Paper No. 64
Filed: May 7, 2026

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyme Inc.,
Patentee.

Case No. PGR2025-00052
U.S. Patent No. 12,264,345

PETITIONER'S REPLY

TABLE OF CONTENTS

Page

I. Introduction 1

II. Claim Construction and Scope 1

III. The Claims Are Unpatentable Under § 112 3

A. The Claims Define Structurally Heterogenous Genera 3

B. Determining the Properly Folded and Active PH20s in the Sequence Space is Impossible 6

C. Written Description 9

1. The Disclosure Does Not Describe the Common Structural Features of Enzymatically Active PH20s 10

(a) Sequence Identity Is Not a "Structural Feature" 10

(b) Enzymatically Active PH20s Must Possess Several Structural Features, Not One 11

(c) No Description of "PH20 α/β Barrel" or Its Unique Nature in the Disclosure 13

(d) No Description of the PH20 Hyal-EGF 16

(e) "Hyaluronidase Domain" Is Not a Common Structure Feature 18

2. Single Substitutions Provide No Structure-Function Correlation 19

3. Representative Species Not Described 20

D. Enablement 22

1. Multiple Concurrent Mutations Are Unpredictable 23

2. The α/β Barrel Motif Does Not Make Multiply-Modified PH20s Stable or Predictable 30

3. Dr. Petsko's Tolerance Ratings Are Not Credible or Predictive of Combinations 32

E. Halozyme's § 112 Positions Conflict with the Disclosure.....34

1. Dr. Petsko Mischaracterizes How the Disclosure Proposes Making Multiply-Modified PH20s.....34

2. $PH20_{1-430}$ and $PH20_{1-431}$ Are Not "Inactive".....35

3. Following Petsko's Tolerance Ratings Leads POSAs Into Conflict with the Disclosure.....37

4. Wrong Substrate Binding Sites.....38

5. No Rescue Mutation Theory.....39

F. No Credible Utility for Inactive PH20s.....39

G. Indefiniteness.....42

IV. Obviousness.....42

V. Conclusion.....48

TABLE OF AUTHORITIES

Page(s)

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Ariad Pharms., Inc. v. Eli Lilly & Co.,
598 F.3d 1336 (Fed. Cir. 2010) ("*Ariad*") 10, 11

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441 F.3d 945 (Fed. Cir. 2006) ("*Bicon*") 2

Boston Sci. Corp. v. Johnson & Johnson,
647 F.3d 1353 (Fed. Cir. 2011) ("*Boston*") 14

Duke Univ. v. Sandoz Inc.,
160 F.4th 1305 (Fed. Cir. 2025) ("*Duke*") 2, 11

In re Fisher,
421 F.3d 1365 (Fed. Cir. 2005) ("*Fisher*") 42

Idenix Pharm., LLC v. Gilead Scis., Inc.,
941 F.3d 1149 (Fed. Cir. 2019) ("*Idenix*") 20

Juno Therapeutics, Inc. v. Kite Pharma, Inc.,
10 F.4th 1330 (Fed. Cir. 2021) ("*Juno*") 14

In re McLeay,
No. 2023-2338, 2025 WL 516809 (Fed Cir. Feb. 18, 2025) ("*McLeay*") 39

Novozymes A/S v. DuPont Nutrition Biosciences APS,
723 F.3d 1336 (Fed Cir. 2013) ("*Novozymes*") 19

Regents of the Univ. of Minn. v. Gilead Scis.,
61 F.4th 1350 (Fed. Cir. 2023) ("*Gilead*") 2, 10

TIP Sys., LLC v. Phillips & Brooks/Gladwin, Inc.,
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37 C.F.R. § 42.65 38

MPEP § 2107.01 42

I. Introduction

Halozyme's response abandons its disclosure, invents new research plans, and disparages its earlier PH20 patents. Its experts propose conflicting pictures of claim coverage but concede "PH20" means a folded protein. Its "common structural feature" (α/β barrel) nowhere appears in the disclosure, omits the PH20 active site, and is misdescribed. Its expert concedes predicting which mutated sequences will "properly fold" is impossible and admits "billions" will not. Halozyme ignores failures that foreclose using PH20s as contraceptive vaccines. Finally, Halozyme's experts endorsed Merck's expert's prior art-based methods that identified the obvious M313K $PH20_{1-447}$ mutant, and evidence refutes Halozyme's false "hindsight" narrative.

II. Claim Construction and Scope

The claim construction dispute is narrow: are the claims limited to "properly folded" modified PH20 polypeptides (*i.e.*, a "***structurally and functionally distinct genus***" of PH20s),[1] or do they ***also*** include 10^{43}+ other PH20 sequences in the claim parameter's "sequence space" (*i.e.*, a genus outweighing Earth)?[2] Resolving

[1] POR, 31-32; EX2068, ¶ 33; EX2070, ¶¶ 51, 58, 128-FN12; EX1130, 62:13-23; 68:6-69:5; EX1133, ¶¶ 77-80, 44-46, 55-58, 92-101; § III.C.1(b).

[2] EX1003, ¶¶ 141-142.

that issue is unnecessary: (1) Halozyme admits the disclosure "must enable POSAs to reliably distinguish, create, and utilize the ***full range of active … modified PH20 polypeptides*** encompassed by the claims" (but it does not),[3] and (2) the M313K $PH20_{1-447}$ mutant is claimed but obvious.

Halozyme's proposed construction is legal error—it ignores the claim term "PH20."[4] When ***all*** claim terms and the preamble are credited, the claims clearly require "***properly folded***" modified PH20s. In particular, as Halozyme's expert Dr. Simpson testified, "PH20" ***provides context*** to "modified PH20 polypeptide,"[5] while another Halozyme expert Dr. Petsko provided that context: "***POSAs think of PH20 as a folded protein***."[6] Dr. Simpson likewise testified the disclosure's definition of PH20[7] refers to properly folded and enzymatically active proteins.[8]

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3 POR, 43-44; *Duke*, 1310; *Gilead*, 1356-57.

4 POR, 31-44; EX1130, 55:23-56:7, 57:9-58:4, 90:1-16; Pet., 18; EX1026, 50:31-32, 54:5-10; *Bicon*, 950-51.

5 EX1130, 57:9-58:4; *Bicon*, 952.

6 EX2070, ¶ 345.

7 EX1026, 50:31-32; EX1130, 60:14-61:12.

8 EX1130, 61:19-23; EX2070, ¶ 128-FN12; EX1133, ¶¶ 92-104. Halozyme's experts use "polypeptide" interchangeably with "protein." EX1133, ¶¶ 87-89;

Giving effect to both defined terms, the preamble requires a "***properly folded*** PH20 polypeptide with ***at least one modification***."

The claims do not define sequences outside of positions 3-339, but per the disclosure, those sequences must also meet the definition of "PH20."[9] POSAs thus read the claims ***as a whole*** as directed to properly folded PH20s, which either encompass or require activity.[10]

III. The Claims Are Unpatentable Under § 112

A. The Claims Define Structurally Heterogenous Genera

Merck's description of the claims' "sequence space" is not a "parlor trick"—

EX1131, 32:8-37:20, 146:14-148:8; EX2068, ¶¶ 283, 376; EX2070, ¶¶ 50, 434. The disclosure also portrays "active" and "inactive" PH20s as mutually exclusive embodiments. Pet. 26-31; EX1026, 253, 251:2-4, 272:3-5; EX1003, ¶¶ 102-105, 117.

9 Pet., 18-26, 41-43, 50-51; EX1003, ¶¶ 126-138.

10 Pet., 28-31; EX1026, 90:33-34; EX1003, ¶¶ 146-152; EX1133, ¶¶ 105-110. *TIP*, 1375. Merck's position is that the claims require PH20s with hyaluronidase activity; >40% value is the disclosure's classification threshold.

