search**
CPC C12N 9/2474; G01N 2333/926; G01N 2333/928; A61K 9/0019; A61K 38/28; A61K 38/47; A61K 45/06; A61K 47/10; A61K 38/00; A61P 35/00; C07K 14/47;
(Continued)

(56) **References Cited**

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Primary Examiner — Randall L Beane
(74) *Attorney, Agent, or Firm* — Morgan, Lewis & Bockius LLP

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LGYYPYIDSITGVTVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVIDWEEWRPTWA 120
RNWKPKDVYKNRSIELVQQQNVQLSLTEATEKAKQEFEKAGKDFLVETIKLGKLLRPNHL 180
WGYYLFPDCYNHHYKKPGYNGSCFNVEIKRNDDLSWLWNESTALYPSIYLNTQQSPVAAT 240
LYVRNRVREAIRVSKIPDAKSPLPVFAYTRMVFTDQVLKFLSQDELVYTFGETVALGASG 300
IVIWGTLSIMRSMKSCLLLDNYMETILNPYIINVTLAAKMCSQVLCQEQGVCIRKNWNSS 360
DYLHLNPDNFAIQLEKGGKFTVRGKPTLEDLEQFSEKFYCSCYSTLSCKEKADVKDTDAV 420
DVCIADGVCIDAFLKPPMETEEPQIFYNASPSTLSATMFIVSILFLIISSVASL 474
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PGR2025-00052

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

“Modified PH20 Polypeptide” Definition

-52 PGR, EX. 1001, 47:2-8

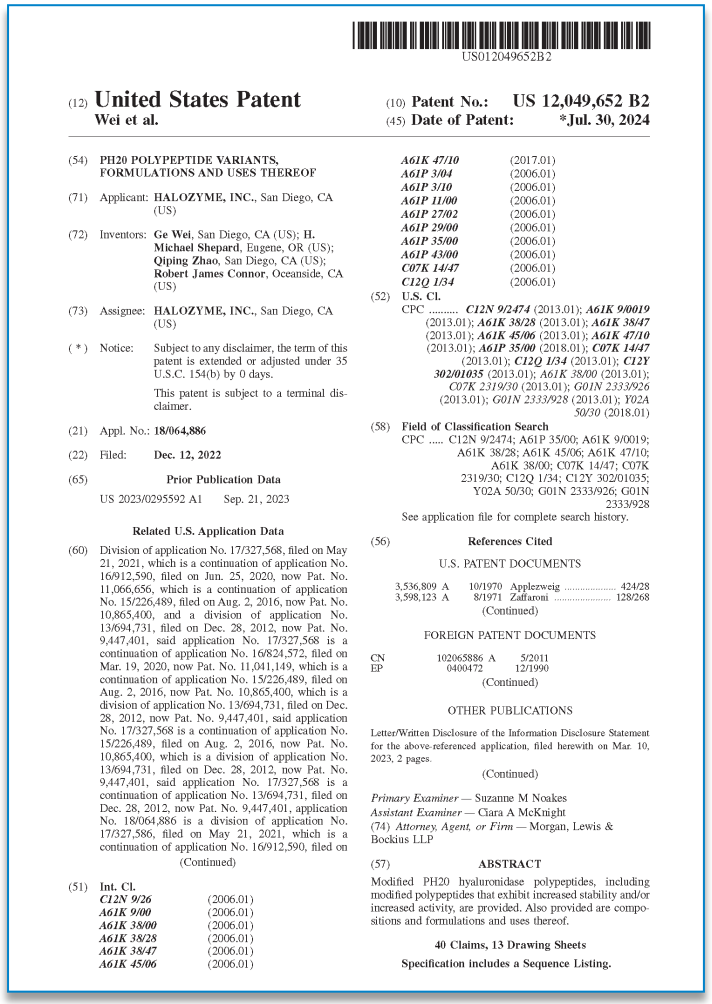
The sequence and structure of PH20 polypeptides is highly conserved. Sequence identity between and among PH20 proteins from various species is about 50% to 90%. The hydrophobic N-terminal signal sequence of 35 amino acids in length is generally conserved among PH20 hyaluronidase polypeptides. PH20 hyaluronidases contain a common core hyaluronidase domain region of about 340 amino acids in length that corresponds to amino acid residues 38-374 of the precursor human PH20 sequence set forth in SEQ ID NO:6. A mature PH20 polypeptide lacking the signal sequence and containing a contiguous sequence of amino acids having a C-terminal amino acid residue corresponding to amino acid residue 464 of SEQ ID NO:6 (e.g., amino acid residues corresponding to positions 36-464 of the amino acid sequence set forth in SEQ ID NO:6) is the minimal sequence required for hyaluronidase activity (see e.g., U.S. patent application Ser. No. 10/795,095, which is issued as U.S. Pat. No. 7,767,429; see also U.S. Publication No. US20100143457).

Hyaluronidase Domain

-52 PGR, EX. 1001, 68:14-32

Detailed Structure/Function Mapping

’652 Patent



US012049652B2

(12) **United States Patent**
Wei et al.

(10) **Patent No.: US 12,049,652 B2**
(45) **Date of Patent: *Jul. 30, 2024**

(54) **PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF**

(71) Applicant: **HALOZYME, INC.**, San Diego, CA (US)

(72) Inventors: **Ge Wei**, San Diego, CA (US); **H. Michael Shepard**, Eugene, OR (US); **Qiping Zhao**, San Diego, CA (US); **Robert James Connor**, Oceanside, CA (US)

(73) Assignee: **HALOZYME, INC.**, San Diego, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **18/064,886**

(22) Filed: **Dec. 12, 2022**

(65) **Prior Publication Data**

US 2023/0295592 A1 Sep. 21, 2023

Related U.S. Application Data

(60) Division of application No. 17/327,568, filed on May 21, 2021, which is a continuation of application No. 16/912,590, filed on Jun. 25, 2020, now Pat. No. 11,066,656, which is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, and a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, said application No. 17/327,568 is a continuation of application No. 16/824,572, filed on Mar. 19, 2020, now Pat. No. 11,041,149, which is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, which is a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, said application No. 17/327,568 is a continuation of application No. 15/226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, which is a division of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, said application No. 17/327,568 is a continuation of application No. 13/694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, application No. 18/064,886 is a division of application No. 17/327,586, filed on May 21, 2021, which is a continuation of application No. 16/912,590, filed on

(Continued)

(51) **Int. Cl.**

C12N 9/26	(2006.01)
A61K 9/00	(2006.01)
A61K 38/00	(2006.01)
A61K 38/28	(2006.01)
A61K 38/47	(2006.01)
A61K 45/06	(2006.01)
A61K 47/10	(2017.01)
A61P 3/04	(2006.01)
A61P 3/10	(2006.01)
A61P 11/00	(2006.01)
A61P 27/02	(2006.01)
A61P 29/00	(2006.01)
A61P 35/00	(2006.01)
A61P 43/00	(2006.01)
C07K 14/47	(2006.01)
C12Q 1/34	(2006.01)

(52) **U.S. Cl.**

CPC ***C12N 9/2474*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 38/28*** (2013.01); ***A61K 38/47*** (2013.01); ***A61K 45/06*** (2013.01); ***A61K 47/10*** (2013.01); ***A61P 35/00*** (2018.01); ***C07K 14/47*** (2013.01); ***C12Q 1/34*** (2013.01); ***C12Y 302/01035*** (2013.01); *A61K 38/00* (2013.01); *C07K 2319/30* (2013.01); *G01N 2333/926* (2013.01); *G01N 2333/928* (2013.01); *Y02A 50/30* (2018.01)

(58) **Field of Classification Search**

CPC C12N 9/2474; A61P 35/00; A61K 9/0019; A61K 38/28; A61K 45/06; A61K 47/10; A61K 38/00; C07K 14/47; C07K 2319/30; C12Q 1/34; C12Y 302/01035; Y02A 50/30; G01N 2333/926; G01N 2333/928

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,536,809 A	10/1970	Applezweig	424/28
3,598,123 A	8/1971	Zaffaroni	128/268

(Continued)

FOREIGN PATENT DOCUMENTS

CN	102065886 A	5/2011
EP	0400472	12/1990

(Continued)

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(Continued)

Primary Examiner — Suzanne M Noakes
Assistant Examiner — Ciara A McKnight
(74) *Attorney, Agent, or Firm* — Morgan, Lewis & Bockius LLP

(57) **ABSTRACT**

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

40 Claims, 13 Drawing Sheets

Specification includes a Sequence Listing.

PGR2025-00033

- “Detailed structure/function of virtually each amino acid in a PH20 polypeptide is provided herein, as well as the identification of residues and loci that contribute to alteration of a property....”

  EX. 1001, 4:58-61

- Unprecedented comprehensive mutagenesis study.

  EX. 2068, ¶¶162-164; EX. 2070, ¶¶233-237

Key Patent Examples

’652 Patent

US012049652B2

(12) **United States Patent**
Wei et al.

(10) **Patent No.: US 12,049,652 B2**
(45) **Date of Patent: *Jul. 30, 2024**

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(73) Assignee: **HALOZYME, INC.**, San Diego, CA (US)

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C12N 9/26	(2006.01)
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A61P 3/04	(2006.01)
A61P 3/10	(2006.01)
A61P 11/00	(2006.01)
A61P 27/02	(2006.01)
A61P 29/00	(2006.01)
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A61P 43/00	(2006.01)
C07K 14/47	(2006.01)
C12Q 1/34	(2006.01)

(52) **U.S. Cl.**

CPC ***C12N 9/2474*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 38/28*** (2013.01); ***A61K 38/47*** (2013.01); ***A61K 45/06*** (2013.01); ***A61K 47/10*** (2013.01); ***A61P 35/00*** (2018.01); ***C07K 14/47*** (2013.01); ***C12Q 1/34*** (2013.01); ***C12Y 302/01035*** (2013.01); *A61K 38/00* (2013.01); *C07K 2319/30* (2013.01); *G01N 2333/926* (2013.01); *G01N 2333/928* (2013.01); *Y02A 50/30* (2018.01)

(58) **Field of Classification Search**

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See application file for complete search history.

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3,598,123	A	8/1971	Zaffaroni	128/268

(Continued)

FOREIGN PATENT DOCUMENTS

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(Continued)

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Letter/Written Disclosure of the Information Disclosure Statement for the above-referenced application, filed herewith on Mar. 10, 2023, 2 pages.

(Continued)

Primary Examiner — Suzanne M Noakes
Assistant Examiner — Ciara A McKnight
(74) *Attorney, Agent, or Firm* — Morgan, Lewis & Bockius LLP

(57) **ABSTRACT**

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

40 Claims, 13 Drawing Sheets

Specification includes a Sequence Listing.

PGR2025-00033

- Example 2: Generation of PH20 variant library (Table 8).
  EX. 1001, 200:43-231:40
- Example 3: Test methods for activity assays.
  EX. 1001, 231:41-234:14
- Example 4: Results of activity assays.
  EX. 1001, 234:16-269:8
  - Table 9: “Active” variants (>40% wildtype activity).
    EX. 1001, 234:26-257:22
  - Table 10: “Inactive” mutants (<20% activity).
    EX. 1001, 257:23-269:8
- Data teaches tolerance/intolerance at each of 447 positions.
  EX. 2070, ¶¶263-428

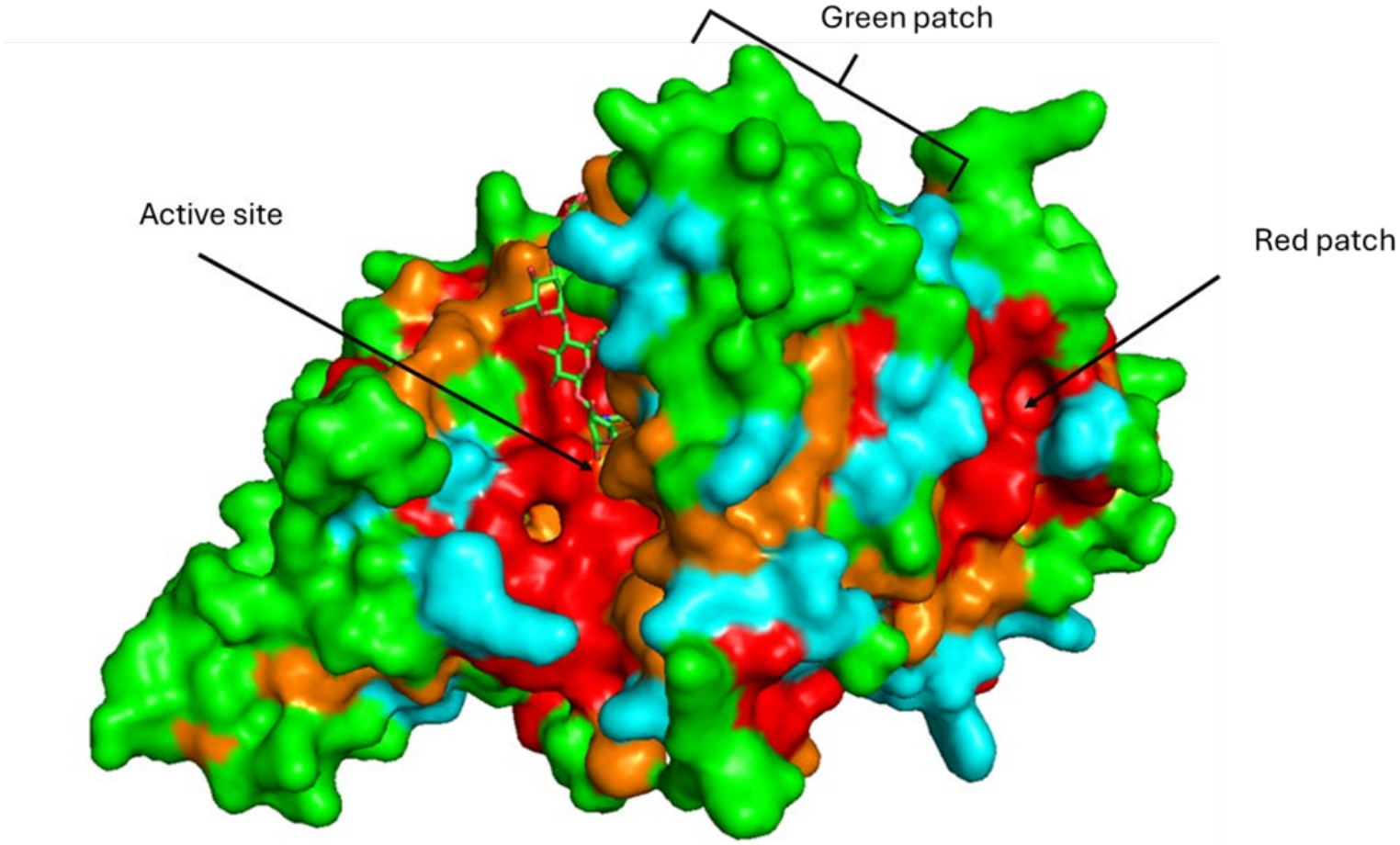
Patent's Mutagenesis Data

		30	D	61	L	92	A	123	W	154	K	185	L	216	W	247	V	278	L	309	I	340	M	371	A	402	C	433	F
Position	WT	31	E	62	G	93	K	124	K	155	Q	186	F	217	L	248	R	279	K	310	M	341	C	372	I	403	Y	434	L
1	L	32	P	63	Y	94	K	125	P	156	E	187	P	218	W	249	E	280	F	311	R	342	S	373	Q	404	S	435	K
2	N	33	L	64	Y	95	D	126	K	157	F	188	D	219	N	250	A	281	L	312	S	343	Q	374	L	405	T	436	P
3	F	34	D	65	P	96	I	127	D	158	E	189	C	220	E	251	I	282	S	313	M	344	V	375	E	406	L	437	P
4	R	35	M	66	Y	97	T	128	V	159	K	190	Y	221	S	252	R	283	Q	314	K	345	L	376	K	407	S	438	M
5	A	36	S	67	I	98	F	129	Y	160	A	191	N	222	T	253	V	284	D	315	S	346	C	377	G	408	C	439	E
6	P	37	L	68	D	99	Y	130	K	161	G	192	H	223	A	254	S	285	E	316	C	347	Q	378	G	409	K	440	T
7	P	38	F	69	S	100	M	131	N	162	K	193	H	224	L	255	K	286	L	317	L	348	E	379	K	410	E	441	E
8	V	39	S	70	I	101	P	132	R	163	D	194	Y	225	Y	256	I	287	V	318	L	349	Q	380	F	411	K	442	E
9	I	40	F	71	T	102	V	133	S	164	F	195	K	226	P	257	P	288	Y	319	L	350	G	381	T	412	A	443	P
10	P	41	I	72	G	103	D	134	I	165	L	196	K	227	S	258	D	289	T	320	D	351	V	382	V	413	D	444	Q
11	N	42	G	73	V	104	N	135	E	166	V	197	P	228	I	259	A	290	F	321	N	352	C	383	R	414	V	445	I
12	V	43	S	74	T	105	L	136	L	167	E	198	G	229	Y	260	K	291	G	322	Y	353	I	384	G	415	K	446	F
13	P	44	P	75	V	106	G	137	V	168	T	199	Y	230	L	261	S	292	E	323	M	354	R	385	K	416	D	447	Y
14	F	45	R	76	N	107	M	138	Q	169	I	200	N	231	N	262	P	293	T	324	E	355	K	386	P	417	T		
15	L	46	I	77	G	108	A	139	Q	170	K	201	G	232	T	263	L	294	V	325	T	356	N	387	T	418	D		
16	W	47	N	78	G	109	V	140	Q	171	L	202	S	233	Q	264	P	295	A	326	I	357	W	388	L	419	A		
17	A	48	A	79	I	110	I	141	N	172	G	203	C	234	Q	265	V	296	L	327	L	358	N	389	E	420	V		
18	W	49	T	80	P	111	D	142	V	173	K	204	F	235	S	266	F	297	G	328	N	359	S	390	D	421	D		
19	N	50	G	81	Q	112	W	143	Q	174	L	205	N	236	P	267	A	298	A	329	P	360	S	391	L	422	V		
20	A	51	Q	82	K	113	E	144	L	175	L	206	V	237	V	268	Y	299	S	330	Y	361	D	392	E	423	C		
21	P	52	G	83	I	114	E	145	S	176	R	207	E	238	A	269	T	300	G	331	I	362	Y	393	Q	424	I		
22	S	53	V	84	S	115	W	146	L	177	P	208	I	239	A	270	R	301	I	332	I	363	L	394	F	425	A		
23	E	54	T	85	L	116	R	147	T	178	N	209	K	240	T	271	I	302	V	333	N	364	H	395	S	426	D		
24	F	55	I	86	Q	117	P	148	E	179	H	210	R	241	L	272	V	303	I	334	V	365	L	396	E	427	G		
25	C	56	F	87	D	118	T	149	A	180	L	211	N	242	Y	273	F	304	W	335	T	366	N	397	K	428	V		
26	L	57	Y	88	H	119	W	150	T	181	W	212	D	243	V	274	T	305	G	336	L	367	P	398	F	429	C		
27	G	58	V	89	L	120	A	151	E	182	G	213	D	244	R	275	D	306	T	337	A	368	D	399	Y	430	I		
28	K	59	D	90	D	121	R	152	K	183	Y	214	L	245	N	276	Q	307	L	338	A	369	N	400	C	431	D		
29	F	60	R	91	K	122	N	153	A	184	Y	215	S	246	R	277	V	308	S	339	K	370	F	401	S	432	A		

EX. 1001, Tables 3, 5, 9, and 10; EX2070, Petsko Decl., ¶¶263-274

Patent Disclosure Makes Multiply Mutating PH20 Predictable

Halozyme Expert | **Dr. Petsko**



Claim Construction

The Claims Are Structure Only For Categories III-IV, and VI

Idenix Pharmaceuticals LLC v. Gilead Sciences Inc., 941 F.3d 1149 (2019)

941 F.3d 1149
United States Court of Appeals, Federal Circuit.

IDENIX PHARMACEUTICALS LLC, Universita Degli Studi Di Cagliari, Plaintiffs-Appellants
v.
GILEAD SCIENCES INC., Defendant-Appellee

2018-1691

Affirmed in part and reversed in part.