Halozyme's experts ***confirmed*** it was correct (~10^{43} to ~10^{56} sequences).[11] Also undisputed is that the claims permit (i) modifications at any non-recited position, (including up to 19 modifications anywhere in the "hyaluronidase domain"), (ii) additions/deletions, and (iii) substitutions to any of 19 other amino acids.[12]

The sequence space thus contains immense structural diversity, with an unknowable subset of sequences that will properly fold.[13] "Properly folded"[14] active PH20s exist within one corner of the sequence space. Many sequences will never leave the cell (*e.g.*, those that cannot be made or are not secreted), while others yield unstable PH20s that exist in unfolded and/or aggregated forms, including partially-folded, misfolded, or initially natively-folded sequences.[15]

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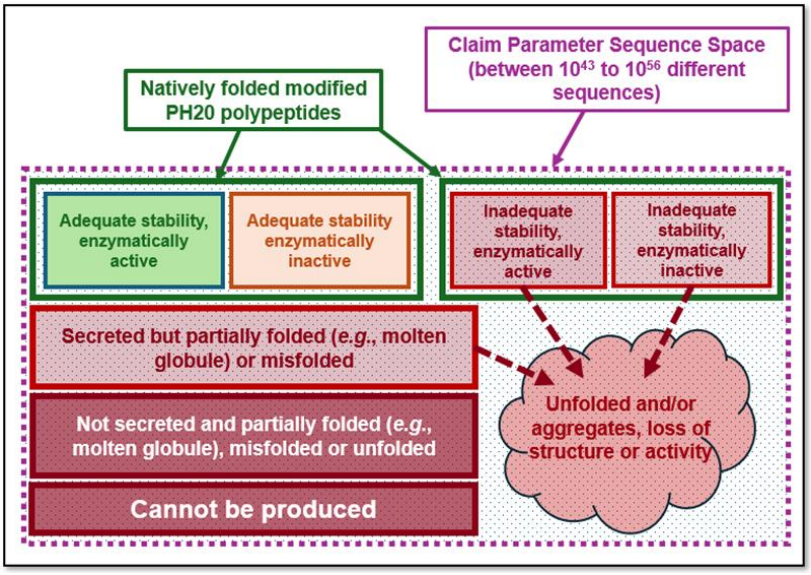
11 POR, 4; Pet., 18-20; EX1003, ¶¶ 139-141; EX1004, ¶¶ 175-176; EX1130, 90:1-16, 91:18-92:1; EX1131, 58:18-59:19, 61:6-8, 65:18-66:3; EX2070, ¶¶ 235-236.

12 Pet., 18-20, 41-43; EX1003, ¶¶ 126, 135, 190-192; EX1026, 53:1-7, 68:18-34; EX1130, 90:25-91:5; EX1131, 54:24-55:6.

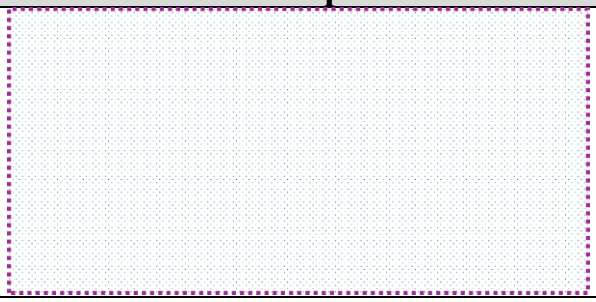
13 EX1130, 92:2-94:14; EX1131, 61:15-62:5; EX1133, ¶¶ 60-61, 77-80.

14 POR, 5-6, 63-64; EX1131, 78:6-25; EX2068, ¶¶ 105-106; EX2070, ¶¶ 51, 128-FN12, 431.

15 EX1133, ¶¶ 77-80, 327-334; EX1131, 42:20-43:7; 47:7-19.



Halozyme's experts contend the claims define a "structurally homogeneous" set of modified PH20s but disagree about what that set constitutes: Dr. Petsko says it is proteins that have ***folded***,[16] while Dr. Simpson portrays it as ***the entire sequence space***.[17]

"structurally homogeneous" claimed PH20s	
Dr. Petsko	**Dr. Simpson**
	

[16] EX2070, ¶¶ 391, 51; EX1131, 72:7-19, 65:6-66:17, 68:6-69:4, 69:17-70:15, 71:6-14, 78:14-25.

[17] EX2068, ¶ 33; EX1130, 89:16-90:16; EX1133, ¶¶ 52-57.

Halozyme embraces this confusion—it contends ***both*** sets are "structurally homogeneous."[18] But they plainly are not—even active PH20s are structurally heterogeneous.[19]

B. Determining the Properly Folded and Active PH20s in the Sequence Space is Impossible

The Petition explained it was impossible to determine the active species within the 10^{43}+ sequences meeting the claims' parameters.[20] Dr. Petsko agreed: he testified it is impossible to calculate or experimentally determine what portion of the sequence space will properly fold and be active, and could not approximate their number.[21] He also admits "billions" of these sequences will not properly fold—those with "substantial modifications to residues known to be invariant because they are involved in … protein structure."[22] Critically, the disclosure does

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18 POR, 63-64, 54-57, 7, 3-4.

19 Pet., 9-10; EX1003, ¶¶ 56-62, 67, 70, 182, 194; EX1133, ¶¶ 40-44, 70-80, 85-86.

20 Pet., 43, 52-72, 74-80; EX1003, ¶¶ 196-197, 198-206, 220-223, 226-227; EX1133, ¶¶ 112, 120, 123, 126.

21 EX1131, 63:19-64:17; EX1133, ¶¶ 121-122.

22 EX2070, ¶ 347.

not (and could not) identify all residues involved in protein structure, while the claims ***expressly permit*** any change at any non-recited position (§ III.A).

Experimental techniques in 2011-2012 also could not determine or estimate the portion of the sequence space that will properly fold and exhibit activity.[23] Dr. Hecht explained why directed evolution techniques could not.[24] Drs. Petsko and Naismith confirmed his opinions.[25] For example, assays used in directed evolution techniques max out at a fraction of the smallest sequence space here: ~10^9 to ~10^{12} mutants (*e.g.*, a PH20 with <5 modifications):[26]

Total Change	Total Sequences	#
1	19	1.90E+01
2	121,315	1.21E+05
3	386,145,835	3.86E+08
4	816,956,680,475	8.17E+11
5	1,292,427,399,847,290	1.29E+15
6	1,630,788,162,499,110,000	1.63E+18
7	1,709,613,901,169,040,000,000	1.71E+21
8	1,531,574,487,979,880,000,000,000	1.53E+24
9	1,196,929,740,471,240,000,000,000,000	1.20E+27
10	828,943,748,674,655,000,000,000,000,000	8.29E+29
11	515,108,042,352,483,000,000,000,000,000,000	5.15E+32
12	290,100,993,201,624,000,000,000,000,000,000,000	2.90E+35
13	149,306,171,064,744,000,000,000,000,000,000,000,000	1.49E+38
14	70,714,146,737,250,300,000,000,000,000,000,000,000,000	7.07E+40
15	31,003,316,043,500,200,000,000,000,000,000,000,000,000,000	3.10E+43

[23] Pet., 13-16, 43, 71-91.

[24] EX1003, ¶¶ 218-227.

[25] EX1133, ¶ 123; EX2070, ¶¶ 347, 349.

[26] EX1133, ¶¶ 124-127; EX1004, ¶¶ 175-176.

Rational design (*e.g.*, picking and choosing combinations and using homology modeling) also could not. *See* § III.D. Homology models cannot (i) accurately model more than a few substitutions, (ii) detect structural changes below ~1-3 Å, or (iii) detect epistatic, physicochemical, or long-range effects.[27] Computational tools in 2011-2012 also could not reliably model protein structures with 10+ changes from native.[28] And individual assessments are impossible.[29]

In 2011-2012, POSAs would need to perform experiments to identify modified PH20s with 5+ mutations that properly fold and exhibit activity.[30] Doing so for even a sliver of the claims' sequence space is impossible.

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27 EX1004, ¶¶ 167-169; EX1003, ¶ 264; EX1133, ¶¶ 130-132, 195, 260-263, 268, 270-274, 281-284.

28 EX1027, 6-9; EX1133, ¶¶ 124, 128-129, 132-133, 257.

29 EX1133, ¶¶ 131-132.

30 EX1133, ¶¶ 131-132; EX1003, ¶¶ 196, 226-227; EX1004, ¶¶ 167-169.

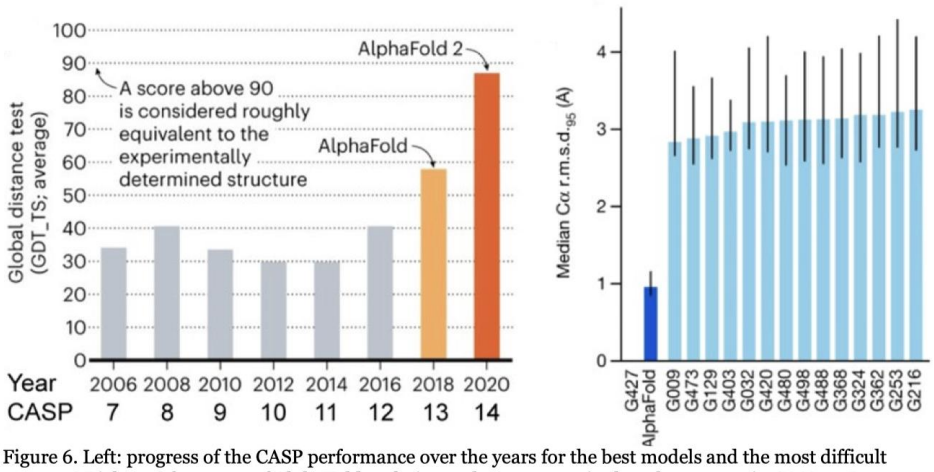


Figure 6. Left: progress of the CASP performance over the years for the best models and the most difficult targets.[38] Right: performance of AlphaFold2 relative to the top 15 entries by other groups in CASP14. Data are the median coordinate error and the 95% confidence interval of the median, estimated from 10 000 bootstrap samples.[41]

This evidence is dispositive on written description ***and*** enablement.[31] If a POSA cannot identify the active PH20s within the claims' sequence space, the disclosure cannot demonstrate possession of them. Impossibility exceeds undue experimentation and establishes non-enablement.

Finally, the disclosure describes no examples of and does not teach how to identify or produce active modified PH20s with more than 456 residues (*i.e.*, PH20s a POSA would expect to remain membrane bound and/or be insoluble).[32]

C. Written Description

Description of a genus requires "the disclosure of either a representative number of species falling within the scope of the genus or structural features

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31 Pet., 31-33, 63-67, 81-91.

32 Pet., 12, 41-43; EX1003, ¶¶ 93-94, 232; EX1133, ¶ 119.

common to the members of the genus ***so that one of skill in the art can 'visualize or recognize' the members of the genus***."[33] Visualizing or recognizing the members of the claimed genus here is impossible (§ III.B).

1. The Disclosure Does Not Describe the Common Structural Features of Enzymatically Active PH20s

The Petition explained why the disclosure did not describe common structural features of the claimed active PH20s.[34] In response, Halozyme contends it "characterizes the common structural features" of the claimed PH20s.[35] Only properly folded PH20s could have a common set of structural features, but the disclosure fails to identify what those features are and which of the 10^{43}+ sequences will fold to have them.

(a) Sequence Identity Is Not a "Structural Feature"

Halozyme and its experts contend the requirement of "no more than 20 total modifications in the hyaluronidase domain" is a "common structural feature" of the claimed PH20 polypeptides.[36] It is not—it is a ***mathematical*** requirement (*i.e.*, is

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33 *Ariad*, 1350; *Gilead*, 1356.

34 Pet., 67-69; EX1003, ¶¶ 70, 179-186, 189, 190-197.

35 POR, 45.

36 POR, 63-64; EX2068, ¶¶ 287, 358; EX1131, 65:18-66:17.

the "hyaluronidase domain" portion of two sequences 94%+ identical?).[37]

"Structural features" are ***physical*** attributes of ***a*** PH20 polypeptide (*e.g.*, a particular amino acid at a position or features of its tertiary structure).[38] Common "structural features" are the ***set*** of those ***physical*** attributes "common to the members of the genus" (properly folded, active PH20s).[39]

As a ***claim element***, the "hyaluronidase domain" modification simply defines the boundaries of the "sequence space"—the set of amino acid sequences within which the claimed PH20 polypeptides must be found.[40] Every one of those "primary sequences," ***by definition,*** has "hyaluronidase domain" residues that are up to ~12% ***different*** than every other one in the set.[41]

(b) Enzymatically Active PH20s Must Possess Several Structural Features, Not One

Halozyme and its experts contend the claimed active PH20s "all share a

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37 EX1026, 66:32-67:9, 68:18-34; EX1133, ¶¶ 80, 83; EX2068, ¶ 287.

38 EX1003, ¶ 186; EX1133, ¶¶ 83-86.

39 *Duke*, 1311.

40 *Ariad*, 1349.

41 EX1133, ¶¶ 48-51.

tertiary structure POSAs would recognize as an 'alpha-beta barrel ***fold***.'"[42] But Halozyme misleadingly portrays the α/β barrel ***motif*** as being the ***entire*** tertiary structure of PH20s, including the catalytic site.[43] As Dr. Petsko conceded, the α/β barrel ***motif*** in PH20 is only "***part*** of the tertiary structure because there are other elements in the protein besides that particular subdomain…"[44]

A "properly folded" PH20 is one with the same stable tertiary structure (the native fold) of wild-type human PH20, and only "properly folded" PH20s exhibit enzymatic activity.[45] The ***tertiary*** structure of human PH20, however, is not described in the disclosure—it was not reported until 2024.[46]

Before 2011, the prior art identified at least three structural features shared by enzymatically active mammalian hyaluronidases:

(i) the PH20 active site, which spatially positions catalytic residues

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42 POR, 13; EX2068, ¶¶ 33, 106, 289, 305; EX2070, ¶¶ 432, 51, 58, 101, 128, 345, 396, 400.

43 POR, 54-55; EX2070, ¶ 51; EX1133, ¶ 135.

44 EX1131, 69:2-5; EX1133, ¶¶ 153, 160.

45 EX2070, ¶¶ 51, 128-FN12; EX1131, 78:6-25; 86:23-87:7; EX1003, ¶¶ 37, 63, 194, 261; EX1133, ¶¶ 17, 58-59, 96-97, 159.

46 EX1126, 1068.

D111, E113, and E249 and substrate binding residues R176, R246, and R252 correctly within a folded substrate-binding cleft;[47]

(ii) a "distorted" (non-canonical) PH20 α/β barrel motif;[48] and

(iii) the Hyal-EGF domain (Leu336 to Asp416 in PH20).[49]

Each is essential to active PH20s—mutations of active site residues[50] or deleting all or part of the Hyal-EGF domain "abolished" activity.[51]

(c) No Description of "PH20 α/β Barrel" or Its Unique Nature in the Disclosure

Halozyme anchors its "common structural feature" arguments on the "α/β barrel" motif in human PH20.[52] But the disclosure nowhere mentions a "PH20 α/β barrel," discusses this motif, or portrays it as a common structural feature of any

47 EX1026, 80:11-18; EX1010, 9437; EX1133, ¶¶ 96, 167.

48 EX1008, 824, 829, 833; EX1006, 6913; EX1133, ¶¶ 140-150.

49 EX1006, 6913; EX1010, 9441; EX1003, ¶¶ 85-92; EX1004, ¶¶ 97-100; EX1133, ¶¶ 189-192.

50 EX1003, ¶ 90; EX1133, ¶¶ 96, 304; EX2070, ¶ 128-FN12.

51 EX1003, ¶¶ 90-91, 99, 101, 137, 172, 176-178, 222; EX1133, ¶¶ 186-188; EX1010, 9439, 9441; EX1011, 813-14.

52 POR, 45-48, 63-64; EX2068, ¶¶ 294-295, 305; EX2070, ¶¶ 51, 128, 396, 430.

set of modified PH20s.[53] It also does not identify any amino acid sequences for the PH20 α/β barrel motif or its elements.[54] Nor does it reference the "distorted" (α/β) barrel motif in human PH20, explain that it does not contain PH20's active site, or explain how it differs from the canonical α/β structure.[55] ***Any*** of these omissions doom Halozyme's attempt to retroactively import into the disclosure the "α/β barrel" label as a "structural feature" of the claimed PH20s.[56]

Publications before 2011 also reveal why the phrase "α/β barrel" is incapable of supporting the claimed PH20s as § 112 requires. First, the "unusual" α/β barrel motif in hyaluronidases is "only loosely associated" with the canonical α/β motif.[57] It has a large gap, two irregular strands, and its shape is distorted (PH20: yellow, canonical: pink).[58]

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53 EX1133, ¶¶ 165-170.

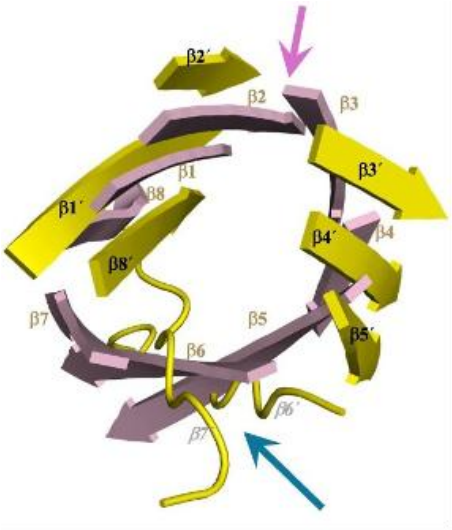
54 EX1133, ¶¶ 151, 168.

55 EX1133, ¶¶ 152-158, 165-167; EX1008, 824-825, 829, 833; EX1006, 6911-13; EX1033, 1027.

56 *Juno*, 1339; *Boston*, 1366-67.

57 EX1008, 833; EX1133, ¶¶ 141-147.

58 EX1033, 1027-28; EX1133, ¶ 144.



A POSA could not have used knowledge of the ***canonical*** "α/β barrel" motif to visualize the ***structurally distinct*** PH20's α/β motif because the two ***are materially different***.[59]

Second, the conserved features of the hyaluronidase active site that Dr. Petsko referenced ***are not contained within*** the PH20 α/β motif.[60] The words "PH20 α/β barrel" do not describe the ***structure*** of the PH20 active site.

Knowledge of individual active site residues in the PH20 sequence is insufficient. What is required is the identity of the ***particular amino acid sequences that will create the three-dimensional structure*** that spatially positions the catalytic and substrate binding residues correctly within the properly folded

[59] EX1133, ¶¶ 136-139, 144, 150-152; EX2070, ¶ 52.