Newman, Circuit Judge, filed dissenting opinion.

Procedural Posture(s): On Appeal; Motion for Judgment as a Matter of Law (JMOL)/Directed Verdict.

***1152** Appeal from the United States District Court for the District of Delaware in No. 1:14-cv-00846-LPS, Chief Judge

Courts "… do not interpret claim terms in a way that excludes embodiments disclosed in the specification."

Oatey Co. v. IPS Corp., 514 F.3d 1271, 1276 (Fed. Cir. 2008)

quantity of experimentation factor in enablement inquiry could support finding only of non-enablement;

jury reasonably could have found in enablement analysis that synthesis of individual compound was largely routine;

finding of non-enablement was supported on basis that patent did not provide meaningful guidance as to which 2'-methyl-up nucleosides were effective against HCV and only working examples provided were exceedingly narrow relative to claim scope;

unpredictability of art of using modified nucleosides to treat HCV could weigh only in favor of non-enablement of patent;

immense breadth of claim could support finding only of non-enablement; and

patent providing 18 position-by-position formulas describing "principal embodiments" of compounds that might treat HCV did not satisfy written description requirement.

Shear, Jonathan Elliot Singer, San Diego, CA.

Before Prost, Chief Judge, Newman and Wallach, Circuit Judges.

Opinion

Dissenting opinion filed by Circuit Judge Newman.

Prost, Chief Judge.

***1153** Idenix Pharmaceuticals LLC and Universita Degli Studi Di Cagliari (collectively, "Idenix") appeal from the decision of the U.S. District Court for the District of Delaware granting judgment as a matter of law ("JMOL") against Idenix and finding that U.S. Patent No. 7,608,597 is invalid for lack of enablement. *Idenix Pharm. LLC v. Gilead Scis., Inc.*, 2018 WL 922125, at *25 (D. Del. Feb. 16, 2018) ("JMOL Opinion"). Gilead Sciences Inc., ("Gilead") argues that the patent is also invalid for failure to meet the written description requirement, and that the district court erred by failing to grant JMOL on that ground as well. We affirm as to non-enablement

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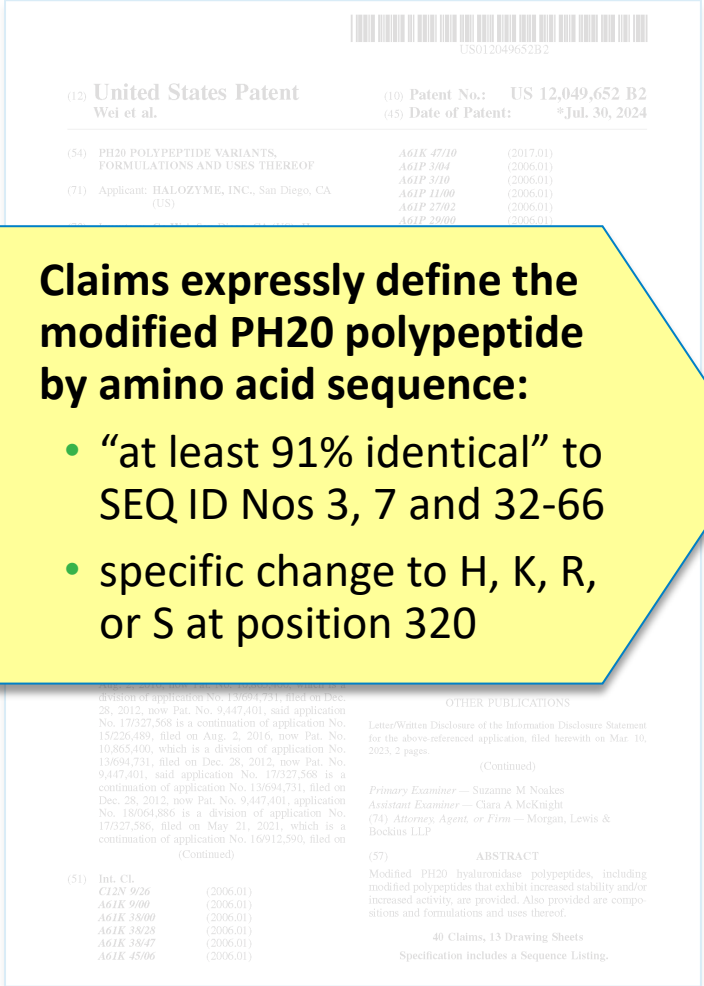
Categories III-IV, and VI
Claims Define The Invention By Structure

’652 Patent


US012049652B2

(12) United States Patent
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(10) Patent No.: US 12,049,652 B2
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A61P 11/00 (2006.01)
A61P 27/02 (2006.01)
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Assistant Examiner — Ciara A McKnight
(74) Attorney, Agent, or Firm — Morgan, Lewis & Bockius LLP

(57) ABSTRACT

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

40 Claims, 13 Drawing Sheets
Specification includes a Sequence Listing.

Claims expressly define the modified PH20 polypeptide by amino acid sequence:

- “at least 91% identical” to SEQ ID Nos 3, 7 and 32-66
- specific change to H, K, R, or S at position 320

Claim 1

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

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of **SEQ ID NO: 3, 7 and 32-66**;

amino acid modifications are selected from the group consisting of amino acid replacements(s), deletion(s), and/or insertion(s);

the modified PH20 polypeptide comprises **an amino acid replacement at a position corresponding to residue 320**, with reference to amino acid positions set forth in SEQ ID NO:3;

the replacement at the position corresponding to residue 320 is selected from the group consisting of H, K, R, and S;

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

the modified PH20 polypeptide has **at least 91% sequence identity** to a polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7 and 32-66.

PGR2025-00033

EX. 1001

Petitioner's Construction Rewrites The Claims

Paper No. 1
Filed: March 7, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyme Inc.,
Patent Owner.

Case No. PGR2025-00033
U.S. Patent No. 12,049,652

PETITION FOR POST GRANT REVIEW

"[T]he claims are limited to one: 'active mutants' … that 'exhibit at least 40% of the hyaluronidase activity of the corresponding PH20 polypeptide not containing the amino acid modification (e.g., amino acid replacement.).'"

Pet. at 21-22

Paper No. 22
Filed: August 8, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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Petitioner,

v.

Halozyme Inc.,
Patent Owner.

Case No. PGR2025-00033
U.S. Patent No. 12,049,652

REPLY IN SUPPORT OF PETITION FOR POST GRANT REVIEW

"[T]he claims … requir[e] modified PH20s that are 'properly folded and enzymatically active.'"

Reply at 2

"Modified PH20 Polypeptide" Definition

Definitional

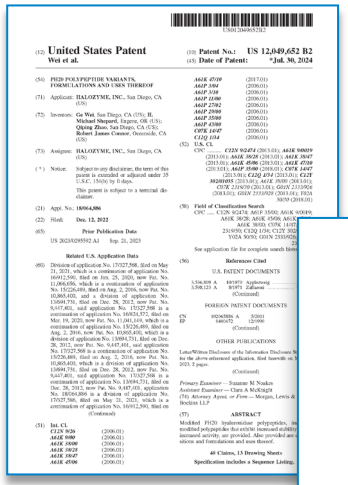
Not Definitional

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

EX. 1001, 48:41-56

Petitioner's Construction Contradicts Specification

'652 Patent


(12) United States Patent
Wei et al.

(10) Patent No.: US 12,049,652 B2
(45) Date of Patent: *Jul. 30, 2024

(54) PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF

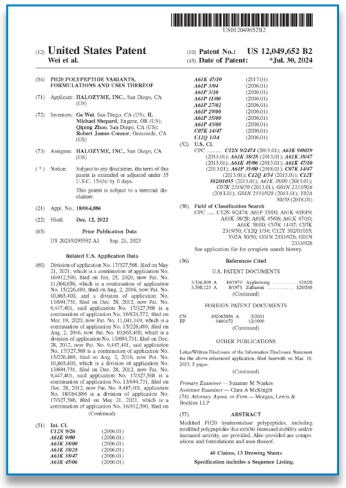
PGR2025-00033

Provided herein are modified PH20 polypeptides that contain one or more amino acid replacements in a PH20 polypeptide and that are inactive, whereby the polypeptides do not exhibit hyaluronidase activity or exhibit low or diminished hyaluronidase activity. The modified PH20 poly-

EX. 1001, 115:59-63

Petitioner's Construction Contradicts Specification

'652 Patent



(12) **United States Patent**
Wei et al.

(10) **Patent No.: US 12,049,652 B2**
(45) **Date of Patent: *Jul. 30, 2024**

(54) **PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF**

(71) Applicant: **HALOZYME, INC.**, San Diego, CA (US)

(72) Inventors: **Ge Wei**, San Diego, CA (US); **H. Michael Shepard**, Eugene, OR (US); **Qiying Zhao**, San Diego, CA (US); **Robert James Connor**, Oceanside, CA (US)

(73) Assignee: **HALOZYME, INC.**, San Diego, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **18/064,806**

(22) Filed: **Dec. 12, 2022**

(65) **Prior Publication Data**

US 2023/0295592 A1 Sep. 21, 2023

Related U.S. Application Data

(60) Division of application No. 17/327,568, filed on May 21, 2021, which is a continuation of application No. 16/912,590, filed on Jun. 25, 2020, now Pat. No. 11,041,169, which is a continuation of application No. 15/226,484, filed on Aug. 2, 2016, now Pat. No. 10,865,403, and a division of application No. 13/694,774, filed on Dec. 28, 2012, now Pat. No. 9,447,401, and application No. 17/327,568 is a continuation of application No. 16/824,572, filed on Mar. 19, 2020, now Pat. No. 11,041,169, which is a continuation of application No. 15/226,484, filed on Aug. 2, 2016, now Pat. No. 10,865,403, which is a division of application No. 13/694,774, filed on Dec. 28, 2012, now Pat. No. 9,447,401, and application No. 17/327,568 is a continuation of application No. 15/226,484, filed on Aug. 2, 2016, now Pat. No. 10,865,403, which is a division of application No. 13/694,774, filed on Dec. 28, 2012, now Pat. No. 9,447,401, and application No. 17/327,568 is a continuation of application No. 16/912,590, filed on Jun. 25, 2020, which is a continuation of application No. 16/824,572, filed on Mar. 19, 2020, which is a continuation of application No. 16/912,590, filed on Jun. 25, 2020, and application No. 18/064,806 is a division of application No. 17/327,568, filed on May 21, 2021, which is a continuation of application No. 16/912,590, filed on (Continued)

(51) **Int. Cl.**
C12N 9/26 (2006.01)
A61K 9/00 (2006.01)
A61K 38/00 (2006.01)
A61K 38/24 (2006.01)
A61K 38/47 (2006.01)
A61K 47/06 (2006.01)
A61K 47/10 (2017.01)
A61P 3/04 (2006.01)
A61P 3/10 (2006.01)
A61P 13/00 (2006.01)
A61P 27/02 (2006.01)
A61P 29/00 (2006.01)
A61P 35/00 (2006.01)
A61P 43/00 (2006.01)
C07K 14/47 (2006.01)
C12Q 1/54 (2006.01)

(52) U.S. Cl.
CPC **C12N 9/2474** (2013.01); **A61K 9/0019** (2013.01); **A61K 38/28** (2013.01); **A61K 38/47** (2013.01); **A61K 47/06** (2013.01); **A61K 47/10** (2013.01); **A61P 35/00** (2013.01); **C07K 14/47** (2013.01); **C12Q 1/54** (2013.01); **C12Y M200105** (2013.01); **A61K 9/00** (2013.01); C07K 2319/70 (2013.01); G01N 2333/954 (2013.01); G01N 2333/928 (2013.01); A61K 2300/00 (2013.01); H02A 50/30 (2018.01)

(58) **Field of Classification Search**
CPC C12N 9/2474; A61P 35/00; A61K 9/0019; A61K 38/28; A61K 38/56; A61K 47/10; A61K 38/02; C07K 14/47; C07K 2319/70; C12Q 1/54; C12Y 3020105; Y02A 50/30; G01N 2333/928; G01N 2333/928
See application file for complete search history.

(56) **References Cited**
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3,598,123 A 8/1971 Zaffaroni 128/268
(Continued)
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CN 102365094 A 2/2012
EP 0460572 12/1990
(Continued)
OTHER PUBLICATIONS
Letter/Written Disclosure of the Information Disclosure Statement for the above-referenced application, filed herewith on Mar. 16, 2023, 2 pages.
(Continued)
Primary Examiner — Suzanne M Noakes
Assistant Examiner — Clara A McKnight
(74) *Attorney, Agent, or Firm* — Morgan, Lewis & Bockius LLP

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

40 Claims, 13 Drawing Sheets
Specification includes a Sequence Listing.

PGR2025-00033

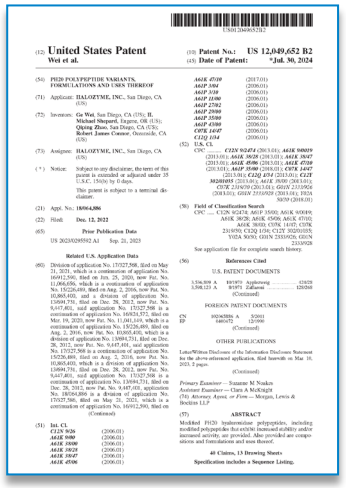
DETAILED DESCRIPTION

Outline
- A. DEFINITIONS
- B. PH20 HYALURONIDASE
  - 1. Structure
  - 2. Function
  - 3. Soluble PH20 Polypeptides
- C. MODIFIED PH20 POLYPEPTIDES
  - 1. Active Mutants
    - a. Increased Activity
    - b. Increased Stability
      - i. Phenophiles
      - ii. Thermophiles
      - iii. Absence of Salt
  - 2. Inactive Mutants
  - 3. Additional Modifications and Conjugates
    - a. Decreased Immunogenicity
    - b. Conjugation to Polymers

EX. 1001, 43:49-67

Term "PH20" Is Distinct From "Modified PH20 Polypeptide"

'652 Patent



US012049652B2

(12) **United States Patent**
Wei et al.

(10) **Patent No.: US 12,049,652 B2**
(45) **Date of Patent: *Jul. 30, 2024**

(54) PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF

(71) Applicant: HALOZYME, INC., San Diego, CA (US)

(72) Inventors: **Ge Wei**, San Diego, CA (US); **R. Michael Shepard**, Eugene, OR (US); **Qiying Zhao**, San Diego, CA (US); **Robert James Connor**, Oceanside, CA (US)

(73) Assignee: HALOZYME, INC., San Diego, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.
This patent is subject to a terminal disclaimer.

(21) Appl. No.: **18/084,886**

(22) Filed: **Dec. 12, 2022**

(65) **Prior Publication Data**
US 2023/0295592 A1 Sep. 21, 2023

Related U.S. Application Data

(60) Division of application No. 17/727,588, filed on May 21, 2020, which is a continuation of application No. 16/912,590, filed on Jun. 25, 2020, now Pat. No. 11,345,910, which is a continuation of application No. 15/226,484, filed on Aug. 2, 2016, now Pat. No. 10,865,400, and a division of application No. 13/894,791, filed on Dec. 28, 2012, now Pat. No. 9,447,401, and application No. 17/727,588 is a continuation of application No. 16/824,572, filed on Mar. 19, 2020, now Pat. No. 11,041,169, which is a continuation of application No. 16/691,390, filed on Nov. 22, 2019, now Pat. No. 10,865,400, which is a division of application No. 13/894,791, filed on Dec. 28, 2012, now Pat. No. 9,447,401, and application No. 17/727,588 is a continuation of application No. 15/226,484, filed on Aug. 2, 2016, now Pat. No. 10,865,400, which is a division of application No. 13/894,791, filed on Dec. 28, 2012, now Pat. No. 9,447,401, and application No. 17/727,588 is a continuation of application No. 16/824,572, filed on Mar. 19, 2020, which is a continuation of application No. 16/691,390, filed on Nov. 22, 2019, which is a division of application No. 18/084,886 is a division of application No. 17/727,588, filed on May 21, 2020, which is a continuation of application No. 16/912,590, filed on (Continued)

(51) **Int. Cl.**
C12N 9/26 (2006.01)
A61K 9/00 (2006.01)
A61K 35/00 (2006.01)
A61K 39/21 (2006.01)
A61K 39/47 (2006.01)
A61K 47/06 (2006.01)
A61K 47/10 (2017.01)
A61P 3/04 (2006.01)
A61P 3/10 (2006.01)
A61P 11/00 (2006.01)
A61P 27/02 (2006.01)
A61P 29/00 (2006.01)
A61P 35/00 (2006.01)
A61P 43/00 (2006.01)
C07K 14/47 (2006.01)
C12Q 1/34 (2006.01)

(52) U.S. Cl.
CPC **C12N 9/2474** (2013.01); **A61K 9/0019** (2013.01); **A61K 35/28** (2013.01); **A61K 39/47** (2013.01); **A61K 47/06** (2013.01); **A61K 47/10** (2013.01); **A61P 35/00** (2013.01); **C07K 14/47** (2013.01); **C12Q 1/34** (2013.01); **C12Y 3020103** **M20103** (2013.01); **A61K 39/00** (2013.01); **C07K 2319/70** (2013.01); **G01N 2333/904** (2013.01); **G01N 2333/929** (2013.01); H02A 50/30 (2018.01)

(58) **Field of Classification Search**
CPC C12N 9/2474; A61P 35/00; A61K 9/0019; A61K 38/28; A61K 45/06; A61K 47/10; A61K 38/02; C07K 14/47; C07K 2319/70; C12Q 1/34; C12Y 3020103; Y02A 50/30; G01N 2333/929; G01N 2333/928
See application file for complete search history.