[60] EX1008, 829; EX1133, ¶ 149.

PH20.[61] This is unknowable for the vast majority of the genus (*i.e.*, ***multiply***-modified PH20s).

Thus, Halozyme and its experts did not (i) describe the unique structural features of the α/β barrel motif in PH20, (ii) identify where it is described in the disclosure, (iii) identify its relationship to PH20's active site, or (iv) reveal that it is only ***part*** of the PH20 tertiary structure necessary for activity.

(d) No Description of the PH20 Hyal-EGF

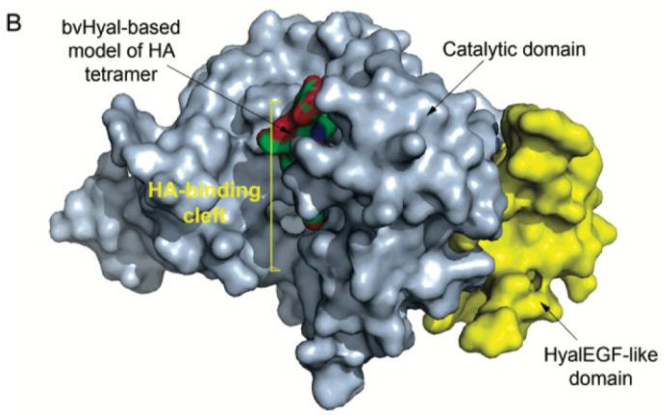
The disclosure contains no description of the Hyal-EGF domain or its sequence, despite its essential role in the structure and function of enzymatically active PH20s.[62] Before 2011, Chao reported the Hyal-EGF structure and that it is shared by human hyaluronidases (what Dr. Simpson portrayed as "a huge breakthrough in the field").[63]

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61 EX1003, ¶¶ 43, 60; EX1133, ¶¶ 96-97.

62 EX1003, ¶¶ 89, 222; EX1133, ¶¶ 185, 187, 190-193, 198; Pet., 55-58, 67-68, 70-71, 76-78.

63 EX1130, 114:23-116:9; EX1003, ¶¶ 82-92; EX1004, ¶¶ 90-100; EX1006, 6915-6917 (Figs. 2, 4).



Despite this, there is no mention in the disclosure of the Hyal-EGF.[64] That omission is fatal to written description, because the Hyal-EGF is a "common structural feature" of at least the subset of active PH20s being claimed.[65]

Dr. Petsko strains to downplay the Hyal-EGF's importance to the structure and activity of PH20s.[66] But Zhang reported that deleting the Hyal-EGF "abolished" enzymatic activity and prevented secretion, while Dr. Simpson explained "the EGF-like motif is not a separate domain" but instead "packs tightly against the rest of the protein as a single domain."[67]

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64 EX1003, ¶¶ 89, 222; EX1133, ¶¶ 185, 187, 190-193, 198.

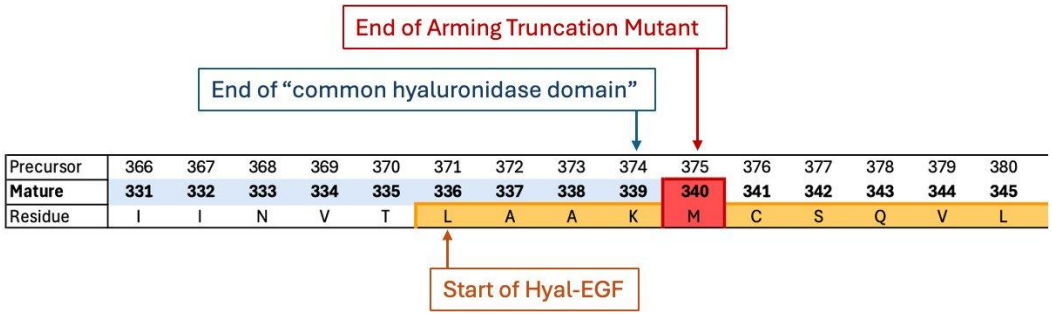
65 EX1003, ¶¶ 85-92, 96-101, 222; EX1133, ¶¶ 163, 168, 185-189.

66 EX2070, ¶¶ 209, 211.

67 EX1003, ¶¶ 90-92; EX1004, ¶¶ 95-100; EX1010, 9439, 9441; EX2068, ¶ 143; EX1006, 6913; EX1133, ¶¶ 187-189.

(e) "Hyaluronidase Domain" Is Not a Common Structure Feature

What the disclosure calls the "hyaluronidase domain" (*i.e.*, $PH20_{3-339}$) is not a common structural feature of enzymatically active PH20s. Mammalian hyaluronidases (including PH20) require the Hyal-EGF for activity, which is not within the "hyaluronidase domain" (below).[68] Unlike bee venom hyaluronidase, when PH20 is truncated at position 340, it does not properly fold or exhibit activity.[69]



Precursor	366	367	368	369	370	371	372	373	374	375	376	377	378	379	380
Mature	**331**	**332**	**333**	**334**	**335**	**336**	**337**	**338**	**339**	**340**	**341**	**342**	**343**	**344**	**345**
Residue	I	I	N	V	T	L	A	A	K	M	C	S	Q	V	L

The disclosure does not identify the location of or how the Hyal-EGF relates to the "hyaluronidase domain." Dr. Hecht also explained that changes within the Hyal-EGF unpredictably destabilize PH20.[70] There are thus no "blaze marks" to guide making multiple modifications within or outside the "hyaluronidase

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68 EX1026, 79:20-31; EX1003, ¶¶ 90-91; EX1133, ¶¶ 187-188, 192-193.

69 EX1011, 813-814; EX1133, ¶¶ 161-163, 189-193; Pet., 86-88; EX1003, ¶ 192; EX2068, ¶ 125.

70 Pet., 86-88; EX1003, ¶ 192.

domain."[71]

Halozyme ignores these issues and contends "a POSA's knowledge included possession" of homology models based on bee venom hyaluronidase (bvH) and Hyal-1 structures published before 2011.[72] But written description is judged by the disclosure, not a POSA's ***mind***, and ***this*** disclosure describes ***no*** structural or homology models. And, in Dr. Simpson's own words, bvH "did ***not*** provide a complete picture of the structure for" human PH20.[73]

2. Single Substitutions Provide No Structure-Function Correlation

Halozyme incorrectly contends its examples of singly-substituted PH20s "provide structure/function correlations POSAs can use to identify the active M313" PH20s.[74]

First, effects on PH20 folding and activity from single substitutions cannot predict effects of ***combinations*** of changes.[75] *See* § III.D.1. Even positions Dr.

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71 Pet., 31-32, 43-49, 65-67; *Novozymes*, 1348-49.

72 POR, 12-13.

73 EX2068, ¶ 125.

74 POR, 50.

75 EX1003, ¶¶ 55-62, 180-184; EX1133, ¶¶ 115, 232-233, 252-259.

Petsko labeled "100% tolerated" varied extensively in activity, demonstrating the unpredictability of single substitutions.[76]

Second, listing options and leaving a POSA to figure out which combinations yield active PH20s does not describe species of multiply-modified PH20s.[77]

Finally, problems with the disclosure's experimental data and their reporting negate the "functional" insights Halozyme contends exist, and the disclosure does not describe the PH20 tertiary structure that must be maintained.[78]

3. Representative Species Not Described

Halozyme points to 7 alleged "examples" of "M313 variants."[79] None are described in the disclosure. Three are based on native ***primate*** sequences with known activity, while four were tested.[80] None of the 7 illustrate the

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76 EX1133, ¶¶ 264-269.

77 *Idenix*, 1164-65.

78 § III.D.3; Pet., 58-63, 67-69; EX1003, ¶¶ 68-77, 107-116, 184; EX1133, ¶¶ 151, 246-251, 307-309.

79 POR, 54-55; EX2070, ¶¶ 434-437.

80 EX1133, ¶¶ 114-119.

unpredictability of making 5+ changes to a native sequence.[81] They also are not representative—they do not reflect the types or physicochemical diversity of modified PH20s claimed, including those with truncations or changes beyond position 447 (for which no examples are provided).[82]

Halozyme's overlaid models can be ignored.[83] They all suffer from Dr. Petsko's flawed "α/β barrel" opinions (§ III.C.1(c)) and cannot reveal spatial differences <1.5 Å or any physicochemical or epistatic effects.[84] A comparable overlay of the 5 human hyaluronidases shows virtually identical structures despite their known functional differences.[85]

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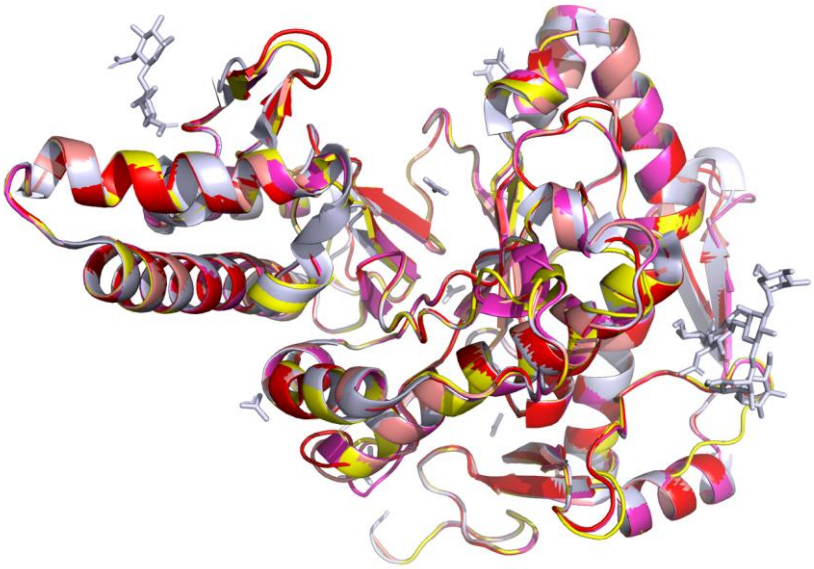
81 EX1133, ¶¶ 114-119; EX1003, ¶¶ 55-62.

82 Pet., 43, 53, 55-58, 69-72, 81; EX1003, ¶¶ 95, 98, 101, 180-184, 193-197, 201; EX1133, ¶¶ 77-80, 114-120, 221.

83 POR, 45-48; EX2070, ¶¶ 434-437.

84 EX1133, ¶¶ 197, 281-284.

85 EX1133, ¶¶ 183-184.



D. Enablement

The scale of experimentation required to practice the full scope of claimed properly folded, active PH20s is impossible, rendering the claims non-enabled for the reasons in § III.B.

Halozyme and its experts now propose a new research plan: use the data in the patent "as [a] starting point," select combinations of substitutions using Dr. Petsko's positional tolerance analysis (avoiding certain positions), and evaluate each mutant in a PH20 homology model.[86] Even a project with 5 substitutions

[86] EX2070, ¶¶ 323-324, 351, 355-360, 364; EX1130, 93:20-24; EX1133, ¶¶ 198-202.

would require billions of days to practice.[87] In 2011-2012, a POSA could not use this plan to predict whether PH20s with 5+ changes will properly fold and exhibit activity.[88]

1. Multiple Concurrent Mutations Are Unpredictable

When ***multiple*** mutations are made together, they affect a protein's structure, folding capacity, and stability differently than how each does alone.[89] Each can cause effects remote from the mutation that change how the protein reacts to subsequent changes.[90] The unpredictable effects of combinations of mutations ("epistasis") prevent POSAs from predicting whether the vast majority of multiply-modified PH20s will "properly fold."[91]

The complexity of folding illustrates why. After an amino acid sequence is synthesized, it must fold into the protein's native state. It samples a tremendous

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87 EX1133, ¶¶ 131-132; Pet., 66-67, 88-91; EX1003, ¶ 227.

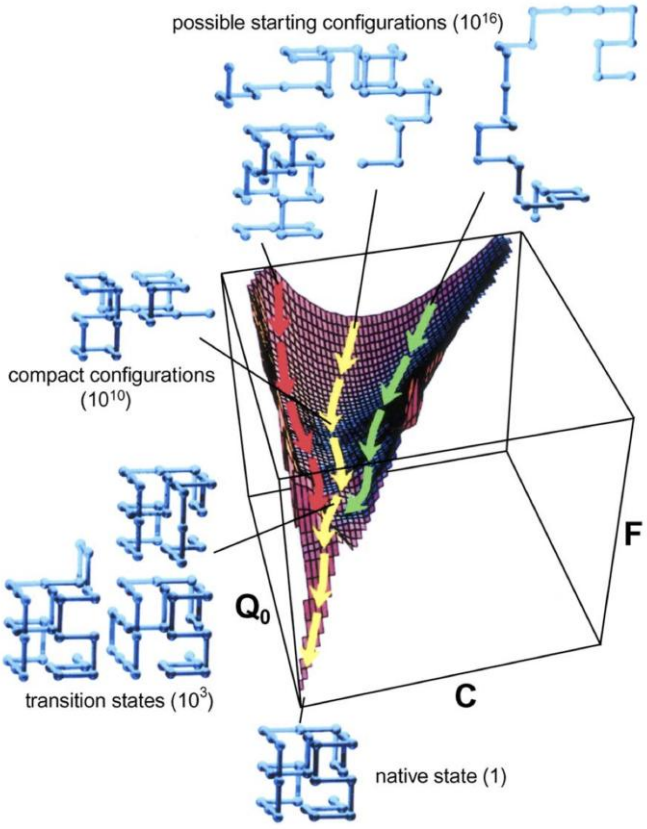
88 EX1003, ¶¶ 62, 194-197, 220; EX1133, ¶¶ 260-263, 278, 317, 325.

89 Pet., 10-11, 67-69; EX1003, ¶¶ 56-62; EX1133, ¶¶ 232, 252-255, 262, 330, 222.

90 EX1133, ¶¶ 125-126, 255-259; EX1131, 79:15-22, 89:21-90:24; 270:9-17.

91 EX1003, ¶¶ 62, 194-197; EX1133, ¶¶ 123, 252-259; EX1160, 383-85.

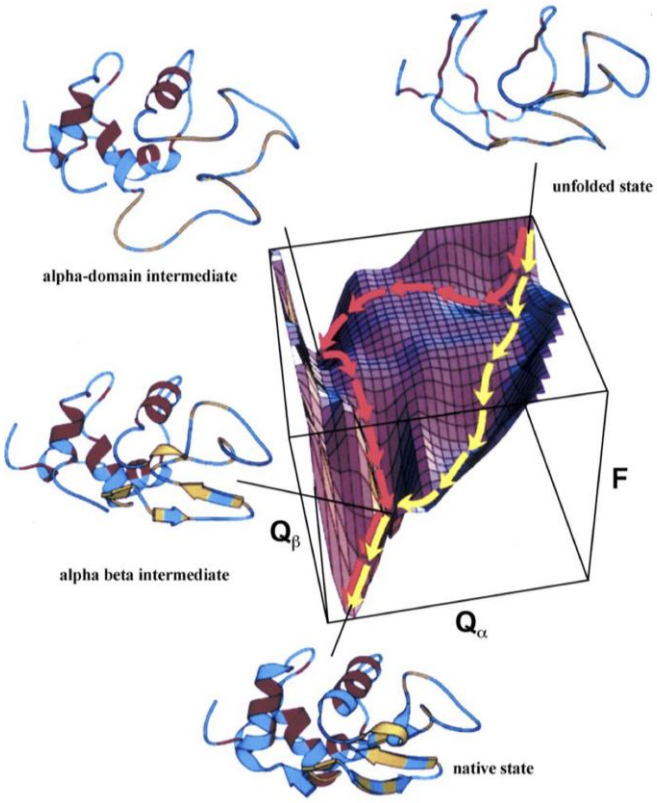
number of conformations (10^{27} for a small protein) during its folding process, adopting energetically preferred ones as it proceeds:[92]



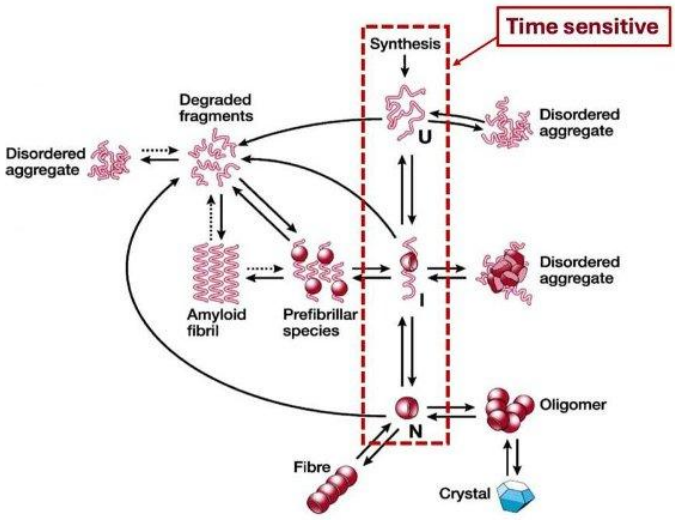
Intermediate conformations can get trapped in energetic "valleys," preventing them from efficiently folding into the native state (red path below):[93]

92 Pet., 10-11; EX1003, ¶¶ 56-60; EX1133, ¶¶ 68-72; EX1136, 4-6.

93 EX1133, ¶¶ 70-72; EX1136, 4-6.



The folding process must complete quickly, otherwise the protein will degrade:[94]



94 EX1131, 43:15-23; EX1133, ¶¶ 64-77; EX1139, 351.

All these challenges exist for the ***native*** sequence, evolutionarily selected for efficient folding and stability. Mutated sequences do not have that benefit—mutations alter the protein's net free energy of stabilization in unpredictable ways, which affects each sequence's folding ability and the protein's stability.[95] Even ***one*** mutation can prevent folding, cause misfolding or incomplete folding, or adoption of an unstable native fold that unfolds outside the cell and forms aggregates—Dr. Petsko's textbook illustrates this:[96]