(56) **References Cited**
U.S. PATENT DOCUMENTS
3,536,809 A 10/1970 Applicheim 424/28
3,548,123 A 8/1971 Zallanis 120/268
(Continued)
FOREIGN PATENT DOCUMENTS
CN 102428056 A 5/2012
EP 0460572 12/1990
(Continued)
OTHER PUBLICATIONS
Letter/Written Disclosure of the Information Disclosure Statement for the above-referenced application, filed herewith on Mar. 16, 2023, 2 pages.
(Continued)
Primary Examiner — Suzanne M Noakes
Assistant Examiner — Clara A McKnight
(74) *Attorney, Agent, or Firm* — Morgan, Lewis & Bockius LLP

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

40 Claims, 13 Drawing Sheets
Specification includes a Sequence Listing.

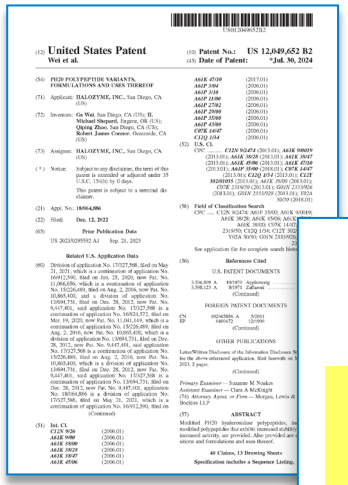
PGR2025-00033

As used herein, PH20 refers to a type of hyaluronidase that occurs in sperm and is neutral-active. PH-20 occurs on the sperm surface, and in the lysosome-derived acrosome, where it is bound to the inner acrosomal membrane. PH20 includes those of any origin including, but not limited to, human, chimpanzee, Cynomolgus monkey, Rhesus monkey, murine, bovine, ovine, guinea pig, rabbit and rat origin. Exemplary PH20 polypeptides, including precursor and mature forms, include those from human (SEQ ID NOs:6 and 7), chimpanzee (SEQ ID NOs:8, 9, 10, 869 and 870), Rhesus monkey (SEQ ID NOs:11 and 12), Cynomolgus monkey (SEQ ID NOs:13 and 14), cow (e.g., SEQ ID NOs:15-18); mouse (SEQ ID NOs:19 and 20); rat (SEQ ID NOs:21 and 22); rabbit (SEQ ID NOs:23 and 24); sheep (SEQ ID NOs:25-27), guinea pig (SEQ ID NOs:28 and 29); fox (SEQ ID NOs: 30 and 31); Gibbon (SEQ ID NOs:856 and 857), Marmoset (SEQ ID NOs:858 and 859) and orang-utan (SEQ ID NOs:860 and 861). Reference to PH20

EX. 1001, 45:59-46:9

PH20, Modified PH20 Have Different Properties, Activities

’652 Patent



PGR2025-00033

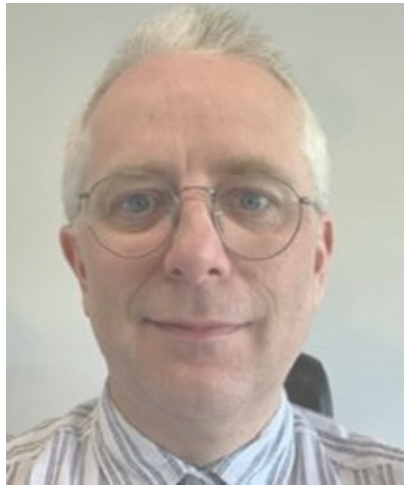
Provided herein are modified or variant PH20 polypeptides. The modified PH20 polypeptides provided herein exhibit altered activities or properties compared to a wild-type, native or reference PH20 polypeptide. Included among

* * *

EX. 1001, 75:44-47

Petitioner's Expert Invented New, Unsupported Constructions

Merck Expert | **Dr. Naismith**



43. … I read the claims as a whole as being directed to modified PH20 polypeptides that (i) contain an amino acid sequence that satisfies the sequence identity claim parameters, (ii) meet the position 313 substitution requirement, and (iii) have folded to adopt the same tertiary fold found in the native state of the wild-type PH20 protein.[15]

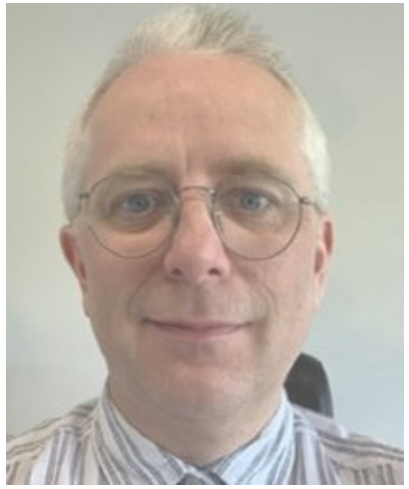
-46 PGR, EX1133, ¶43

43. … I read the claims as a whole as being directed to modified PH20 polypeptides that (i) contain an amino acid sequence that satisfies the sequence identity claim parameters, (ii) meet the position 313 substitution requirement, (iii) have folded to adopt the same tertiary structure found in the native state of the wild-type PH20 protein and (iv) are enzymatically active.[15]

-04 PGR, EX1133, ¶43

Petitioner's Expert Invented New, Unsupported Constructions

Merck Expert | **Dr. Naismith**



108. I believe Dr. Hecht more accurately describes why a POSA would have read the claims as a whole as being directed to modified PH20 polypeptides that are properly folded, and **certain of those** being enzymatically active ....

109. ... I believe that when a POSA considers all of the language used in **certain** claims (e.g., claim 5) and does that in conjunction with the common disclosure, she would have concluded that the claims define a set of modified PH20s that exhibit hyaluronidase activity.

-46 PGR, EX1133, ¶¶108-109

Q. ...The last sentence in paragraph 109 you say that a POSA: "... when a POSA considers all of the language used in **certain** claims (e.g., claim 5) and does that in conjunction with the common disclosure, she would have concluded that the claims define a set of modified PH20s that exhibit hyaluronidase activity." Right?

A. Yes, that's what this sentence says, and concluded that the claims, meaning all the claims, define a set of modified PH20s that exhibit hyaluronidase activity.

Q. Okay, so you're now saying that all of the claims require hyaluronidase activity and not just claim 5?

A. I'm not now saying that, that's what the declaration says.

EX2304, 34:13-35:9

Grounds 1 And 2 Fail For Categories III-IV, and VI

The Claims Are Structure Only

Halozyme

Structural Only Claims: Common Structural Features

The claims define the genus by a common mutation at position 320 and sequence identity to a set number of specific sequences.

POPR at 15-25; POR at 31-44

Merck's claim:

"Visualizing or recognizing the members of the claimed genus here is impossible"

Reply at 10

Structural Only Claims: Petitioner's Expert Can Recognize Genus

Merck Expert | **Dr. Hecht**

Q. Okay. I want to be very clear. Can you tell from an amino acid sequence whether that amino acid sequence is 95 percent identical to, for example, SEQ ID 3 or not?

A. One can do that, yes.

Q. So an amino acid sequence of a polypeptide gives you enough information to tell whether that amino acid sequence is 95 percent identical to, for example, SEQ ID 3; correct?

A. The sequence tells you whether, what percentage is identical, yes.

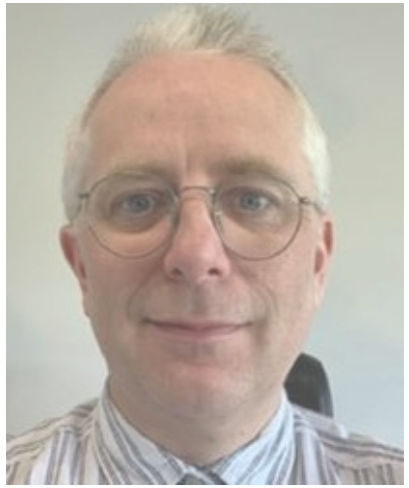
Q. And the sequence would also tell you whether there's a mutation at position 320; correct?

A. That it would.

EX. 2076 (Hecht), 203:18-204:10

Petitioner Agrees It Would Have Been Routine To Generate Multiply Substituted Modified PH20s

Merck Expert | **Dr. Naismith**



Q. Do you agree that the cell culture techniques that were described in the patent would have been routine in 2012?

A. Sorry, were what in 2012?

Q. The cell culture techniques described in the patent?

A. Were what in 2012, sorry?

Q. Would have been routine in 2012?

A. They were within the skill of a POSA 2012, yes.

EX. 2301 (Naismith), 311:23-312:8

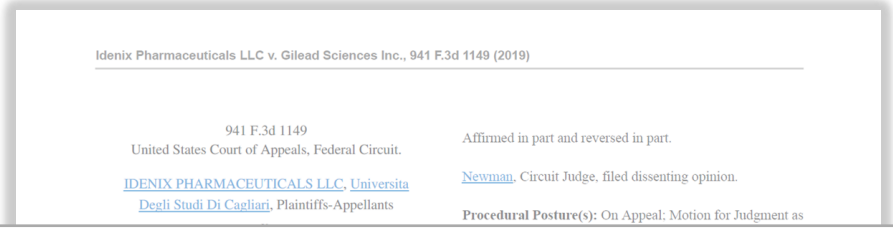
Q. So if I gave you an amino acid sequence that had 16 changes in it from wild-type PH20, is it your testimony that you would not know how to make that protein?

A. So, I could make the protein but I would have no way to know whether it was an active form or whether it was inactive, I think I could make it. So sometimes you can't make, you get stalling on the ribosome, so if you gave me a nucleotide sequence, I could make the nucleotide sequence and do the experiment if that is your question. But by the time you get to that large number of mutations there are many reasons that could lead to the protein appearing in a different, entirely different region of structure, unfolded, aggregated, whatever.

EX. 2301 (Naismith), 244:22-245:15; *see also* Pet., 13-16

Grounds 1 And 2 Fail For Categories III-IV, and VI

The Claims Are Structure Only


Idenix Pharmaceuticals LLC v. Gilead Sciences Inc., 941 F.3d 1149 (2019)

941 F.3d 1149
United States Court of Appeals, Federal Circuit.

IDENIX PHARMACEUTICALS LLC, Universita Degli Studi Di Cagliari, Plaintiffs-Appellants

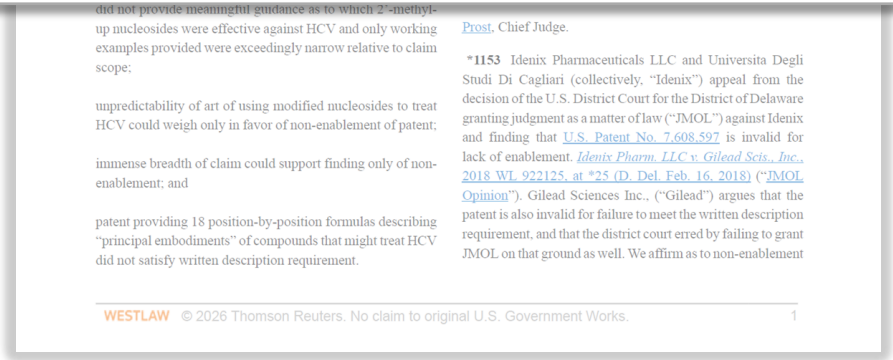
Affirmed in part and reversed in part.

Newman, Circuit Judge, filed dissenting opinion.

Procedural Posture(s): On Appeal; Motion for Judgment as

Petitioner's Section 112 argument improperly "focuses on certain functional characteristics disclosed in the Specification that are not recited in the challenged claims, and therefore, lacks sufficient merit in the context of the challenged claims."

Boehringer Ingelheim Animal Health USA Inc. v. Kansas State Univ. Res. Foundation ("Boehringer II") PGR2022-00021, Paper 13, 25-26 (P.T.A.B. Mar. 22, 2023).


did not provide meaningful guidance as to which 2'-methyl-up nucleosides were effective against HCV and only working examples provided were exceedingly narrow relative to claim scope;

unpredictability of art of using modified nucleosides to treat HCV could weigh only in favor of non-enablement of patent;

immense breadth of claim could support finding only of non-enablement; and

patent providing 18 position-by-position formulas describing "principal embodiments" of compounds that might treat HCV did not satisfy written description requirement.

Prost, Chief Judge.

*1153 Idenix Pharmaceuticals LLC and Universita Degli Studi Di Cagliari (collectively, "Idenix") appeal from the decision of the U.S. District Court for the District of Delaware granting judgment as a matter of law ("JMOL") against Idenix and finding that U.S. Patent No. 7,608,597 is invalid for lack of enablement. *Idenix Pharm. LLC v. Gilead Scis., Inc.*, 2018 WL 922125, at *25 (D. Del. Feb. 16, 2018) ("JMOL Opinion"). Gilead Sciences Inc., ("Gilead") argues that the patent is also invalid for failure to meet the written description requirement, and that the district court erred by failing to grant JMOL on that ground as well. We affirm as to non-enablement

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Contraceptive Utility Is Scientifically Credible

- Patent enables use of claimed PH20 variants as contraceptives **in females**
- Sufficient guidance for credible utility
- Prior art established PH20 as contraceptive target and taught known ways to enhance contraceptive effect
  - PH20 was known to play a key role in fertilization
  - Prior studies showed PH20 could induce infertility / contraceptive effects
  - PH20 vaccines were known to generate anti-PH20 antibodies that bind sperm PH20
    - Mucosal delivery could increase antibodies in the female reproductive tract
    - Adjuvants and booster doses could strengthen the antibody response
    - Sialidase could expose sperm-surface PH20 to anti-PH20 antibodies
- Anti-PH20 antibodies could be delivered locally by gels, films, or intravaginal rings

Reference: POR, 74–82; Sur-Reply 27–29; EX2072 ¶¶19–61; EX2074 ¶¶20–63.

Contraceptive Utility Is Scientifically Credible

- An invention that is at least partially successful in achieving a useful result has credible utility.

  In re Brana, 51 F.3d 1560 (Fed. Cir. 1995).

- Petitioner applied a 100% effectiveness standard.

  Reply at 39-40

- Petitioner's expert agrees that common contraceptives achieve less than 100% effectiveness.

  EX. 2302 (Kelsoe), 131:10-132:19

Contraceptive Utility Is Scientifically Credible

Merck Expert | **Dr. Kelsoe**

Q. And you would agree that contraceptives have been and are still used today as tools for population control in animals, correct?

A. Contraceptives?

Q. Yes.

A. Yes.

Q. And you would agree that a method for population control in animals would not need to cause complete infertility to be useful –

A. That's my --

Q. You would agree that, as a method for population control, a contraceptive would not need to cause incomplete fertility to be useful, correct?

A. I think that -- and, again, as I described in the sense of ecological control for a species, a 50 percent reduction of the fecundity would have an important and valuable role.

EX. 2302 (Kelsoe), 134:5-135:3 (objections omitted)

Petitioner's Deviation From Patent Teaching Is Insufficient To Disprove Enablement As A Matter Of Law

Attorneys and Law Firms

"A party who wishes to prove that the claims of a patent are not enabled by means of a failed attempt to make the disclosed invention must show that the patent's disclosure was followed. Because Sutherland deviated from the teachings of the patent in his failed attempts to make the claimed antibodies, his testimony is insufficient to disprove enablement as a matter of law."

"[I]t is imperative when attempting to prove lack of enablement to show that *one of ordinary skill in the art* would be unable to make the claimed invention without undue experimentation... CellPro's evidence concerning Civin's subsequent work is insufficient as a matter of law."

Johns Hopkins Univ. v. CellPro, Inc., 152 F.3d 1342, 1360 (Fed. Cir. 1998).

Judgment; Motion for Judgment as a Matter of Law (JMOL)/ 24, 1997). We affirm-in-part, vacate-in-part, and remand.
Directed Verdict.

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Patent Owner Also Prevails For All Categories Even If Enzymatic Activity Is Required

Similarity To Sequence Is A Common Structural Feature; WD Does Not Require Perfect Correspondence To Structure

Ajinomoto Co., Inc. v. International Trade Commission, 932 F.3d 1342 (2019)

"CJ disputes that similarity to the consensus sequence defines a common structural feature, citing several articles as indicating that a promoter closer to the consensus sequence will not always be stronger than one farther from that sequence."

Ajinomoto Co. v. Int'l Trade Comm'n, 932 F.3d 1342, 1360 (Fed. Cir. 2019).

"CJ's argument both assumes too strict a legal standard and reads too much into its cited references. 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.'"

Ajinomoto Co. v. Int'l Trade Comm'n, 932 F.3d 1342, 1360 (Fed. Cir. 2019).

under function-way-result framework;

increased activity of YddG protein at least partly contributed to enhanced resistance of later strains of accused product;

Taranto, Circuit Judge.

Ajinomoto Co., Inc. and Ajinomoto Heartland Inc. (collectively, Ajinomoto) filed a complaint against CJ

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Claims Are Enabled Even If Enzymatic Activity Is Required

Ajinomoto Co., Inc. v. International Trade Commission, 932 F.3d 1342 (2019)

"From this it follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. *Id.* at 224, 169 USPQ at 370. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility."

In re Brana, 51 F.3d 1560, 1566 (Fed. Cir. 1995).

"A specification which contains a statement of the manner and process of using the invention in terms which corresponds in scope to those used in defining the subject sought to be patented must be taken as in compliance with the "how to use" requirement of the first paragraph of 35 U.S.C. § 112 unless there is a reason to double the objective truth of the statement."

In re Brana, 51 F.3d 1560, 1566 (Fed. Cir. 1995).

under function-way-result framework;

increased activity of YddG protein at least partly contributed to enhanced resistance of later strains of accused product;

Taranto, Circuit Judge.

Ajinomoto Co., Inc. and Ajinomoto Heartland Inc. (collectively, Ajinomoto) filed a complaint against CJ

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Board's Preliminary Construction Of "Modified PH20 Polypeptide" Is Addressed Through Remainder Of The Presentation

- The Board preliminarily construed claims to require "some" hyaluronidase activity.

  ID at 15-19

- Patent Owner and Patent Owner's experts addressed the Board's Construction in POR and sur-reply.

  POR, 31-44; Sur-Reply, 1-4; EX. 2068, ¶350

- Patent Owner assumed that specification must allow POSAs to reliably distinguish, create, and utilize actives.

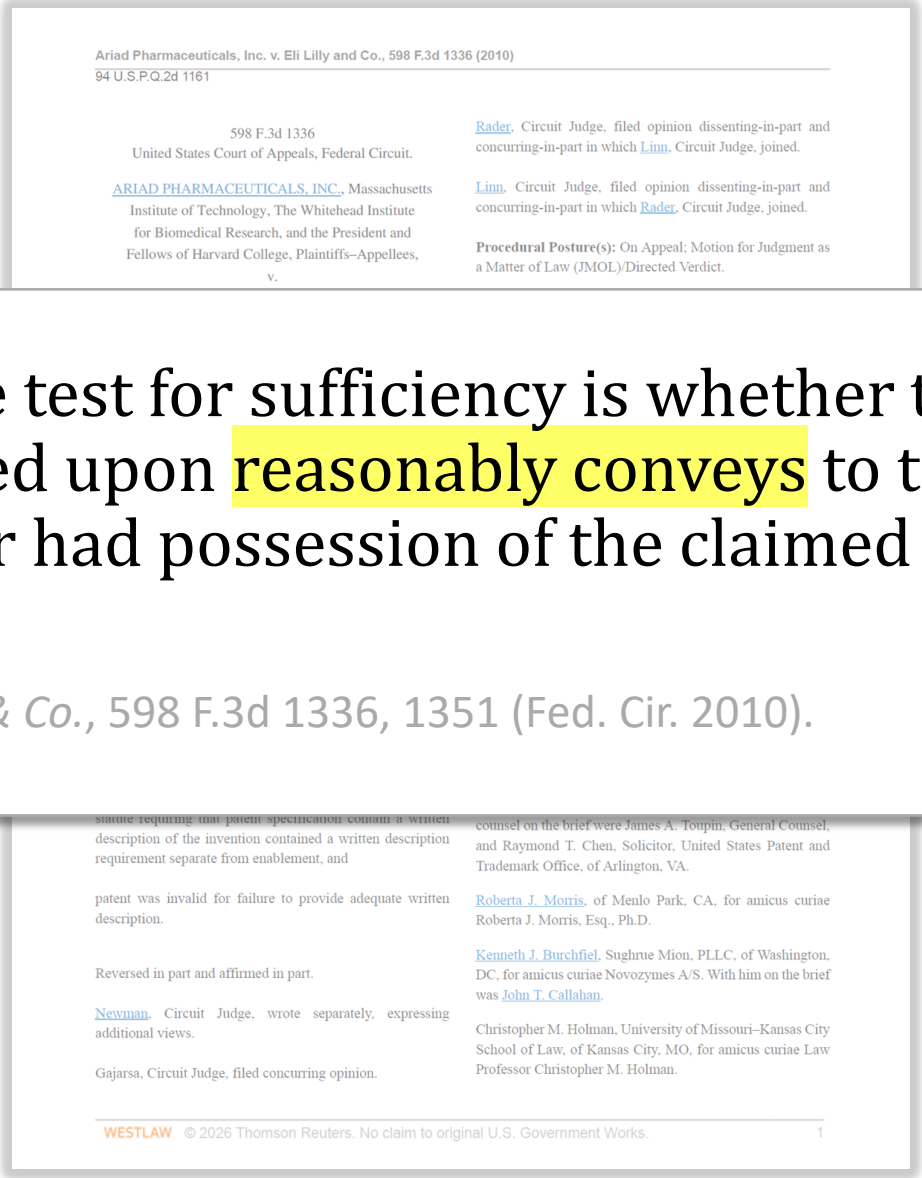
  POR, 31-44; Sur-Reply, 3-27

- Under the Board's construction, patent provides written description and enablement.

  POR, 44-82; Sur-Reply, 3-27

Written Description (Ground 1)

Specification Must Reasonably Convey Possession



Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co., 598 F.3d 1336 (2010)
94 U.S.P.Q.2d 1161

598 F.3d 1336
United States Court of Appeals, Federal Circuit.

ARIAD PHARMACEUTICALS, INC., Massachusetts Institute of Technology, The Whitehead Institute for Biomedical Research, and the President and Fellows of Harvard College, Plaintiffs–Appellees,
v.

Rader, Circuit Judge, filed opinion dissenting-in-part and concurring-in-part in which Linn, Circuit Judge, joined.

Linn, Circuit Judge, filed opinion dissenting-in-part and concurring-in-part in which Rader, Circuit Judge, joined.

Procedural Posture(s): On Appeal; Motion for Judgment as a Matter of Law (JMOL)/Directed Verdict.

statute requiring that patent specification contain a written description of the invention contained a written description requirement separate from enablement, and

patent was invalid for failure to provide adequate written description.

Reversed in part and affirmed in part.

Newman, Circuit Judge, wrote separately, expressing additional views.

Gajarsa, Circuit Judge, filed concurring opinion.

counsel on the brief were James A. Toupin, General Counsel, and Raymond T. Chen, Solicitor, United States Patent and Trademark Office, of Arlington, VA.

Roberta J. Morris, of Menlo Park, CA, for amicus curiae Roberta J. Morris, Esq., Ph.D.

Kenneth J. Burchfiel, Sughrue Mion, PLLC, of Washington, DC, for amicus curiae Novozymes A/S. With him on the brief was John T. Callahan.

Christopher M. Holman, University of Missouri–Kansas City School of Law, of Kansas City, MO, for amicus curiae Law Professor Christopher M. Holman.

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"In other words, the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date."

Ariad Pharms., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1351 (Fed. Cir. 2010).

Common Structural Features, Structure/Function Correlation

Common Structural Features:

1. **Primary Structure:** ≥91% identical amino acid sequence.
2. **Key Mutation:** D320 substitution (H, K, R, or S).
3. **For Actives**:
   - Common active site.
     EX. 1001, 70:34-54; EX. 2068, ¶303; EX. 2070, ¶¶148-206
   - Same catalytic, binding residues.
     EX. 1001, 70:34-41; EX. 2068, ¶303; EX. 2070, ¶¶148-206
   - Conserved disulfide bridges, essential glycosylation sites.
     EX. 1001, 70:14-33; EX. 2068, ¶303; EX. 2070, ¶¶214-217
   - Lack of disclosed inactivating changes.
     EX. 2068, ¶¶303, 323; EX. 2070, ¶44
   - Tertiary structure: PH20 α-β barrel fold.
     EX. 2068, ¶¶289, 316-323; EX. 2070, ¶¶345, 396, 400-420

Patent's Structure/Function Correlations

- Patent provides comprehensive mutagenesis data for all 447 positions.
  EX. 1001, 234:15-269:8
- Identifies which positions tolerate substitutions.
  EX. 1001, 234:15-269:8; EX. 2068, ¶¶243-247; EX. 2070, ¶¶ 263-428
- Identifies which types of amino acids work at each position.
  EX. 1001, 234:15-269:8; EX. 2068, ¶¶243-247; EX. 2070, ¶¶ 263-428
- Enables POSA to reliably predict effects of single and multiple mutations.
  EX. 2068, ¶¶305-315, 378-390; EX. 2070, ¶¶343-428
- "Detailed structure/function of virtually each amino acid...."
  EX. 1001, 4:58-59

How POSAs Visualize The Patent Disclosure

Position	WT																																		
1	L	30	D	61	L	92	A	123	W	154	K	185	L	216	W	247	V	278	L	309	I	340	M	371	A	402	C	433	F
2	N	31	E	62	G	93	K	124	K	155	Q	186	F	217	L	248	R	279	K	310	M	341	C	372	I	403	Y	434	L
3	F	32	P	63	Y	94	K	125	P	156	E	187	P	218	W	249	E	280	F	311	R	342	S	373	Q	404	S	435	K
4	R	33	L	64	Y	95	D	126	K	157	F	188	D	219	N	250	A	281	L	312	S	343	Q	374	L	405	T	436	P
5	A	34	D	65	P	96	I	127	D	158	E	189	C	220	E	251	I	282	S	313	M	344	V	375	E	406	L	437	P
6	P	35	M	66	Y	97	T	128	V	159	K	190	Y	221	S	252	R	283	Q	314	K	345	L	376	K	407	S	438	M
7	P	36	S	67	I	98	F	129	Y	160	A	191	N	222	T	253	V	284	D	315	S	346	C	377	G	408	C	439	E
8	V	37	L	68	D	99	Y	130	K	161	G	192	H	223	A	254	S	285	E	316	C	347	Q	378	G	409	K	440	T
9	I	38	F	69	S	100	M	131	N	162	K	193	H	224	L	255	K	286	L	317	L	348	E	379	K	410	E	441	E
10	P	39	S	70	I	101	P	132	R	163	D	194	Y	225	Y	256	I	287	V	318	L	349	Q	380	F	411	K	442	E
11	N	40	F	71	T	102	V	133	S	164	F	195	K	226	P	257	P	288	Y	319	L	350	G	381	T	412	A	443	P
12	V	41	I	72	G	103	D	134	I	165	L	196	K	227	S	258	D	289	T	320	D	351	V	382	V	413	D	444	Q
13	P	42	G	73	V	104	N	135	E	166	V	197	P	228	I	259	A	290	F	321	N	352	C	383	R	414	V	445	I
14	F	43	S	74	T	105	L	136	L	167	E	198	G	229	Y	260	K	291	G	322	Y	353	I	384	G	415	K	446	F
15	L	44	P	75	V	106	G	137	V	168	T	199	Y	230	L	261	S	292	E	323	M	354	R	385	K	416	D	447	Y
16	W	45	R	76	N	107	M	138	Q	169	I	200	N	231	N	262	P	293	T	324	E	355	K	386	P	417	T		
17	A	46	I	77	G	108	A	139	Q	170	K	201	G	232	T	263	L	294	V	325	T	356	N	387	T	418	D		
18	W	47	N	78	G	109	V	140	Q	171	L	202	S	233	Q	264	P	295	A	326	I	357	W	388	L	419	A		
19	N	48	A	79	I	110	I	141	N	172	G	203	C	234	Q	265	V	296	L	327	L	358	N	389	E	420	V		
20	A	49	T	80	P	111	D	142	V	173	K	204	F	235	S	266	F	297	G	328	N	359	S	390	D	421	D		
21	P	50	G	81	Q	112	W	143	Q	174	L	205	N	236	P	267	A	298	A	329	P	360	S	391	L	422	V		
22	S	51	Q	82	K	113	E	144	L	175	L	206	V	237	V	268	Y	299	S	330	Y	361	D	392	E	423	C		
23	E	52	G	83	I	114	E	145	S	176	R	207	E	238	A	269	T	300	G	331	I	362	Y	393	Q	424	I		
24	F	53	V	84	S	115	W	146	L	177	P	208	I	239	A	270	R	301	I	332	I	363	L	394	F	425	A		
25	C	54	T	85	L	116	R	147	T	178	N	209	K	240	T	271	I	302	V	333	N	364	H	395	S	426	D		
26	L	55	I	86	Q	117	P	148	E	179	H	210	R	241	L	272	V	303	I	334	V	365	L	396	E	427	G		
27	G	56	F	87	D	118	T	149	A	180	L	211	N	242	Y	273	F	304	W	335	T	366	N	397	K	428	V		
28	K	57	Y	88	H	119	W	150	T	181	W	212	D	243	V	274	T	305	G	336	L	367	P	398	F	429	C		
29	F	58	V	89	L	120	A	151	E	182	G	213	D	244	R	275	D	306	T	337	A	368	D	399	Y	430	I		
		59	D	90	D	121	R	152	K	183	Y	214	L	245	N	276	Q	307	L	338	A	369	N	400	C	431	D		
		60	R	91	K	122	N	153	A	184	Y	215	S	246	R	277	V	308	S	339	K	370	F	401	S	432	A		

EX. 1001, Tables 3, 5, 9, and 10; EX2070, Petsko Decl., ¶¶263-274

Patent's Informational Content Is Enormous

Halozyme Expert | **Dr. Petsko**

Q. So if you look at the entire genus that it has a set of changes that can include up to 21 or 22 mutations, the portion of the genus that is reflected in the dataset is a tiny, tiny fraction of that genus, right?

A. So the -- what is reflected in the patent is a subset. Okay. Which has a particular number of mutations. A few thousand. Sounds about right.

The real question is: What about the information content? The information content of that particular set of substitutions is enormous. And when combined with the structural information from modeling the PH20 structure, it allows you to visualize and make predictions about much more of the dataset than just what you see here.

EX. 1131 (Petsko), 113:8-18 (objections omitted)

Petitioner Ignores Patent's Structure/Function Correlations

Petitioner's view of the patent data

	Number of Changes																					
SEQ	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
3																						
32																						
33																						
34																						
35																						
36																						
37																						
38																						
39																						
40																						
41																						
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61																						
62																						
63																						
64																						
65																						
66																						

Pet., 57

What the patent data disclose to a POSA

		30	D	61	L	92	A	123	W	154	K	185	L	216	W	247	V	278	L	309	I	340	M	371	A	402	C	433	F
Position	WT	31	E	62	G	93	K	124	K	155	Q	186	F	217	L	248	R	279	K	310	M	341	C	372	I	403	Y	434	L
1	L	32	P	63	Y	94	K	125	P	156	E	187	P	218	W	249	E	280	F	311	R	342	S	373	Q	404	S	435	K
2	N	33	L	64	Y	95	D	126	K	157	F	188	D	219	N	250	A	281	L	312	S	343	Q	374	L	405	T	436	P
3	F	34	D	65	P	96	I	127	D	158	E	189	C	220	E	251	I	282	S	313	M	344	V	375	E	406	L	437	P
4	R	35	M	66	Y	97	T	128	V	159	K	190	Y	221	S	252	R	283	Q	314	K	345	L	376	K	407	S	438	M
5	A	36	S	67	I	98	F	129	Y	160	A	191	N	222	T	253	V	284	D	315	S	346	C	377	G	408	C	439	E
6	P	37	L	68	D	99	Y	130	K	161	G	192	H	223	A	254	S	285	E	316	C	347	Q	378	G	409	K	440	T
7	P	38	F	69	S	100	M	131	N	162	K	193	H	224	L	255	K	286	L	317	L	348	E	379	K	410	E	441	E
8	V	39	S	70	I	101	P	132	R	163	D	194	Y	225	Y	256	I	287	V	318	L	349	Q	380	F	411	K	442	E
9	I	40	F	71	T	102	V	133	S	164	F	195	K	226	P	257	P	288	Y	319	L	350	G	381	T	412	A	443	P
10	P	41	I	72	G	103	D	134	I	165	L	196	K	227	S	258	D	289	T	320	D	351	V	382	V	413	D	444	Q
11	N	42	G	73	V	104	N	135	E	166	V	197	P	228	I	259	A	290	F	321	N	352	C	383	R	414	V	445	I
12	V	43	S	74	T	105	L	136	L	167	E	198	G	229	Y	260	K	291	G	322	Y	353	I	384	G	415	K	446	F
13	P	44	P	75	V	106	G	137	V	168	T	199	Y	230	L	261	S	292	E	323	M	354	R	385	K	416	D	447	Y
14	F	45	R	76	N	107	M	138	Q	169	I	200	N	231	N	262	P	293	T	324	E	355	K	386	P	417	T		
15	L	46	I	77	G	108	A	139	Q	170	K	201	G	232	T	263	L	294	V	325	T	356	N	387	T	418	D		
16	W	47	N	78	G	109	V	140	Q	171	L	202	S	233	Q	264	P	295	A	326	I	357	W	388	L	419	A		
17	A	48	A	79	I	110	I	141	N	172	G	203	C	234	Q	265	V	296	L	327	L	358	N	389	E	420	V		
18	W	49	T	80	P	111	D	142	V	173	K	204	F	235	S	266	F	297	G	328	N	359	S	390	D	421	D		
19	N	50	G	81	Q	112	W	143	Q	174	L	205	N	236	P	267	A	298	A	329	P	360	S	391	L	422	V		
20	A	51	Q	82	K	113	E	144	L	175	L	206	V	237	V	268	Y	299	S	330	Y	361	D	392	E	423	C		
21	P	52	G	83	I	114	E	145	S	176	R	207	E	238	A	269	T	300	G	331	I	362	Y	393	Q	424	I		
22	S	53	V	84	S	115	W	146	L	177	P	208	I	239	A	270	R	301	I	332	I	363	L	394	F	425	A		
23	E	54	T	85	L	116	R	147	T	178	N	209	K	240	T	271	I	302	V	333	N	364	H	395	S	426	D		
24	F	55	I	86	Q	117	P	148	E	179	H	210	R	241	L	272	V	303	I	334	V	365	L	396	E	427	G		
25	C	56	F	87	D	118	T	149	A	180	L	211	N	242	Y	273	F	304	W	335	T	366	N	397	K	428	V		
26	L	57	Y	88	H	119	W	150	T	181	W	212	D	243	V	274	T	305	G	336	L	367	P	398	F	429	C		
27	G	58	V	89	L	120	A	151	E	182	G	213	D	244	R	275	D	306	T	337	A	368	D	399	Y	430	I		
28	K	59	D	90	D	121	R	152	K	183	Y	214	L	245	N	276	Q	307	L	338	A	369	N	400	C	431	D		
29	F	60	R	91	K	122	N	153	A	184	Y	215	S	246	R	277	V	308	S	339	K	370	F	401	S	432	A		

POR at 24-25; EX. 1001, Tables 3, 5, 9, and 10; EX2070, Petsko Decl., ¶¶263-274

Petitioner's Demand For Examples Of Each Species Ignores Informational Content And Misapplies The Law

759 F.3d 1285
United States Court of Appeals, Federal Circuit.

ABBVIE DEUTSCHLAND GMBH & CO., KG, AbbVie Bioresearch Center, Inc., and AbbVie Biotechnology, Ltd., Plaintiffs–Appellants,

district court did not abuse its discretion in excluding evidence of interference proceeding;

district court did not abuse its discretion in trial over written description requirement by excluding additional testimony summarizing prosecution arguments made to PTO; and

"It is important not to take the analogy of a plot of land too far in thinking of written description issues because, even if one builds a house only in one corner of the plot, one may still own the whole plot."

AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc., 759 F.3d 1285, 1300 (Fed. Cir. 2014).

motion for judgment as matter of law. Owner appealed.

Holdings: The Court of Appeals, Lourie, Circuit Judge, held that:

prior interference ruling by the Board of Patent Appeals and Interferences regarding priority and nonobviousness lacked requisite finality for purposes of collateral estoppel;

asserted patent claims for class of fully human antibodies that were defined by their high affinity and neutralizing activity to known human antigen were invalid for lack of adequate written description;

James J. Kelley, Eli Lilly and Company, of Indianapolis, IN, for amicus curiae Eli Lilly and Company. With him on the brief were Ted J. Ebersole, Alexander Wilson, and Sanjay Jivraj. On the brief for amicus curiae Pfizer Inc. was Jeffrey J. Oelke, White and Case LLP, of New York, N.Y.

Oskar Liivak, Cornell Law School, of Ithaca, N.Y., for amicus curiae Professor Oskar Liivak.

Before LOURIE, O'MALLEY, and CHEN, Circuit Judges.

Concurring opinion filed by Circuit Judge O'MALLEY.

Opinion

LOURIE, Circuit Judge.

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How POSAs Would Visualize The Patent Disclosure

Halozyme Expert | **Dr. Petsko**

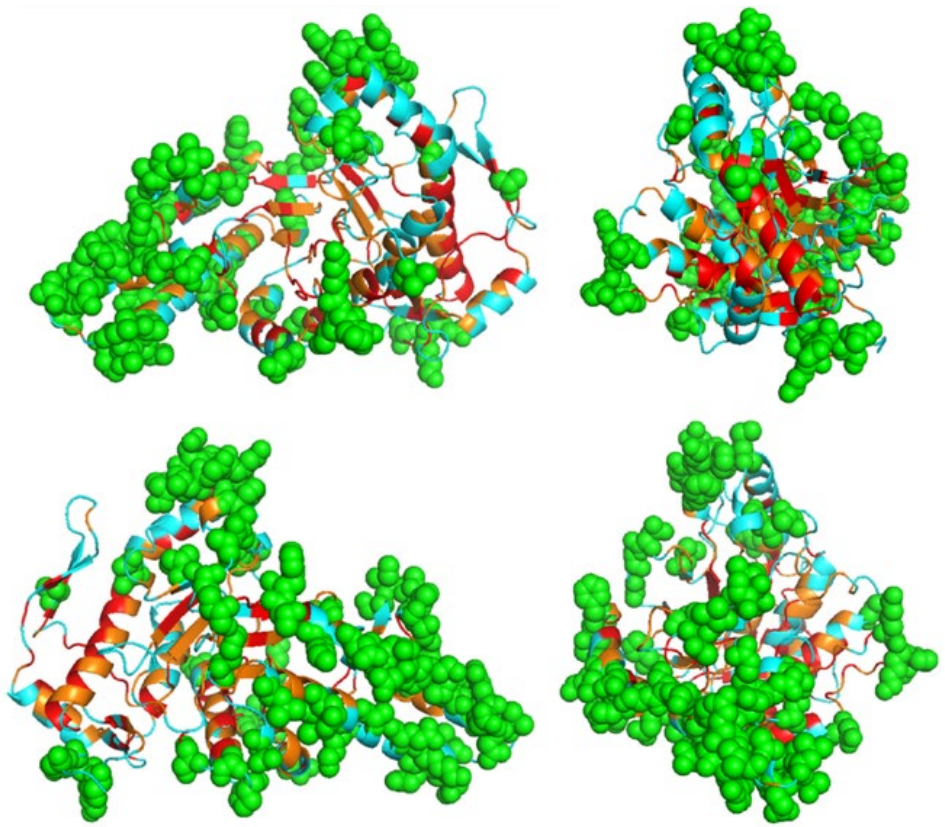
Position-by-position mutagenesis data for all 447 positions in SEQ ID NO 3

~9% (43/447) of positions:
all substitutions tolerated.