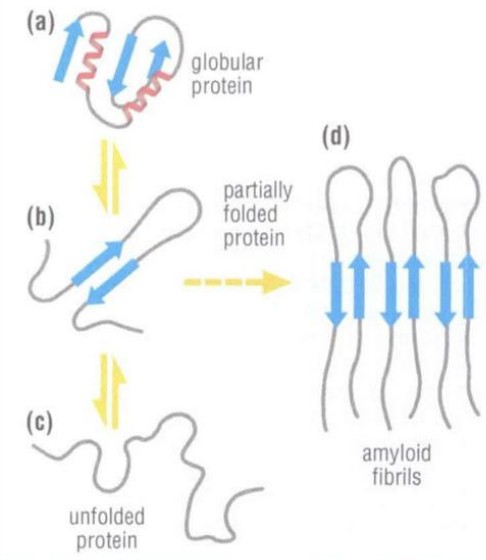


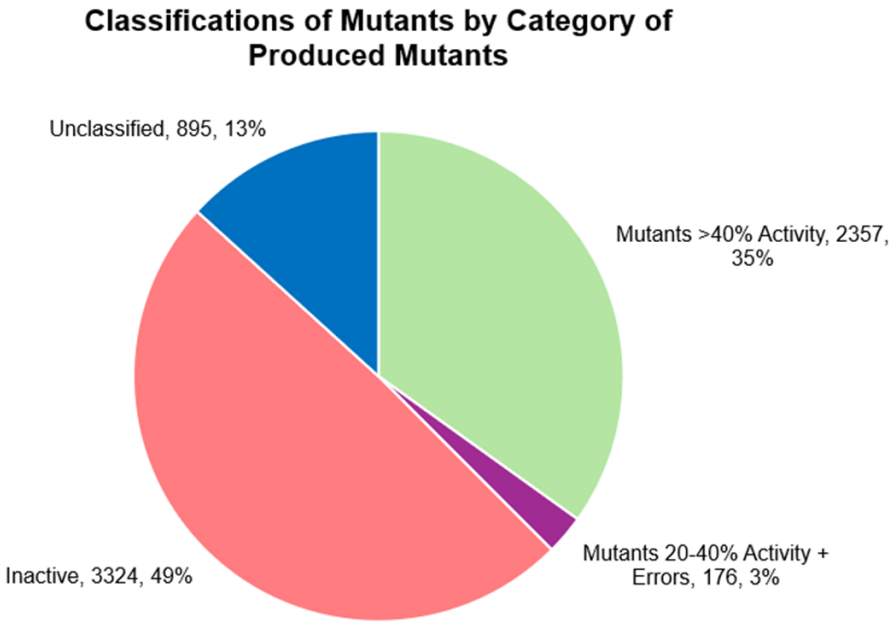
Figure 4-53 A possible mechanism for the formation of amyloid fibrils by a globular protein The correctly folded protein **(a)** is secreted from the cell. Under certain conditions, or because it contains a mutation, the protein unfolds partially **(b)** or completely **(c)**; the unfolded forms can also refold partially or completely. The partially unfolded form is prone to aggregation, which results in the formation of fibrils **(d)** and other aggregates that accumulate in the extracellular space.

95 EX1003, ¶¶ 63-66; EX1133, ¶ 129; EX1131, 99:4-22, 102:1-9.

96 EX2164, 160; EX1133, ¶¶ 73-76, 326; EX1003, ¶ 55; EX1131, 41:22-42:11.

And multiply-mutated PH20 sequences may adopt the ***wrong*** structure.[97]

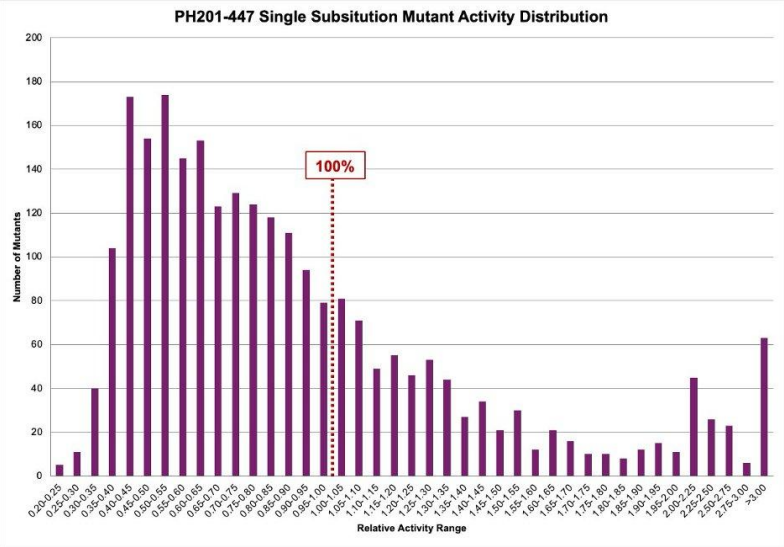
Halozyme's experts downplay unpredictability, contending POSAs could pick combinations of "tolerated" mutations using the disclosure's single-substitution data.[98] That ignores science and the data itself, which shows most single mutations were deleterious.[99]



97 EX1003, ¶¶ 56-57; EX1133, ¶¶ 73-79.

98 EX2070, ¶¶ 317-324, 355-359; EX2068, ¶¶ 311-314, 380-382.

99 Pet., 58-63; EX1003, ¶ 115; EX1133, ¶¶ 170-176, 236, 324-325; EX1146, 22381-82; EX1151, 743-744.

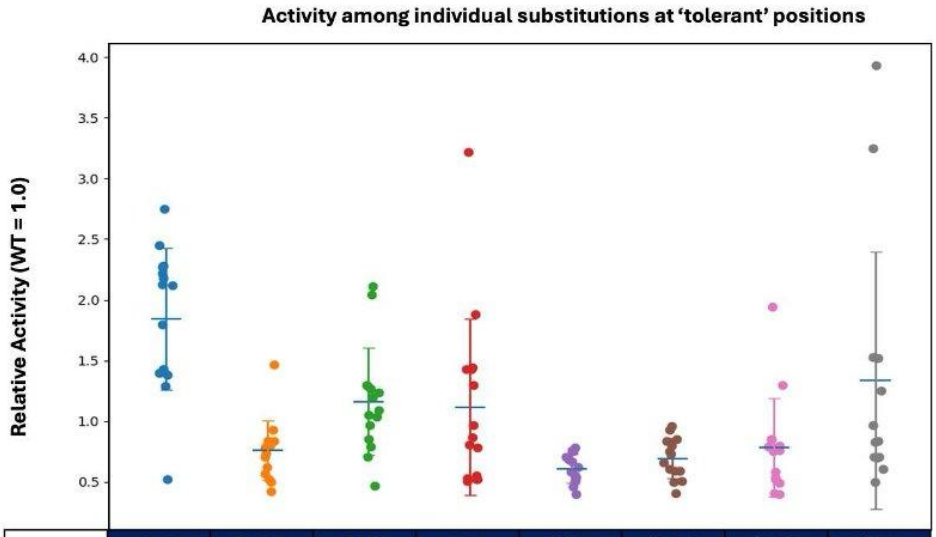


Even positions Dr. Petsko labeled as "100% tolerant" (the ***most*** predictable in his table) exhibit widely varying effects.[100] This reflects that ***each*** substitution causes a ***unique*** effect on ***the entire*** PH20 protein structure not limited to its position.[101]



[100] EX1133, ¶¶ 264-266.

[101] EX1133, ¶¶ 267-269.