~35% (158/447)
all or most substitutions tolerated.

~21% (94/447)
all substitutions not tolerated; includes some essential residues.

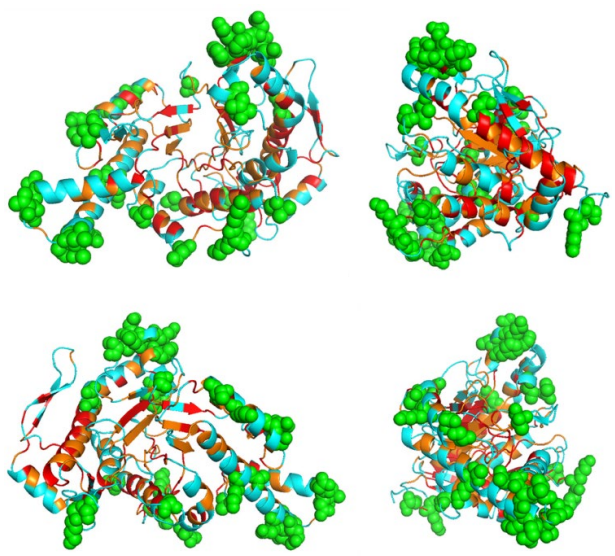
~48% (214/447)
all or most substitutions not tolerated; includes some essential residues



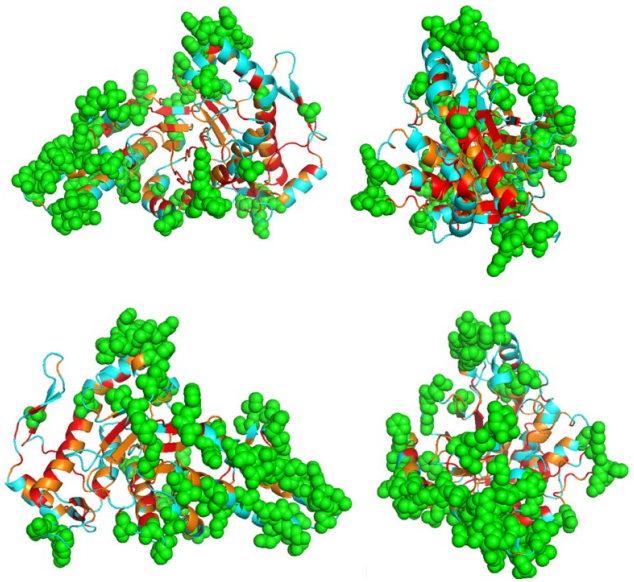
EX. 2070, Petsko Decl., ¶¶264-268, 283-288, 317-321; EX2166

How POSAs Would Visualize The Patent Disclosure

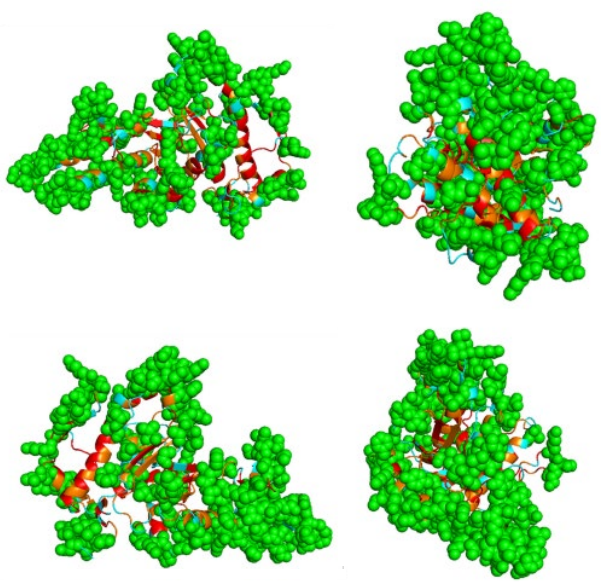
Halozyme Expert | **Dr. Petsko**



43 positions
(green spheres) that tolerated all tested substitutions



87 positions
(green spheres) that tolerated **≥90%** of tested substitutions



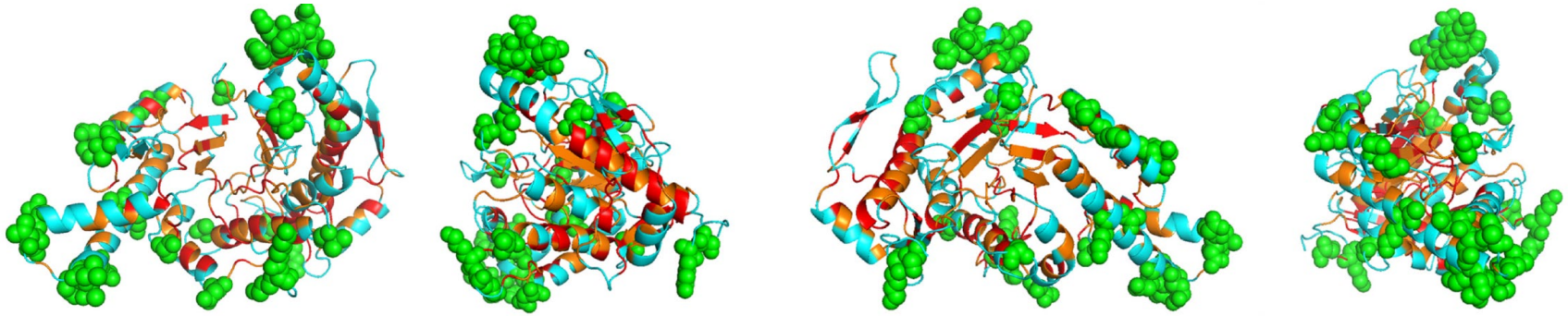
158 positions
(green spheres) that tolerated **≥60%** of tested substitutions

EX. 2070, Petsko Decl. at ¶¶ 317-321, 358-359; EX2166

Patent Disclosure Makes Multiply Mutating PH20 Predictable

Halozyme Expert | **Dr. Petsko**

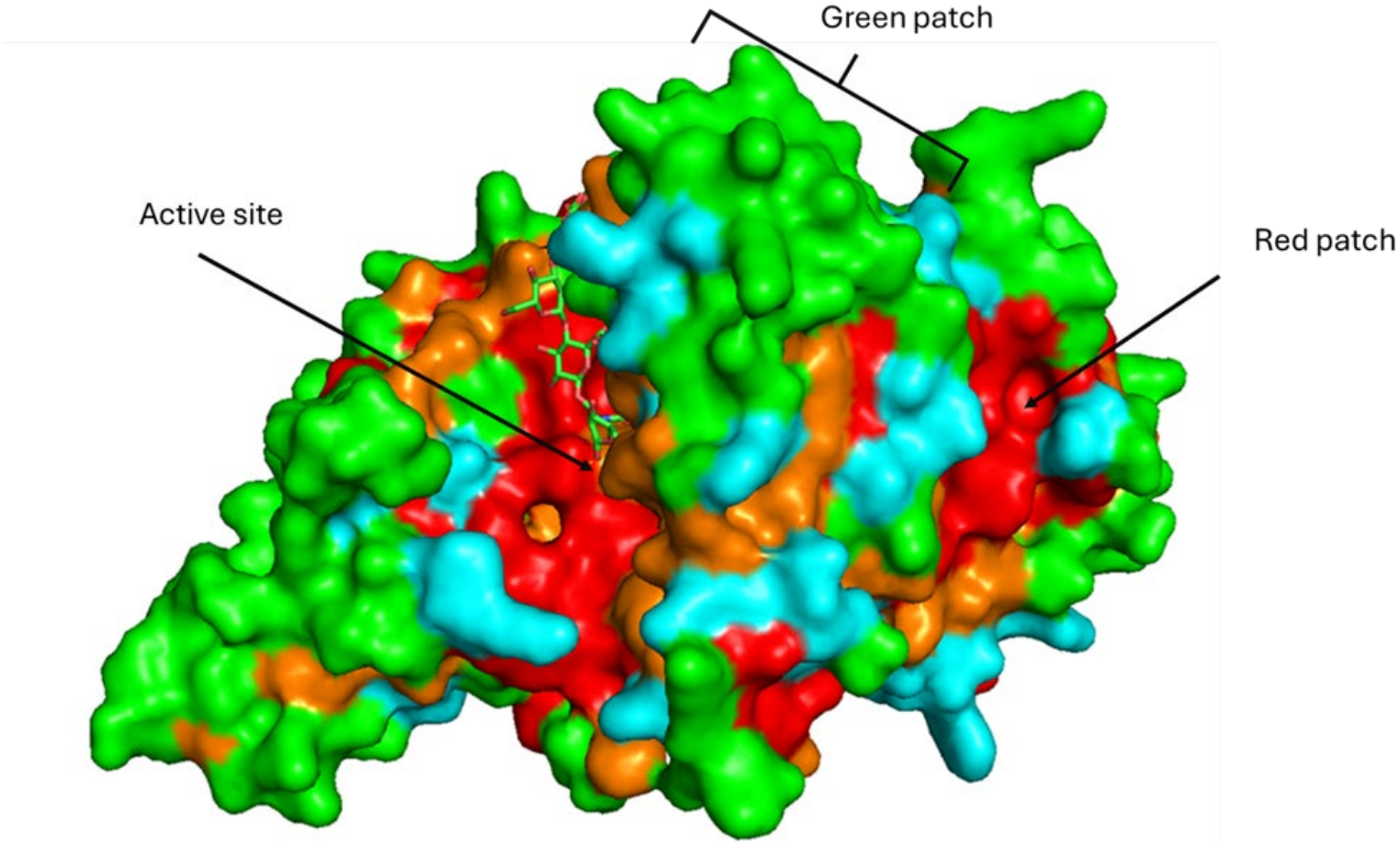
355. Second, the POSA wishing to make multiple modifications but retain activity could select from those positions that best tolerate substitution. The POSA seeking to be conservative in this regard could select positions that tolerated all tested substitutions, as shown in the figures below. A POSA choosing this route has many potential substitution options to consider; as shown below, residues that tolerate all tested substitutions are scattered across the surface of the protein. A POSA would reasonably expect that introducing multiple substitutions at these positions would also not abrogate activity.



EX. 2070, Petsko Decl., ¶355

Patent Disclosure Makes Multiply Mutating PH20 Predictable

Halozyme Expert | **Dr. Petsko**



Patent Disclosure Allows Reliable Predictions About Any Species

Halozyme Expert | **Dr. Petsko**

Q. So using that dataset, the person could predict which combinations might yield an active form of a mutated PH20 polypeptide let's say with 15 changes to it?

A. You could, but as I said, you would not tend to do that. A person of skill in the art would tend to only be interested in a much smaller number of mutations, because you can almost certainly get where you want to go that way.

Q. So a POSA is not interested in trying to practice the entire scope of this genus, they would focus on a portion of it, right?

A. A POSA would have the capability of both visualizing and practicing the full scope of the claims if they needed to. They could -- that is to say, they could look at any particular type of variant that fit the claim and they could make that variant and they would be able to predict beforehand what that variant might do with a -- in many cases, on a high degree of confidence.

Q. And they could do that for 1049 – a number that – I'm sorry. They can do that for a number of modified PH20 polypeptides that approaches 1049 different sequences?

A. They can do that for any member of the 1049 sequences that they wish to examine. Okay? A person of skill in the art would do it that way.

EX. 1131 (Petsko), 113:20-114:24 (objection omitted)

Patent Disclosure Makes Modifying PH20 Predictable

Halozyme Expert | **Dr. Simpson**

"I'm saying that a POSA would have had the information to choose to make a set of PH20 polypeptides that fit the criteria of the claim, and to be able to use them in the manner they intended.

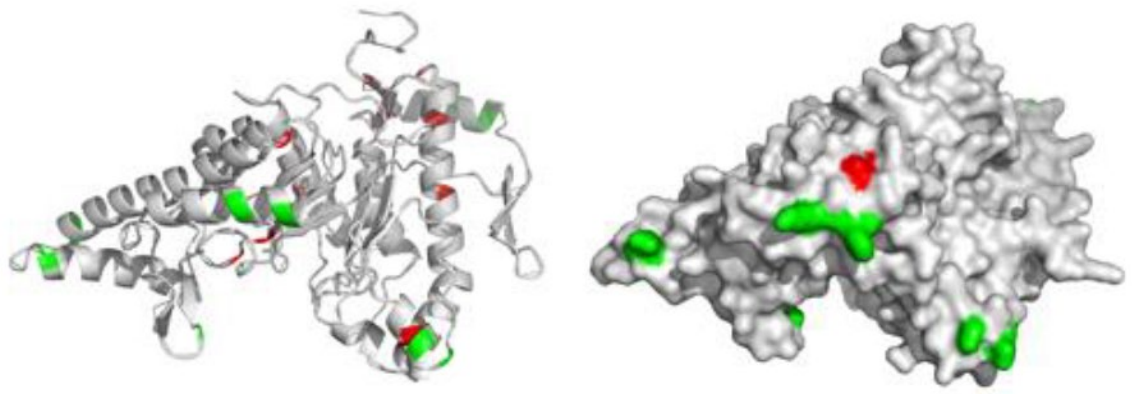
They would be able to visualize the species within the claim."

"The POSA could then use that information to choose, depending on whether their goal was to have the protein remain active or whether they did not care about having activity retained and had a different experimental goal. They would have information that would allow them to make the 95% identical polypeptide that would meet those criteria for them."

EX. 1130 (Simpson), 95:5-10; 98:3-10

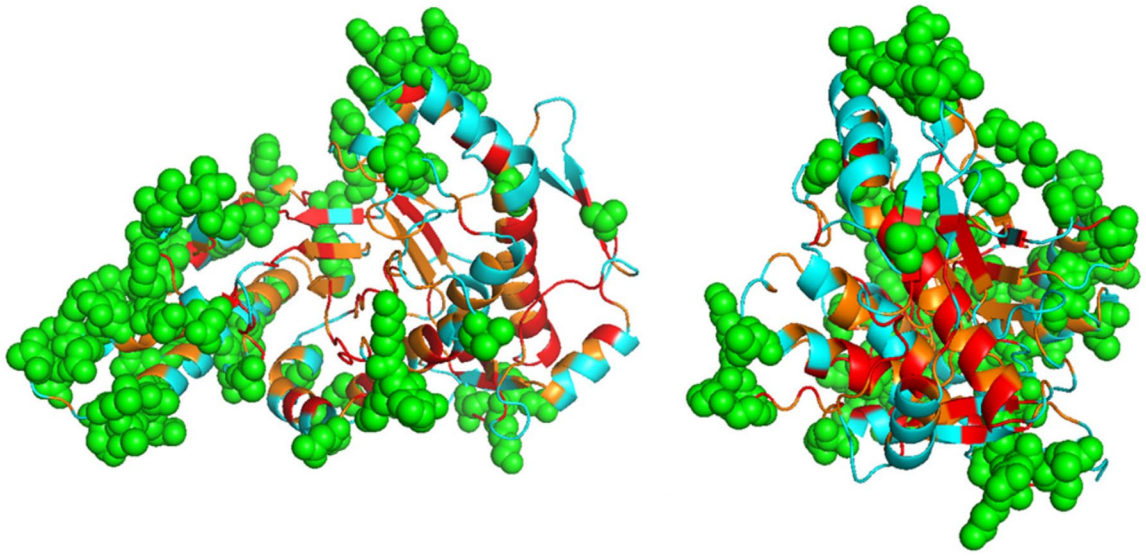
Petitioner's Experts Improperly Disregard Patent Disclosure

Merck Expert | **Dr. Naismith**



EX. 1133, Naismith Decl., ¶ 320

Halozyme Expert | **Dr. Petsko**



EX. 2070, Petsko Decl., ¶ 321

Considering Structural Context Is "Common And Expected"

Merck Expert | **Dr. Park**

"In the year 2011, to consider a mutation, it would have been very common and expected for a POSA to generate a model and consider the substitution in that structural context."

EX. 2077 (Park I), 176:2-5; *see also* Pet., 13-14, 103, 105

POSAs Would Routinely Use Model To Visualize/Practice

Merck Expert | **Dr. Park**

Q. So what's the purpose of generating a homology model for a protein structure?

A. It allows you to look at the molecule, as opposed to imagining it in your head.

Q. And it's useful to be able to look at the molecule, right?

A. Absolutely.

Q. And you can use homology modeling to predict the impact of substitutions in a protein?

A. A homology model can help you to evaluate the impact of a substitution. Yes.

EX. 2077 (Park I), 53:15-54:5 (objections omitted); *see also* Pet., 13-14, 103, 105

POSAs Would Routinely Use Model To Visualize/Practice

Merck Expert | **Dr. Hecht**

"Location, location, location. I mean, it's basically -- one could make a mutation in the abstract of this amino acid to that amino acid. If you do that in the abstract, it's pretty difficult to say anything intelligent about that. However, if you look at it in the context of its physical chemical environment in the protein and in the context of its homologous environment sequence space, then you're better able to come up with an assessment of the properties of a potential mutation. And the location of the position of interest matters, and the location of other amino acids in that neighborhood matters."

EX. 2076 (Hecht), 72:15-73:6

"The core issues in this case deal with making changes in a sequence. And to understand the impact of changes in the sequence, it's wise to look at the sequence and look at the structure to have a more informed -- to be able to make a more informed analysis of what would the impact be of such changes."

EX. 2076 (Hecht), 75:10-17; *see also* Pet., 13-14, 103, 105

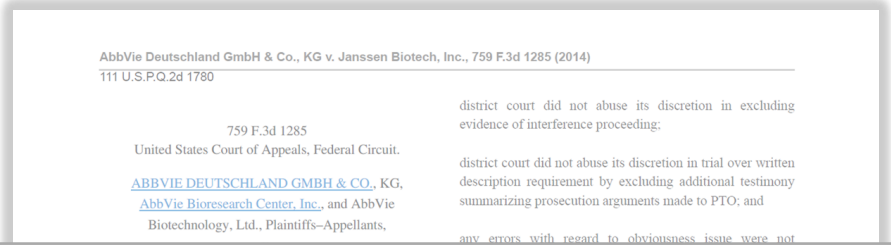
The Use Of Homology Modeling Was Routine

Halozyme Expert | **Dr. Simpson**

109. I agree. In fact, as I explain below, before the Hyal-1 crystal structure was published, I generated a homology model of Hyal-1 using the Swiss Model program and using the bee venom hyaluronidase structure as a template. We (my team and I) used the homology model to guide our mutagenesis experiments in which we sought to identify and experimentally confirm residues important to the Hyal-1 mechanism of action.

EX. 2068, Simpson Decl., ¶ 109; *see also* Pet., 13-14, 103, 105

Structure/Function Correlation Described In Specification And Known In Art Sufficient To Support Written Description


AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc., 759 F.3d 1285 (2014)
111 U.S.P.Q.2d 1780

759 F.3d 1285
United States Court of Appeals, Federal Circuit.

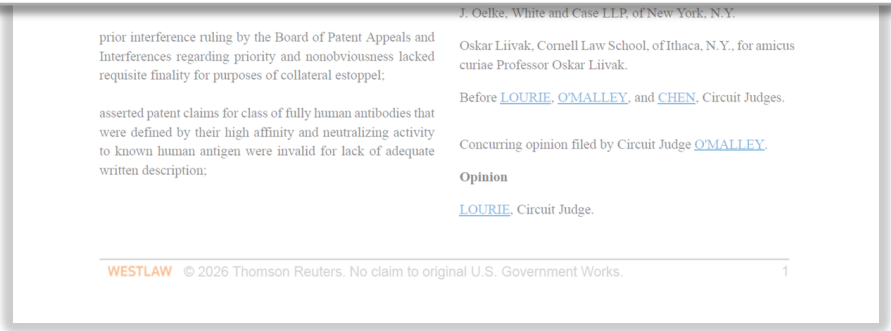
ABBVIE DEUTSCHLAND GMBH & CO., KG, AbbVie Bioresearch Center, Inc., and AbbVie Biotechnology, Ltd., Plaintiffs–Appellants,

district court did not abuse its discretion in excluding evidence of interference proceeding;

district court did not abuse its discretion in trial over written description requirement by excluding additional testimony summarizing prosecution arguments made to PTO; and

"It is true that functionally defined claims can meet the written description requirement if a reasonable structure-function correlation is established, whether by the inventor as described in the specification or known in the art at the time of the filing date."

AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc., 759 F.3d 1285, 1301 (Fed. Cir. 2014).


prior interference ruling by the Board of Patent Appeals and Interferences regarding priority and nonobviousness lacked requisite finality for purposes of collateral estoppel;

asserted patent claims for class of fully human antibodies that were defined by their high affinity and neutralizing activity to known human antigen were invalid for lack of adequate written description;

J. Oelke, White and Case LLP, of New York, N.Y.

Oskar Liivak, Cornell Law School, of Ithaca, N.Y., for amicus curiae Professor Oskar Liivak.

Before LOURIE, O'MALLEY, and CHEN, Circuit Judges.

Concurring opinion filed by Circuit Judge O'MALLEY.

Opinion

LOURIE, Circuit Judge.

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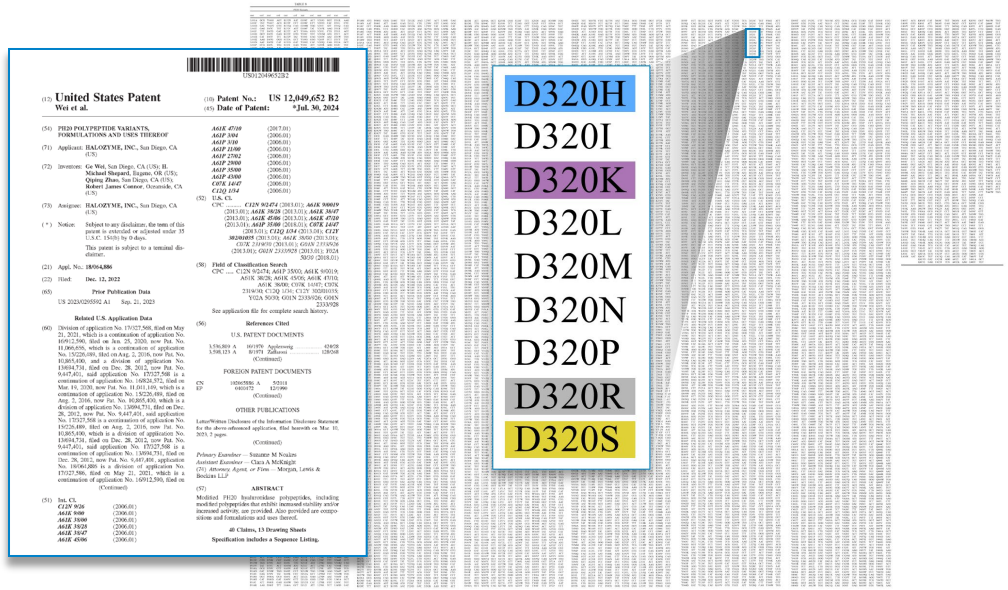
The Specification Discloses Sufficient Representative Species

’652 Patent

Only **Four** P320 variants/sub-variants claimed

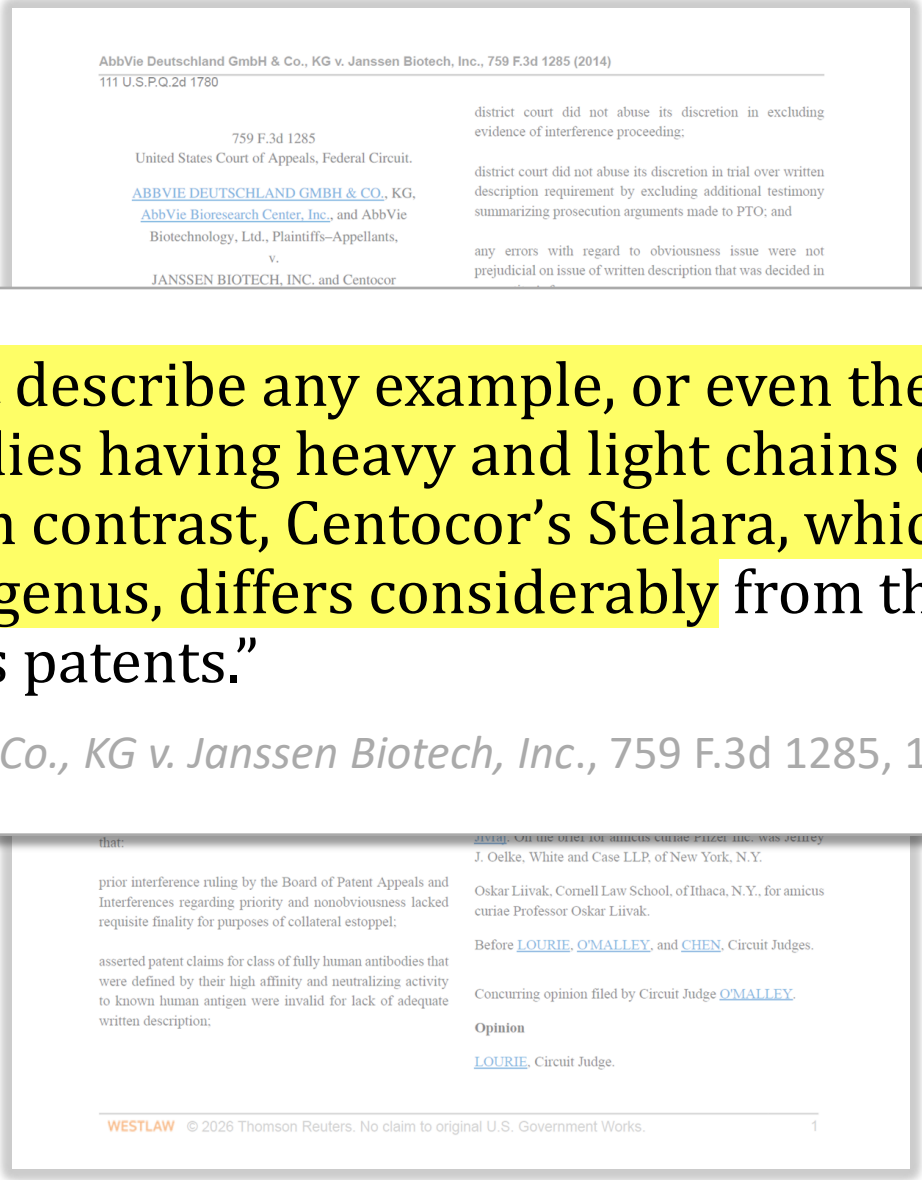


Inventors Did NOT Claim

- All hyaluronan-degrading polypeptides
- All modified PH20s
- PH20s with any substitution at position 320 other than H, K, R, or S

EX. 1001, 200:42-231:17

Petitioner Has Not Shown Genus Is Structurally Heterogeneous


AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc., 759 F.3d 1285 (2014)
111 U.S.P.Q.2d 1780

759 F.3d 1285
United States Court of Appeals, Federal Circuit.

ABBVIE DEUTSCHLAND GMBH & CO., KG, AbbVie Bioresearch Center, Inc., and AbbVie Biotechnology, Ltd., Plaintiffs–Appellants,
v.
JANSSEN BIOTECH, INC. and Centocor

district court did not abuse its discretion in excluding evidence of interference proceeding;

district court did not abuse its discretion in trial over written description requirement by excluding additional testimony summarizing prosecution arguments made to PTO; and

any errors with regard to obviousness issue were not prejudicial on issue of written description that was decided in

that:

prior interference ruling by the Board of Patent Appeals and Interferences regarding priority and nonobviousness lacked requisite finality for purposes of collateral estoppel;

asserted patent claims for class of fully human antibodies that were defined by their high affinity and neutralizing activity to known human antigen were invalid for lack of adequate written description;

J. Oelke, White and Case LLP, of New York, N.Y.

Oskar Liivak, Cornell Law School, of Ithaca, N.Y., for amicus curiae Professor Oskar Liivak.

Before LOURIE, O'MALLEY, and CHEN, Circuit Judges.

Concurring opinion filed by Circuit Judge O'MALLEY.

Opinion

LOURIE, Circuit Judge.

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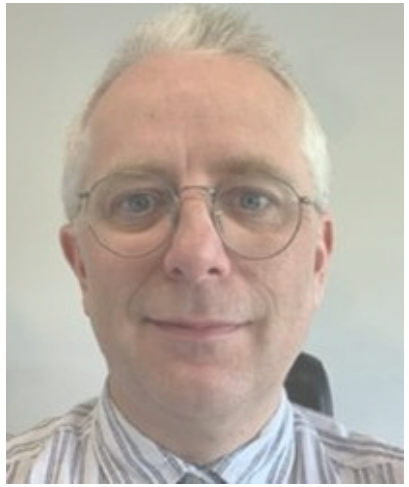
"[T]he patents do not describe any example, or even the possibility, of fully human IL–12 antibodies having heavy and light chains other than the V_H3 and Lambda types. In contrast, Centocor's Stelara, which falls within the scope of the claimed genus, differs considerably from the Joe–9 antibodies described in AbbVie's patents."

AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc., 759 F.3d 1285, 1300 (Fed. Cir. 2014).

Petitioner's Expert Agrees Active PH20s Share Same Fold

Merck Expert | **Dr. Naismith**



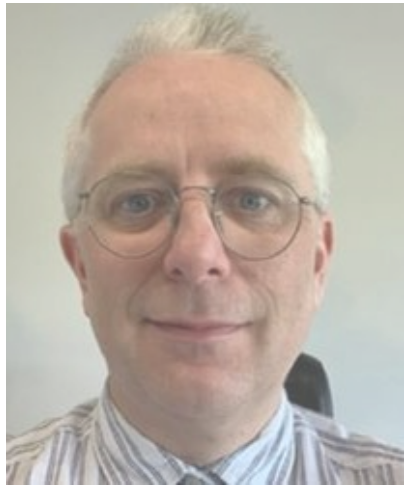
Q. Is it the case that active modified PH20 proteins share a common structure in terms of the native fold of PH20?

A. So they would have the same fold, there could be differences as I described and we know exist between the bee venom and the human hyaluronidase, both are active enzymes.

EX. 2301 (Naismith), 213:10-18 (objections omitted)

Petitioner's Expert Admits Proper Fold Preserves Structure/Function Relationship

Merck Expert | **Dr. Naismith**



Q. Okay. So is it fair to say that if you have an active PH20 you expect that that active PH20 has adopted the native fold?

A. You would assume that if it is properly folded, but there could be structural differences. But the fold is quite a broad term. It is relatively a distance high level term. But you would assume that it preserves a structure function relationship and we talked about the bee venom and the human HYAL1. So there are structural differences. So those are different structures ----

Q. Mmm-hmm.

A. ---- and that was noted in the publication. So you can envisage proteins having a proper fold which is, and we have used this term where it is active it is natively folded. But structurally there still could be differences and structural diversity when you start to introduce mutations.

EX. 2301 (Naismith), 95:9-96:4

Petitioner's Arguments Invite Legal Error

Paper No. 22
Filed: August 8, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyme Inc.,
Patent Owner.

Case No. PGR2025-00033
U.S. Patent No. 12,049,652

PETITIONER'S REPLY

"What is required is the identity of the particular amino acid sequences that will create the three-dimensional structure."

Reply at 16

"Performing that experimentation for the size of the sequence space is impossible. This evidence is dispositive to written description and enablement."

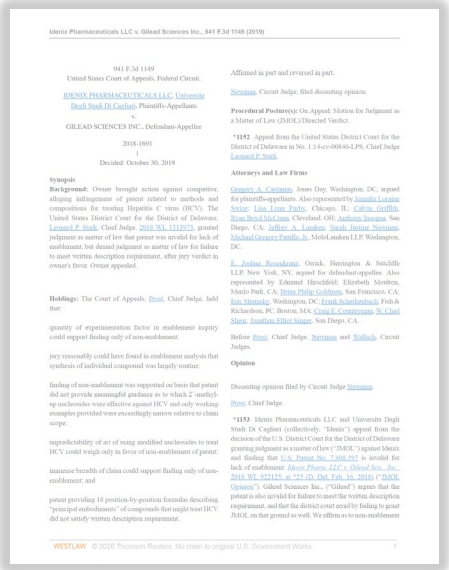
Reply at 9-10

Reference: Reply, 7-16

Petitioner's Arguments Invite Legal Error

"The doctrine never created a heightened requirement to provide a nucleotide-by-nucleotide recitation of the entire genus of claimed genetic material; it has always expressly permitted the disclosure of structural features common to the members of the genus."

Ariad Pharms., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1352 (Fed. Cir. 2010).



"We are mindful of *Ariad*'s caution that written description does not require 'a nucleotide-by-nucleotide recitation of the entire genus.' The purpose of that rule is to allow relatively few representative examples or formulas to support a claim on a structurally similar genus."

Idenix Pharms. LLC v. Gilead Scis. Inc., 941 F.3d 1149, 1165 (Fed. Cir. 2019) (internal citations omitted).

Lack of Inactivating Changes Is Common Feature; Teaches Structure/Function Correlation

Halozyme Expert | **Dr. Petsko**

293. This does not mean PH20 is unpredictable or that making and using the claimed modified polypeptides is unpredictable. It means PH20 is generally intolerant to mutations unless those mutations are made in certain places, and the '652 patent teaches where to make mutations to likely retain activity. The '652 patent renders modifying PH20 predictable by identifying these areas that are particularly intolerant to mutation, and those that are tolerant.

EX. 2070, Petsko Decl.,¶ 293

Inactives Data Distinguishes These Facts From *Idenix*

941 F.3d 1149
United States Court of Appeals, Federal Circuit.

IDENIX PHARMACEUTICALS LLC, Universita Degli Studi Di Cagliari, Plaintiffs-Appellants
v.
GILEAD SCIENCES INC., Defendant-Appellee

Affirmed in part and reversed in part.

Newman, Circuit Judge, filed dissenting opinion.

Procedural Posture(s): On Appeal; Motion for Judgment as a Matter of Law (JMOL)/Directed Verdict.

***1152** Appeal from the United States District Court for the

"The specification, however, provides no method of distinguishing effective from ineffective compounds for the compounds reaching beyond the formulas disclosed in the '597 patent."

Idenix Pharms. LLC v. Gilead Scis. Inc., 941 F.3d 1149, 1164 (Fed. Cir. 2019).

finding of non-enablement was supported on basis that patent did not provide meaningful guidance as to which 2'-methyl-up nucleosides were effective against HCV and only working examples provided were exceedingly narrow relative to claim scope;

unpredictability of art of using modified nucleosides to treat HCV could weigh only in favor of non-enablement of patent;

immense breadth of claim could support finding only of non-enablement; and

patent providing 18 position-by-position formulas describing "principal embodiments" of compounds that might treat HCV did not satisfy written description requirement.

Dissenting opinion filed by Circuit Judge Newman.

Prost, Chief Judge.

***1153** Idenix Pharmaceuticals LLC and Universita Degli Studi Di Cagliari (collectively, "Idenix") appeal from the decision of the U.S. District Court for the District of Delaware granting judgment as a matter of law ("JMOL") against Idenix and finding that U.S. Patent No. 7,608,597 is invalid for lack of enablement. *Idenix Pharm. LLC v. Gilead Scis., Inc.*, 2018 WL 922125, at *25 (D. Del. Feb. 16, 2018) ("JMOL Opinion"). Gilead Sciences Inc., ("Gilead") argues that the patent is also invalid for failure to meet the written description requirement, and that the district court erred by failing to grant JMOL on that ground as well. We affirm as to non-enablement

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Similarity to Sequence Is A Common Structural Feature; WD Does Not Require Perfect Correspondence To Structure

"CJ disputes that similarity to the consensus sequence defines a common structural feature, citing several articles as indicating that a promoter closer to the consensus sequence will not always be stronger than one farther from that sequence."

Ajinomoto Co. v. Int'l Trade Comm'n, 932 F.3d 1342, 1360 (Fed. Cir. 2019).

"CJ's argument both assumes too strict a legal standard and reads too much into its cited references. 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.'"

Ajinomoto Co. v. Int'l Trade Comm'n, 932 F.3d 1342, 1360 (Fed. Cir. 2019).

under function-way-result framework;

increased activity of YddG protein at least partly contributed to enhanced resistance of later strains of accused product;

Taranto, Circuit Judge.

Ajinomoto Co., Inc. and Ajinomoto Heartland Inc. (collectively, Ajinomoto) filed a complaint against CJ

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Misfolding/Aggregation From Mutation Is Rare

Halozyme Expert | **Dr. Petsko**

"That would not be the case for PH20."

EX. 1131 (Petsko), 42:6-7

"… usually not the case for most mutation." and "… it is rare."

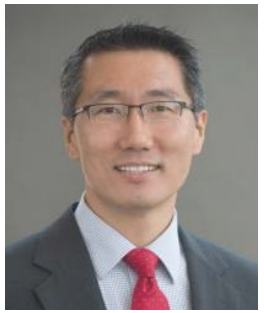
EX. 1131 (Petsko), 40:18-24; 197:6-15

"… not a common consequence"; "If I make, typically, 100 mutations in a protein, okay, one or two might do that. None of them might do that."

EX. 1131 (Petsko), 48:23-49:8

Parties' Experts Agree Distant Effects Are "Not Very Common" And Mutations Can Be Treated Independently

Merck Expert | **Dr. Park**



"Distant residues are known to be coupled in some cases, but they're not very common.

So if you introduce a mutation that are far apart from each other, then each mutation can be treated independently and evaluated independently, and one may be able to estimate the combined effect of the two or more mutations, if necessary, and include whether the mutant would be better or worse than wild-type."

EX. 2077 (Park I), 201:7-13

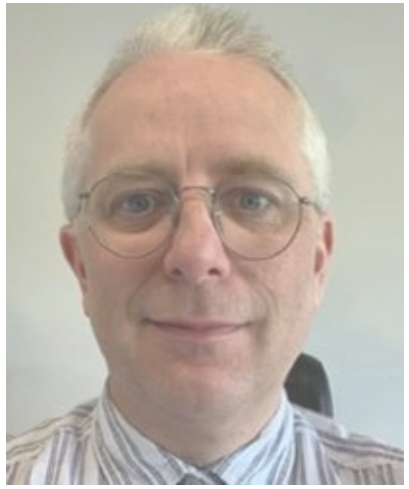
Halozyme Expert | **Dr. Petsko**

Similarly, Dr. Petsko explained that if two mutations "are separated from each other in the structure there is a high degree of likelihood that they will operate independently."