	T74	L146	T147	L26	K28	Q140	N205	K93
Mean activity	1.84	0.76	1.16	1.12	0.61	0.70	0.78	1.33
Std. dev.	0.58	0.25	0.44	0.73	0.12	0.17	0.41	1.06
CV	32%	33%	38%	65%	20%	24%	52%	80%
Tested	15	15	15	15	14	14	14	13
Active (>40%)	15	15	15	15	14	14	14	13

A POSA also could not decipher the impact of many exemplified mutations—at many positions, residues with comparable size or chemistry show widely varying activities.[102] A POSA thus could not predictably determine which combinations of such mutations might affect PH20's structure and activity.[103]

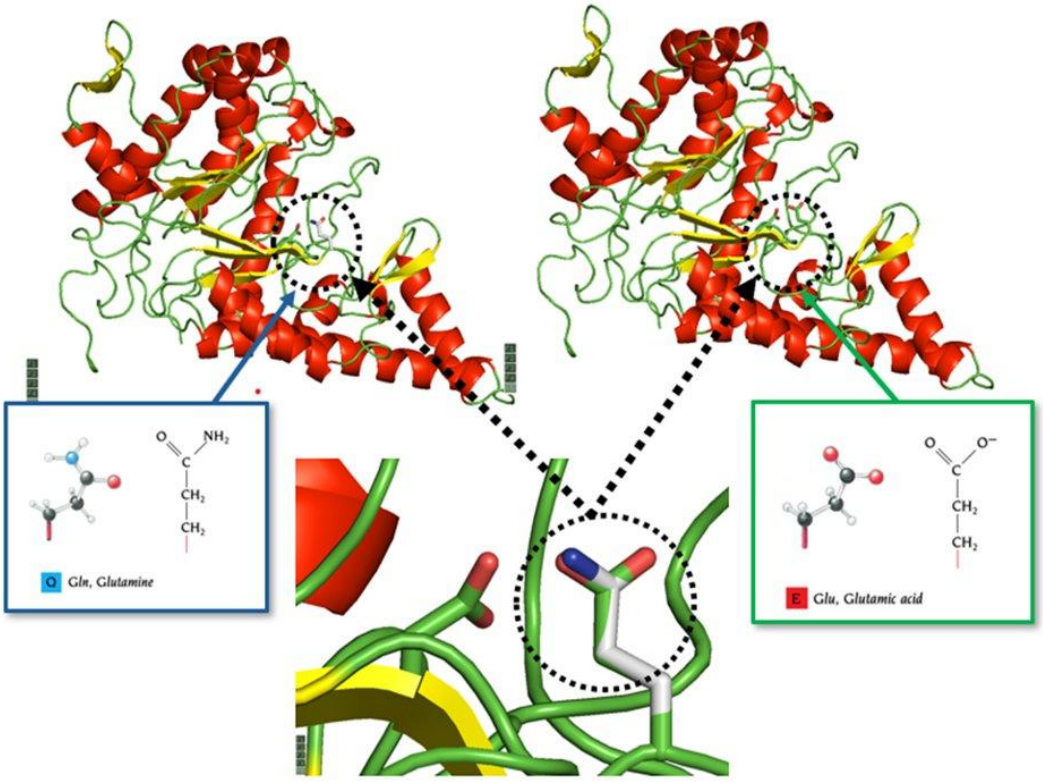
Position	WT	V	S	T	W
33	L	-	0.48	0.45	1.58
165	L	1.22	1.31	-	1.14
175	L	0.94	-	1.43	

Position	WT	V	A	L	S	T	F
47	N	-	0.48	ND	0.85	1.49	1.32
291	G	1.63	-	ND	0.45	-	-
315	S	-	0.85	0.42		0.97	ND

102 EX1133, ¶¶ 273-274.

103 EX1133, ¶¶ 270-274; EX1003, ¶¶ 179-184.

And imperceptible differences in homology models can eliminate activity.[104]



2. The α/β Barrel Motif Does Not Make Multiply-Modified PH20s Stable or Predictable

Halozyme contends the α/β barrel motif in PH20s makes it possible to predict combinations of changes to them.[105] A 2009 paper (EX1144) demonstrates the contrary.

[104] EX1133, ¶¶ 273-274, 281-284.

[105] POR, 50-53; EX2070, ¶¶ 52, 292.

EX1144 reports an experiment where loops in a ***canonical*** α/β enzyme (PRAI) were replaced with loops from other α/β proteins with the ***same*** fold. Positions were chosen to increase odds of being tolerated.

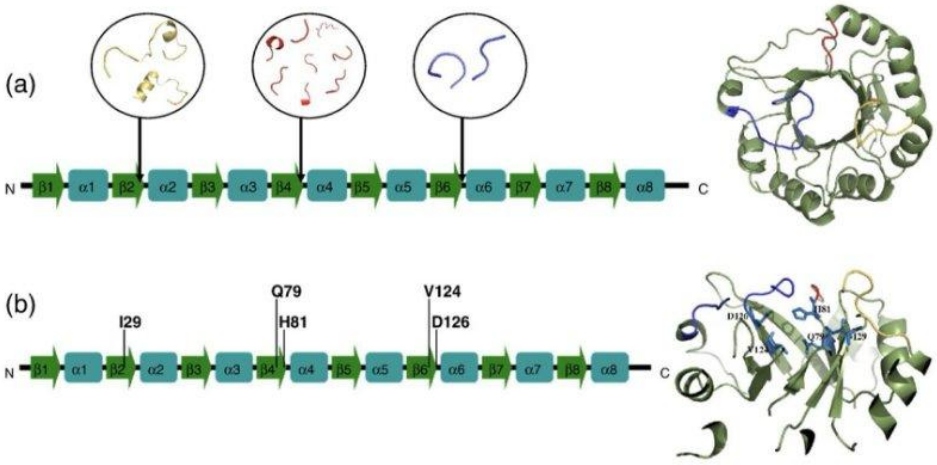


Fig. 1. Secondary-structure elements and tertiary structure (PDB code 1pii) of WT PRAI (ribbon diagram showing a view from the top of the central β-barrel). (a) The loops 2, 4, and 6 are shown in yellow, red, and blue, respectively. The circular insets show the loops to exchange in the PRAI-LoxP scaffold at the three structural positions (β/α 2, β/α 4, and β/α 6). (b) The mutated positions are indicated and a side-view slice of the TIM barrel structure of the PRAI scaffold is shown on the right.

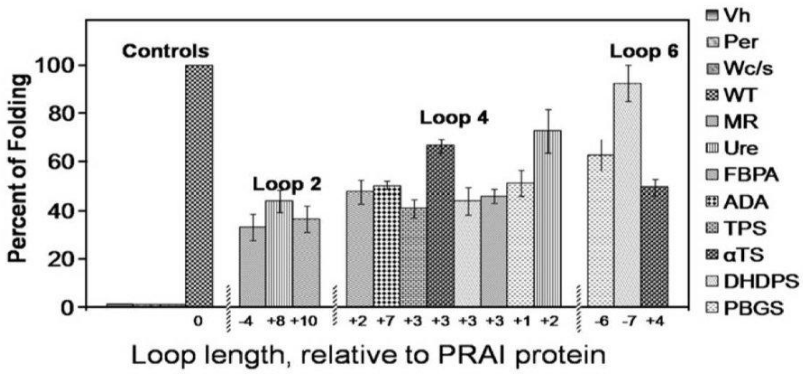
The mutations involve ***4-17*** residues—comparable to the changes permitted here.

Table 1. Characteristics of the exchanged loops in the PRAI-LoxP scaffold

Enzyme (EC number)	Position of the exchanged loop[a]	Sequence of the loop	Lengths
MR (EC 5.1.2.2)	β/α loop 2	GYPAL	5
FBPA (EC 4.1.2.13)	β/α loop 2	SNGGASFIAGKGVKSDVPQ	19
Ure (EC 3.5.1.5)	β/α loop 2	GGTGPAAGTHAITCTPG	17
PRAI WT (5.3.1.24)	β/α loop 2	VATSPRCVN[b]	9
DHDPS (EC 4.2.1.52)	β/α loop 4	PYYNRPS	7
TPS (EC 2.5.1.3)	β/α loop 4	LGQEDLH	7
MR (EC 5.1.2.2)	β/α loop 4	EPTLEHD	7
FBPA (EC 4.1.2.13)	β/α loop 4	DLSEES	6
αTS (EC 4.2.1.20)	β/α loop 4	DVPVQQS	7
Ure (EC 3.5.1.5)	β/α loop 4	EDWGAT	6
ADA (EC 3.5.4.4)	β/α loop 4	GDELGFPGSLF	11
PBGS (EC 4.2.1.24)	β/α loop 4	AAMDG	5
PRAI WT (5.3.1.24)	β/α loop 4	GNEE[b]	4
DHDPS (EC 4.2.1.52)	β/α loop 6	TGNL	4
PBGS (EC 4.2.1.24)	β/α loop 6	PAGAY	5
αTS (EC 4.2.1.20)	β/α loop 6	SRAGVTGAENRAALP	15
PRAI WT (5.3.1.24)	β/α loop 6	NGQGGSGQRFD[b]	11

[a] Structural position in which the WT loop was replaced for the new loop in the PRAI-LoxP scaffold.
[b] Sequence corresponding to the WT loops from PRAI-LoxP.

Despite the constrained choices, most α/β barrel mutants ***did not fold***:[106]



3. Dr. Petsko's Tolerance Ratings Are Not Credible or Predictive of Combinations

Halozyme contends Dr. Petsko's tolerance assessments render selecting combinations of changes in PH20s predictable in 2011-2012.[107] They cannot. § III.D.1.

First, the disclosure does not identify which mutations affected ***folding***. Mutants may exhibit <20% activity for many reasons, including that they were: (i) not produced by the cell, (ii) not secreted, (iii) secreted but partially-folded or misfolded, (iv) natively folded but, due to instability, unfolded, or (v) natively folded and stable, but had mutations that impaired substrate binding or catalysis.[108]

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106 EX1133, ¶¶ 177-182.