EX. 1131 (Petsko), 195:5-10

Epistasis Relates To Degree Of Activity, Not Existence Of Activity

Merck Expert | **Dr. Naismith**



Q. Okay. Is it your testimony – is it your testimony that in order for two mutations to be independent their effects have to be additive?

A. So for them not to have epistasis, for there to be no epistasis the definition is the effects are additive. That is the definition of epistasis.

Q. And so am I understanding "additive" correctly in that if you have one mutation that gives you 100% activity and another mutation that gives you 100% activity, when you combine them you would still have 100% activity?

A. If they were independent of one another, yes.

Q. Okay, and ----

A. Because there is no epistatic effect.

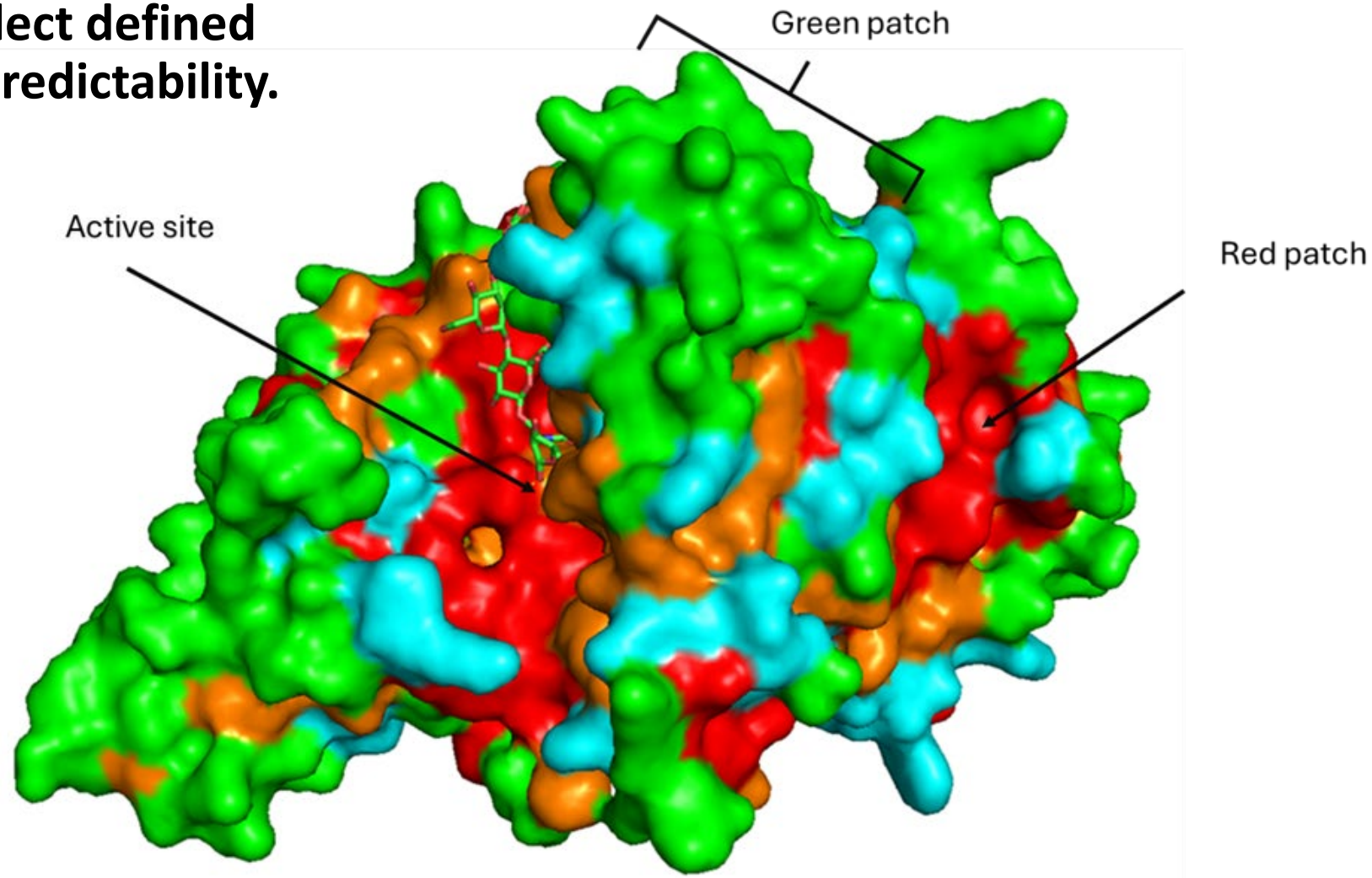
Q. I am trying to understand the additive part?

A. Okay. So it is based on the thermodynamic but then it translates to multiplying the activity measurement; so one times one is one.

EX. 2301 (Naismith), 129:17-130:18 (objections omitted)

Number Of Inactivating Changes Does Not Show Epistasis

Inactivating changes reflect defined structural roles, not unpredictability.



EX. 2070, Petsko Decl., ¶ 339

Enablement (Ground 2)

Halozyme

The *Wands* Factors Weigh In Favor Of Enablement

***In re Wands* factors**

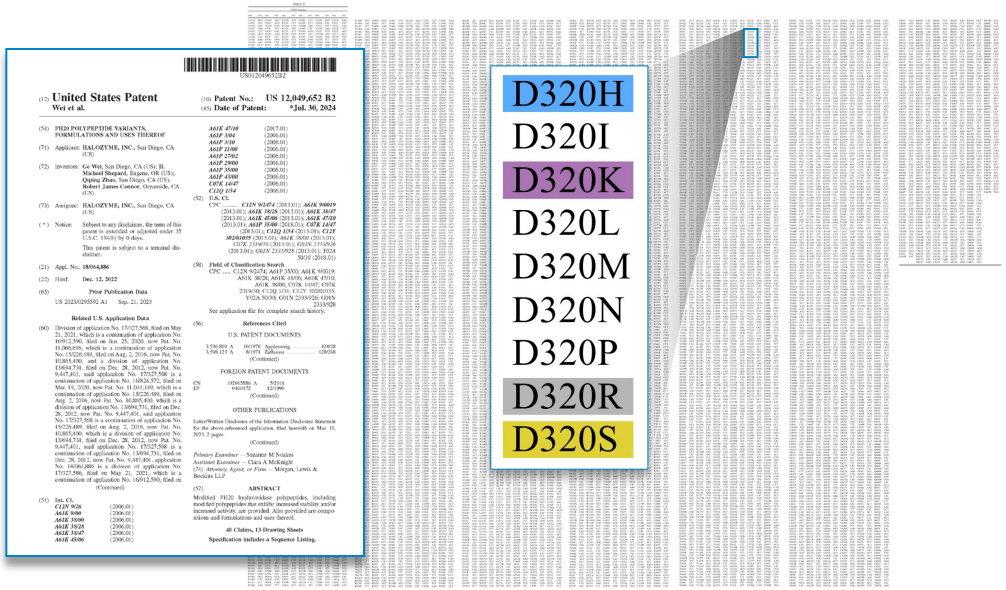
(858 F.2d 731, Fed. Cir. 1988)

- Scope and nature of invention
- Breadth of claims
- Level of skill in art
- State of prior art
- Guidance in specification
- Predictability of field
- Working examples
- Quantity of experimentation required

The Claimed Monopoly Is Extremely Narrow

’652 Patent

Only **Four** D320 variants claimed



Subvariants must share ≥91% sequence identity

Inventors Did NOT Claim

- All hyaluronan-degrading polypeptides
- All modified PH20s
- PH20s with any substitution at position 320 other than H, K, R, or S

EX. 1001, 200:42-231:17

POSAs Were Skilled And State Of Art Was Developed

Petitioner: "a skilled artisan was highly skilled... there was significant knowledge in the public art about hyaluronidases..." Pet. at 76-77

A POSA would know:

1. Where the catalytic and substrate binding residues of PH20 were
2. Where the disulfide bridges and essential glycosylation sites were
3. What the structure of active PH20s were and where the amino acids were positioned in that structure

EX. 1001, 70:9-56; EX. 2068, ¶303; EX. 2070, ¶¶148-217, 263-342

The Guidance In The Disclosure Is Unprecedented

		30	D	61	L	92	A	123	W	154	K	185	L	216	W	247	V	278	L	309	I	340	M	371	A	402	C	433	F
Position	WT	31	E	62	G	93	K	124	K	155	Q	186	F	217	L	248	R	279	K	310	M	341	C	372	I	403	Y	434	L
1	L	32	P	63	Y	94	K	125	P	156	E	187	P	218	W	249	E	280	F	311	R	342	S	373	Q	404	S	435	K
2	N	33	L	64	Y	95	D	126	K	157	F	188	D	219	N	250	A	281	L	312	S	343	Q	374	L	405	T	436	P
3	F	34	D	65	P	96	I	127	D	158	E	189	C	220	E	251	I	282	S	313	M	344	V	375	E	406	L	437	P
4	R	35	M	66	Y	97	T	128	V	159	K	190	Y	221	S	252	R	283	Q	314	K	345	L	376	K	407	S	438	M
5	A	36	S	67	I	98	F	129	Y	160	A	191	N	222	T	253	V	284	D	315	S	346	C	377	G	408	C	439	E
6	P	37	L	68	D	99	Y	130	K	161	G	192	H	223	A	254	S	285	E	316	C	347	Q	378	G	409	K	440	T
7	P	38	F	69	S	100	M	131	N	162	K	193	H	224	L	255	K	286	L	317	L	348	E	379	K	410	E	441	E
8	V	39	S	70	I	101	P	132	R	163	D	194	Y	225	Y	256	I	287	V	318	L	349	Q	380	F	411	K	442	E
9	I	40	F	71	T	102	V	133	S	164	F	195	K	226	P	257	P	288	Y	319	L	350	G	381	T	412	A	443	P
10	P	41	I	72	G	103	D	134	I	165	L	196	K	227	S	258	D	289	T	320	D	351	V	382	V	413	D	444	Q
11	N	42	G	73	V	104	N	135	E	166	V	197	P	228	I	259	A	290	F	321	N	352	C	383	R	414	V	445	I
12	V	43	S	74	T	105	L	136	L	167	E	198	G	229	Y	260	K	291	G	322	Y	353	I	384	G	415	K	446	F
13	P	44	P	75	V	106	G	137	V	168	T	199	Y	230	L	261	S	292	E	323	M	354	R	385	K	416	D	447	Y
14	F	45	R	76	N	107	M	138	Q	169	I	200	N	231	N	262	P	293	T	324	E	355	K	386	P	417	T		
15	L	46	I	77	G	108	A	139	Q	170	K	201	G	232	T	263	L	294	V	325	T	356	N	387	T	418	D		
16	W	47	N	78	G	109	V	140	Q	171	L	202	S	233	Q	264	P	295	A	326	I	357	W	388	L	419	A		
17	A	48	A	79	I	110	I	141	N	172	G	203	C	234	Q	265	V	296	L	327	L	358	N	389	E	420	V		
18	W	49	T	80	P	111	D	142	V	173	K	204	F	235	S	266	F	297	G	328	N	359	S	390	D	421	D		
19	N	50	G	81	Q	112	W	143	Q	174	L	205	N	236	P	267	A	298	A	329	P	360	S	391	L	422	V		
20	A	51	Q	82	K	113	E	144	L	175	L	206	V	237	V	268	Y	299	S	330	Y	361	D	392	E	423	C		
21	P	52	G	83	I	114	E	145	S	176	R	207	E	238	A	269	T	300	G	331	I	362	Y	393	Q	424	I		
22	S	53	V	84	S	115	W	146	L	177	P	208	I	239	A	270	R	301	I	332	I	363	L	394	F	425	A		
23	E	54	T	85	L	116	R	147	T	178	N	209	K	240	T	271	I	302	V	333	N	364	H	395	S	426	D		
24	F	55	I	86	Q	117	P	148	E	179	H	210	R	241	L	272	V	303	I	334	V	365	L	396	E	427	G		
25	C	56	F	87	D	118	T	149	A	180	L	211	N	242	Y	273	F	304	W	335	T	366	N	397	K	428	V		
26	L	57	Y	88	H	119	W	150	T	181	W	212	D	243	V	274	T	305	G	336	L	367	P	398	F	429	C		
27	G	58	V	89	L	120	A	151	E	182	G	213	D	244	R	275	D	306	T	337	A	368	D	399	Y	430	I		
28	K	59	D	90	D	121	R	152	K	183	Y	214	L	245	N	276	Q	307	L	338	A	369	N	400	C	431	D		
29	F	60	R	91	K	122	N	153	A	184	Y	215	S	246	R	277	V	308	S	339	K	370	F	401	S	432	A		

EX. 1001, Tables 3, 5, 9, and 10; EX2070, Petsko Decl., ¶¶263-274

The Guidance In The Disclosure Is Unprecedented

Halozyme Expert | **Dr. Simpson**

163. This level of structure-function detail for an individual protein of this size was virtually unheard of as of 2012. I am not aware of a comparable project.

164. The data are extraordinarily useful to a POSA seeking to make and use modified PH20 polypeptides.

EX. 2068, Simpson Decl., ¶¶ 163-164

Petitioner Errs In Dismissing Guidance As To What Is Operative, Inoperative

"The examples, both operative and inoperative, are the best guidance this art permits, as far as we can conclude from the record."

***

"Depriving inventors of claims which adequately protect them and limiting them to claims which practically invite appropriation of the invention while avoiding infringement inevitably has the effect of suppressing disclosure. What the dissent seems to be obsessed with is the thought of catalysts which won't work to produce the intended result. Appellants have enabled those in the art to see that this is a real possibility, which is commendable frankness in a disclosure....The dissent wants appellants to make everything predictable in advance, which is impracticable and unreasonable."

Application of Angstadt, 537 F.2d 498, 504 (C.C.P.A. 1976).

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Petitioner's Expert Admits Inactives Guide Practice Of Invention

Merck Expert | **Dr. Park**

Q. Would you expect that if you tried to introduce a mutation into a position known to be important for folding, that the -- that the protein would not be able to fold correctly?

A. I would expect that; therefore, I would not try that.

EX. 2077 (Park I), 106:12-17

Predictability:
The Certainty The Law Requires Is Not Greater Than Reasonable

"Similarly, in *Minerals Separation*, the Court dismissed a challenge to a claimed process for separating metal from mineral ores. 242 U.S., at 270, 37 S.Ct. 82. The record showed that 'preliminary tests' were required to adapt the process to any particular ore. *Ibid*. Once more, the Court explained that 'the certainty which the law requires in patents is not greater than is reasonable.' *Ibid*. And because the 'composition of ores varies infinitely,' it was 'impossible to specify in a patent the precise treatment which would be most successful and economical in each case.' *Id.*, at 271, 37 S.Ct. 82."

Amgen Inc. v. Sanofi, 598 U.S. 594, 611–12 (2023)
(citing *Minerals Separation, Ltd. v. Hyde*, 242 U.S. 261 (1916)).

Patent Disclosure Makes Modifying PH20 Predictable

Halozyme Expert | **Dr. Petsko**

Q. So your opinion is that a POSA could use the data from testing single mutants in the patent to select 15 or 20 substitutions in the PH20 sequence, and you would be able to predict whether that mutated 15 or 20 residue-mutated PH20 will exhibit the activity that you are hoping to get?

A. My opinion is that you could do so. My opinion is also that you would almost never do so. You would probably rarely, if ever, make that many substitutions. You wouldn't need to.

EX. 1131 (Petsko), 111:9-19

Patent Disclosure Makes Modifying PH20 Predictable

Halozyme Expert | **Dr. Simpson**

"I'm saying that a POSA would have had the information to choose to make a set of PH20 polypeptides that fit the criteria of the claim, and to be able to use them in the manner they intended.

They would be able to visualize the species within the claim."

"The POSA could then use that information to choose, depending on whether their goal was to have the protein remain active or whether they did not care about having activity retained and had a different experimental goal. They would have information that would allow them to make the 95% identical polypeptide that would meet those criteria for them."

EX. 1130 (Simpson), 95:5-10, 98:3-10

Petitioner's Enablement Theory Starts Where No POSA Would

Halozyme Expert | **Dr. Simpson**

"… no POSA would start with the theoretical maximum number of potential sequence variants as a starting point for making a comparative analysis of what amino acids would retain activity in a PH20 polypeptide."

EX. 1130 (Simpson), 93:20-24

POSAs Would Not Screen Large Combinatorial Libraries

Halozyme Expert | **Dr. Petsko**

Q. Are you saying that, after reading the '600 patent, a POSA would not have tried to make PH20 polypeptides by generating combinatorial libraries of mutants having random combinations of substitutions and screening them for activity.

A. I am saying that under most of the circumstances I can envision, the POSA would not start that way at all. They would start with a much more focused program making use of the data in the patent.

Q. Did you find anything in the common disclosure suggesting that they should do the path -- should take the path of making combinatorial libraries and screening them to produce PH20 proteins with multiple mutations?

A. Didn't suggest that to me. Again, I think as long as you are dealing with a -- with a situation like this where you have a wealth of information at every position in the sequence, you would first start to do it by -- if you – I'm not -- I don't want to use the word "design" in its broadest sense. But if you understand what I mean by that. You would try to -- you would predict -- you would be able to write down sequences where you could predict what you were likely to see and you would test those first.

EX. 1131 (Petsko), 106:16-107:17

Petitioner Misrepresents Patent Disclosure Re: Screening

’652 Patent

In one example, after the method is performed, any modified hyaluronan-degrading enzymes identified as exhibiting stability, such as increased stability, under a denaturation condition can be modified or further modified to increase or optimize the stability. A secondary library can be created by introducing additional modifications in a first identified modified hyaluronan-degrading enzyme.

***

In one aspect of the method, the modified hyaluronan-degrading enzymes are tested or screened for hyaluronidase activity in the presence and absence of one or more denaturation conditions or denaturing agent.

EX. 1001, 142:14-26; 134:60-135:32; Pet., 50

Petitioner Commits Legal Error By Relying On Cumulative Time/Effort

specification did not enable portion of asserted claims directed to class of antibodies with unknown amino acid sequences.

"As Amgen sees it, that court conflated the question whether an invention is enabled with the question how long may it take a person skilled in the art to make every embodiment within a broad claim. We do not see it that way. While we agree with Amgen that enablement is not measured against the cumulative time and effort it takes to make every embodiment within a claim, we are not so sure the Federal Circuit thought otherwise. That court went out of its way to say that it 'do[es] not hold that the effort required to exhaust a genus is dispositive.'"

Amgen Inc. v. Sanofi, 598 U.S. 594, 615 (2023) (internal citations omitted).

Holdings: In a unanimous opinion, the Supreme Court, Justice Gorsuch, held that:

specification enabled portion of asserted claims directed to 26 exemplary antibodies with identified amino acid sequences, but

infringement. Sanofi replied that it was not liable to Amgen for infringement because Amgen's relevant claims were invalid under the Patent Act's "enablement" requirement. That provision requires a patent applicant to describe the invention "in such full, clear, concise, and exact terms as to enable any person skilled in the art ... to make and use the [invention]." 35 U.S.C. § 112(a). Sanofi characterized the methods Amgen outlined for generating additional antibodies

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Petitioner Commits Legal Error By Relying On Cumulative Time/Effort

Paper No. 1
Filed: March 7, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyme Inc.,
Patent Owner.

Case No. PGR2025-00033
U.S. Patent No. 12,049,652

PETITION FOR POST GRANT REVIEW

"[T]he claim language defines enormous genera: between 10^{59} and 10^{112} distinct polypeptides. Their real-world scope is absurd—to practice the claims' full scope requires a skilled artisan to make-and-test at least ~10^{59} mutants. Simply producing one molecule of each mutant—required to know if each is active or inactive or exhibits increased stability—which for each genera's many multisubstituted mutants would consume an aggregate mass (~3.93 x 10^{37} kg) that exceeds the mass of the Earth (~6 x 10^{24} kg).[64] Testing every polypeptide within the claims' scope in search of "active mutants" is impossible—literally. Pet., 25

Petitioner Commits Legal Error By Relying On Cumulative Time/Effort

In re Wands, 858 F.2d 731 (1988)
57 USLW 2264, 8 U.S.P.Q.2d 1400

858 F.2d 731
United States Court of Appeals, Federal Circuit.

(board) affirming the rejection of all remaining claims in appellant's application for a patent, serial No. 188,735, entitled "Immunoassay Utilizing Monoclonal High Affinity

"The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed[.]"

***

"No evidence was presented by either party on how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen. However, it seems unlikely that undue experimentation would be defined in terms of the number of hybridomas that were never screened."

In re Wands, 858 F.2d 731, 737, 740 (Fed. Cir. 1988).

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See also EX. 2301 (Naismith), 244:22-245:15; Petition at 13-14, 16

Petitioner Commits Legal Error By Ignoring POSA Skill, Guidance

Paper No. 1
Filed: March 7, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyme Inc.,
Patent Owner.

Case No. PGR2025-00033
U.S. Patent No. 12,049,652

PETITION FOR POST GRANT REVIEW

"They thus capture a mutant with 5 substituted hydrophobic residues clustered in a small region, as well as one with 42 substitutions mixing polar, charged, aliphatic residues in another, and in any manner."

Pet., 31

"[C]laims referencing SEQ ID NO: 32 that allow between 21 and 42 changes (with any mixture of deletions and substitutions) capture a PH20 terminating at position 416 or below."

Pet., 32

Petitioner's Deviation From Patent Teaching Is Insufficient To Disprove Enablement As A Matter Of Law

Attorneys and Law Firms

"A party who wishes to prove that the claims of a patent are not enabled by means of a failed attempt to make the disclosed invention must show that the patent's disclosure was followed. Because Sutherland deviated from the teachings of the patent in his failed attempts to make the claimed antibodies, his testimony is insufficient to disprove enablement as a matter of law."

"[I]t is imperative when attempting to prove lack of enablement to show that *one of ordinary skill in the art* would be unable to make the claimed invention without undue experimentation... CellPro's evidence concerning Civin's subsequent work is insufficient as a matter of law."

Johns Hopkins Univ. v. CellPro, Inc., 152 F.3d 1342, 1360 (Fed. Cir. 1998).

Judgment; Motion for Judgment as a Matter of Law (JMOL)/ 24, 1997). We affirm-in-part, vacate-in-part, and remand.
Directed Verdict.

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Contraceptive Utility Is Scientifically Credible

- Patent enables use of claimed PH20 variants as contraceptives **in females**
- Sufficient guidance for credible utility
- Prior art established PH20 as contraceptive target and taught known ways to enhance contraceptive effect
  - PH20 was known to play a key role in fertilization
  - Prior studies showed PH20 could induce infertility / contraceptive effects
  - PH20 vaccines were known to generate anti-PH20 antibodies that bind sperm PH20
    - Mucosal delivery could increase antibodies in the female reproductive tract
    - Adjuvants and booster doses could strengthen the antibody response
    - Sialidase could expose sperm-surface PH20 to anti-PH20 antibodies
- Anti-PH20 antibodies could be delivered locally by gels, films, or intravaginal rings

Reference: POR, 74–82; Sur-Reply 27–29; EX2072 ¶¶19–61; EX2074 ¶¶20–63.

Contraceptive Utility Is Scientifically Credible

- An invention that is at least partially successful in achieving a useful result has credible utility.

  In re Brana, 51 F.3d 1560 (Fed. Cir. 1995).

- Petitioner applied a 100% effectiveness standard.

  Reply, 39-40

- Petitioner's expert agrees that common contraceptives achieve less than 100% effectiveness.

  EX. 2302 (Kelsoe), 131:10-132:19

Contraceptive Utility Is Scientifically Credible

Merck Expert | **Dr. Kelsoe**

Q. And you would agree that contraceptives have been and are still used today as tools for population control in animals, correct?

A. Contraceptives?

Q. Yes.

A. Yes.

Q. And you would agree that a method for population control in animals would not need to cause complete infertility to be useful –

A. That's my --

Q. You would agree that, as a method for population control, a contraceptive would not need to cause incomplete fertility to be useful, correct?

A. I think that -- and, again, as I described in the sense of ecological control for a species, a 50 percent reduction of the fecundity would have an important and valuable role.

EX. 2302 (Kelsoe), 134:5-135:3 (objections omitted)

Inactive Mutants Are Inoperative Embodiments

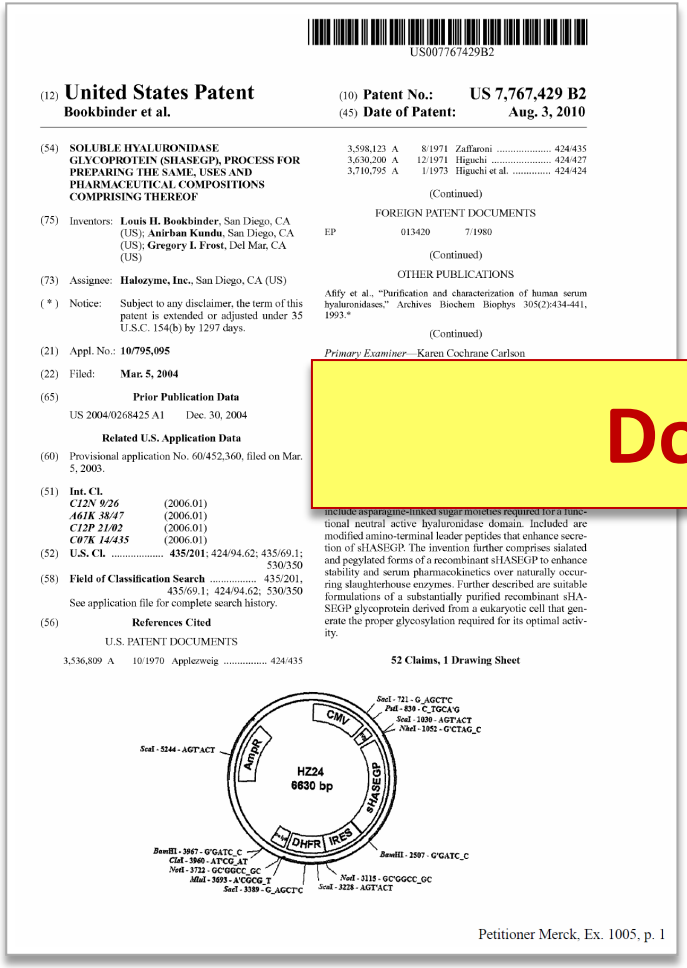
- Even if some variants are inactive, they are merely inoperative
- POSAs can readily identify inactive variants using patent guidance
- Inoperative embodiments do not defeat enablement
- Patent teaches how to distinguish active from inactive

Obviousness (Ground 3)

Halozyme

The Art Did Not Identify The Positions In Question

’429 Patent



US007767429B2

(12) **United States Patent**
Bookbinder et al.

(10) **Patent No.: US 7,767,429 B2**
(45) **Date of Patent: Aug. 3, 2010**

(54) **SOLUBLE HYALURONIDASE GLYCOPROTEIN (SHASEGP), PROCESS FOR PREPARING THE SAME, USES AND PHARMACEUTICAL COMPOSITIONS COMPRISING THEREOF**

(75) Inventors: **Louis H. Bookbinder**, San Diego, CA (US); **Anirban Kundu**, San Diego, CA (US); **Gregory I. Frost**, Del Mar, CA (US)

(73) Assignee: **Halozyme, Inc.**, San Diego, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1297 days.

(21) Appl. No.: **10/795,095**

(22) Filed: **Mar. 5, 2004**

(65) **Prior Publication Data**

US 2004/0268425 A1 Dec. 30, 2004

Related U.S. Application Data

(60) Provisional application No. 60/452,360, filed on Mar. 5, 2003.

(51) **Int. Cl.**
C12N 9/26 (2006.01)
A61K 38/47 (2006.01)
C12P 21/02 (2006.01)
C07K 14/435 (2006.01)

(52) **U.S. Cl.** **435/201**; 424/94.62; 435/69.1; 530/350

(58) **Field of Classification Search** 435/201, 435/69.1; 424/94.62; 530/350
See application file for complete search history.

(56) **References Cited**

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3,536,809 A 10/1970 Applezweig 424/435
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3,630,200 A 12/1971 Higuchi 424/427
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(Continued)

FOREIGN PATENT DOCUMENTS

EP 013420 7/1980

(Continued)

OTHER PUBLICATIONS

Atify et al., "Purification and characterization of human serum hyaluronidases." Archives Biochem Biophys 305(2):434-441, 1993."

(Continued)

Primary Examiner—Karen Cochrane Carlson

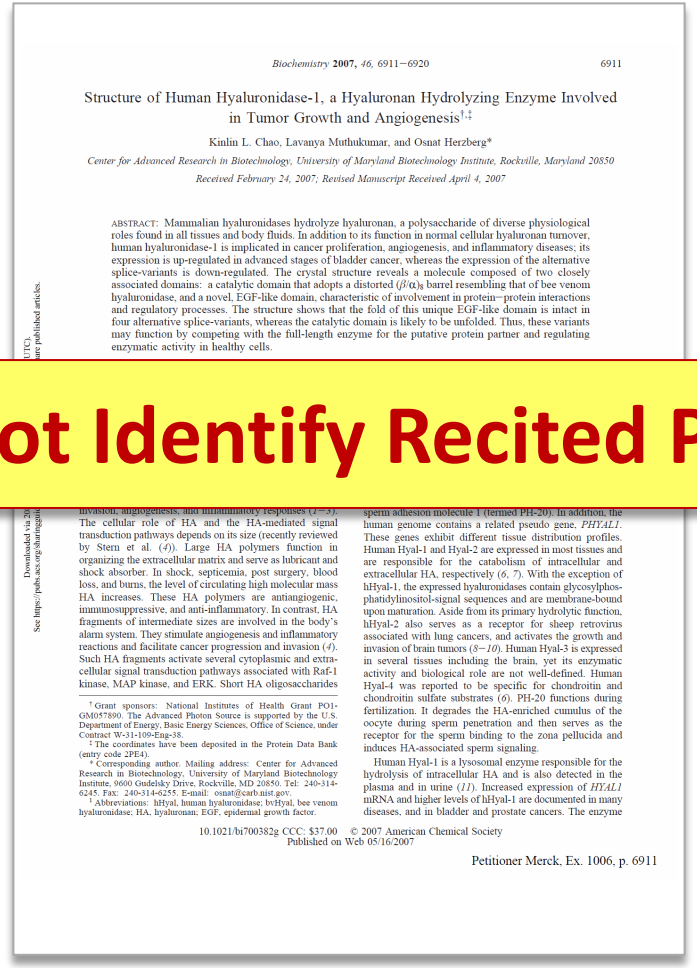
include asparagine-linked sugar moieties required for a functional neutral active hyaluronidase domain. Included are modified amino-terminal leader peptides that enhance secretion of sHASEGP. The invention further comprises sialated and pegylated forms of a recombinant sHASEGP to enhance stability and serum pharmacokinetics over naturally occurring slaughterhouse enzymes. Further described are suitable formulations of a substantially purified recombinant sHASEGP glycoprotein derived from a eukaryotic cell that generate the proper glycosylation required for its optimal activity.

52 Claims, 1 Drawing Sheet

Petitioner Merck, Ex. 1005, p. 1

EX. 1005

Chao



Biochemistry **2007,** *46,* 6911−6920 6911

Structure of Human Hyaluronidase-1, a Hyaluronan Hydrolyzing Enzyme Involved in Tumor Growth and Angiogenesis[†,‡]

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Center for Advanced Research in Biotechnology, University of Maryland Biotechnology Institute, Rockville, Maryland 20850

Received February 24, 2007; Revised Manuscript Received April 4, 2007

ABSTRACT: Mammalian hyaluronidases hydrolyze hyaluronan, a polysaccharide of diverse physiological roles found in all tissues and body fluids. In addition to its function in normal cellular hyaluronan turnover, human hyaluronidase-1 is implicated in cancer proliferation, angiogenesis, and inflammatory diseases; its expression is up-regulated in advanced stages of bladder cancer, whereas the expression of the alternative splice-variants is down-regulated. The crystal structure reveals a molecule composed of two closely associated domains: a catalytic domain that adopts a distorted $(\beta/\alpha)_8$ barrel resembling that of bee venom hyaluronidase, and a novel, EGF-like domain, characteristic of involvement in protein−protein interactions and regulatory processes. The structure shows that the fold of this unique EGF-like domain is intact in four alternative splice-variants, whereas the catalytic domain is likely to be unfolded. Thus, these variants may function by competing with the full-length enzyme for the putative protein partner and regulating enzymatic activity in healthy cells.

invasion, angiogenesis, and inflammatory responses (*1*−*3*). The cellular role of HA and the HA-mediated signal transduction pathways depends on its size (recently reviewed by Stern et al. (*4*)). Large HA polymers function in organizing the extracellular matrix and serve as lubricant and shock absorber. In shock, septicemia, post surgery, blood loss, and burns, the level of circulating high molecular mass HA increases. These HA polymers are antiangiogenic, immunosuppressive, and anti-inflammatory. In contrast, HA fragments of intermediate sizes are involved in the body's alarm system. They stimulate angiogenesis and inflammatory reactions and facilitate cancer progression and invasion (*4*). Such HA fragments activate several cytoplasmic and extracellular signal transduction pathways associated with Raf-1 kinase, MAP kinase, and ERK. Short HA oligosaccharides

sperm adhesion molecule 1 (termed PH-20). In addition, the human genome contains a related pseudo gene, *PHYAL1*. These genes exhibit different tissue distribution profiles. Human Hyal-1 and Hyal-2 are expressed in most tissues and are responsible for the catabolism of intracellular and extracellular HA, respectively (*6*, *7*). With the exception of hHyal-1, the expressed hyaluronidases contain glycosylphosphatidylinositol-signal sequences and are membrane-bound upon maturation. Aside from its primary hydrolytic function, hHyal-2 also serves as a receptor for sheep retrovirus associated with lung cancers, and activates the growth and invasion of brain tumors (*8*−*10*). Human Hyal-3 is expressed in several tissues including the brain, yet its enzymatic activity and biological role are not well-defined. Human Hyal-4 was reported to be specific for chondroitin and chondroitin sulfate substrates (*6*). PH-20 functions during fertilization. It degrades the HA-enriched cumulus of the oocyte during sperm penetration and then serves as the receptor for the sperm binding to the zona pellucida and induces HA-associated sperm signaling.

Human Hyal-1 is a lysosomal enzyme responsible for the hydrolysis of intracellular HA and is also detected in the plasma and in urine (*11*). Increased expression of *HYAL1* mRNA and higher levels of hHyal-1 are documented in many diseases, and in bladder and prostate cancers. The enzyme

[†] Grant sponsors: National Institutes of Health Grant PO1-GM057890. The Advanced Photon Source is supported by the U.S. Department of Energy, Basic Energy Sciences, Office of Science, under Contract W-31-109-Eng-38.

[‡] The coordinates have been deposited in the Protein Data Bank (entry code 2PE4).

* Corresponding author. Mailing address: Center for Advanced Research in Biotechnology, University of Maryland Biotechnology Institute, 9600 Gudelsky Drive, Rockville, MD 20850. Tel: 240-314-6245. Fax: 240-314-6255. E-mail: osnat@carb.nist.gov.

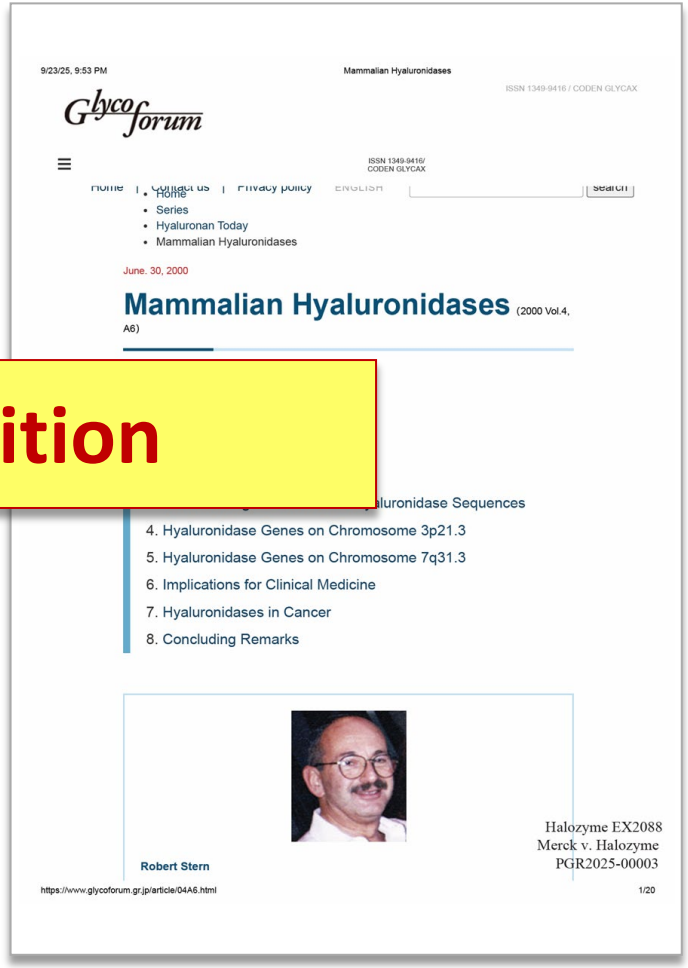
[1] Abbreviations: hHyal, human hyaluronidase; bvHyal, bee venom hyaluronidase; HA, hyaluronan; EGF, epidermal growth factor.

10.1021/bi700382g CCC: $37.00 © 2007 American Chemical Society
Published on Web 05/16/2007

Petitioner Merck, Ex. 1006, p. 6911

EX. 1006

Stern



9/23/25, 9:53 PM Mammalian Hyaluronidases

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June. 30, 2000

Mammalian Hyaluronidases (2000 Vol.4, A6)

4. Hyaluronidase Genes on Chromosome 3p21.3
5. Hyaluronidase Genes on Chromosome 7q31.3
6. Implications for Clinical Medicine
7. Hyaluronidases in Cancer
8. Concluding Remarks

Robert Stern

Halozyme EX2088
Merck v. Halozyme
PGR2025-00003

https://www.glycoforum.gr.jp/article/04A6.html 1/20

EX. 2088

Do Not Identify Recited Position

Petitioner's Obviousness Analysis Is Premised On Hindsight

Merck Expert | **Dr. Park**

- "[A]sked by counsel to report conclusions with respect to position 320" out of 700+ candidate positions he identified through his analysis.

  EX. 1004, ¶103

- Declaration discusses position 320 because "counsel ... asked [him] to."

  EX. 2078, 320:10-20; EX. 2076, 87:1-11

Conclusion