107 POR, 50-53.

108 Pet., 61-63; EX1133, ¶¶ 75, 246-247; EX1131, 240:19-241:16.

Because mutations that impacted ***folding*** are not identified, the disclosure cannot provide "tolerance" insights.[109]

Experimental design flaws and incomplete reporting of results independently render Dr. Petsko's ratings unreliable:[110]

- inadequate numerical, structural context, and physicochemical interrogation of positions prevent reliable ratings of tolerance;
- no use of positive/negative controls in the primary assay, and no evidence of proteins in supernatants or their folded state;
- no activities reported for inactives, precluding differentiation of non-secreted mutants from those with residual activity;
- averaging of activities conceals inter-assay variability;
- unusually high (~40%) assay variability (ordinarily ~10-15%) renders classifications unreliable.

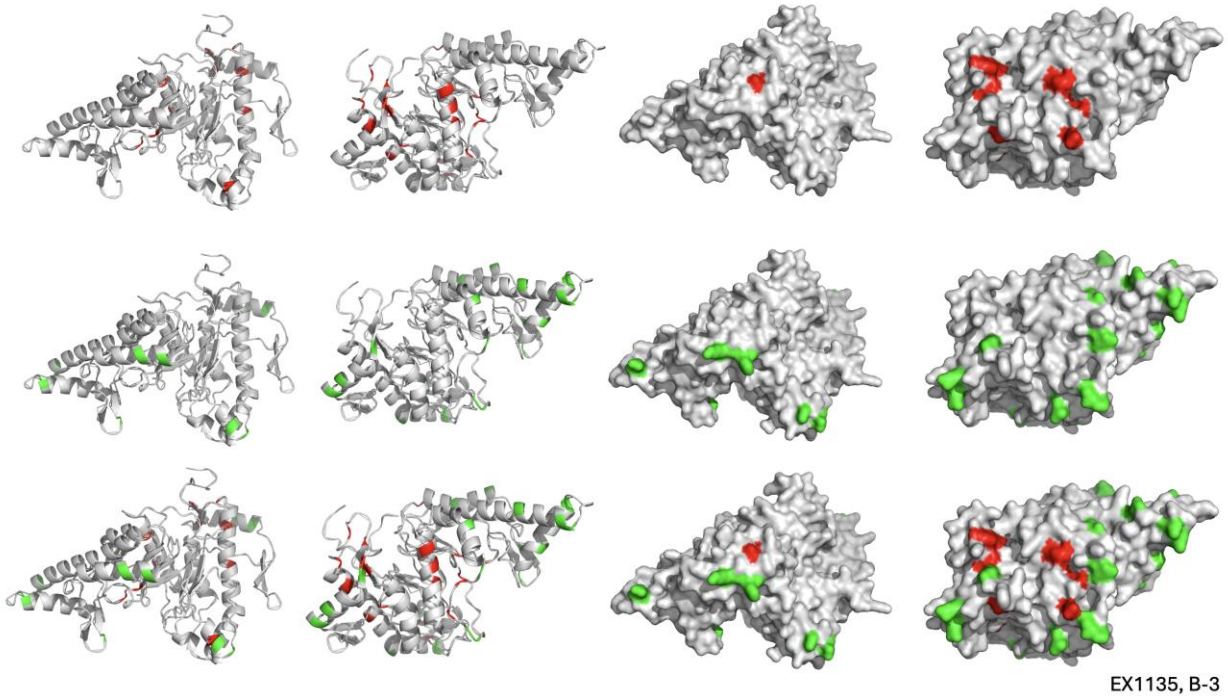
Dr. Naismith showed that correcting for these limitations and problems paints very different pictures than Dr. Petsko presented:[111]

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109 EX1133, ¶ 247.

110 Pet., 58-63; EX1003, ¶¶ 68-77, 100, 107-116; EX1133, ¶¶ 291-315, 244-248, 250, 175, 234-237.

111 EX1133, ¶¶ 304-305, 316-323, 239-242, Appendix B (EX1135).



The disclosure's unreliable and uninformative data, limitations of homology modeling and experimental capabilities, and the unpredictability of multiple mutations refute Halozyme's assertion that POSAs could predict effects of 5+ mutations on proper folding or activity of PH20s in 2011-2012.[112]

E. Halozyme's § 112 Positions Conflict with the Disclosure

1. Dr. Petsko Mischaracterizes How the Disclosure Proposes Making Multiply-Modified PH20s

Halozyme and Dr. Petsko contend POSAs would not use directed evolution techniques to produce multiply-modified PH20s. But the only ***specific*** procedure

[112] Pet., 43, 86-91; EX1003, ¶ 264; EX1004, ¶¶ 167-169; EX1133, ¶¶ 257, 261, 281; EX1027, 6-11.

for doing so in the disclosure (albeit a research plan) uses directed evolution.[113] Dr. Petsko confirmed Dr. Hecht's opinion that this method cannot enable the claimed multiply-modified PH20s—it will make "billions of sequences that… ***are not going to fold*** into PH20 proteins" because the claims permit mutations at invariant residues, and POSAs would have to screen immense libraries to discover which ones do.[114]

2. $PH20_{1-430}$ and $PH20_{1-431}$ Are Not "Inactive"

Halozyme cited US-457 to criticize Dr. Hecht's observation that the '429 Patent reports unusual activity of C-terminal truncation mutants that vary by one residue.[115] But US-457 shows the same phenomenon:[116]

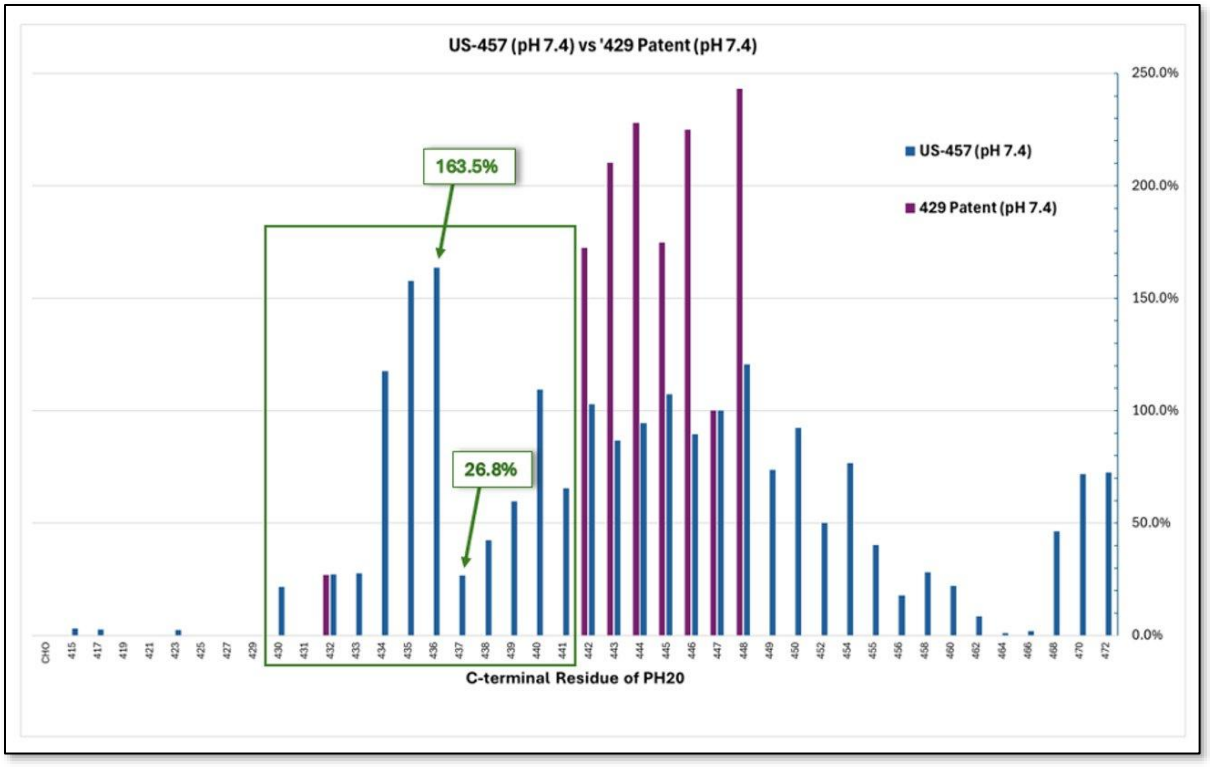
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113 Pet., 64-65; EX1026, 47:11-17, 141:30-33, 150:1-26; EX1003, ¶¶ 51-53, 207-212; EX1133, ¶¶ 204-205.

114 EX2070, ¶ 347; EX1133, ¶ 203; EX1026, 140:15-150:26; EX1003, ¶¶ 207-222. Halozyme did not advance distinct arguments regarding dependent claims in the POR, including claims 2 and 5. Pet., 23-24, 46-49.

115 POR, 60.

116 EX1133, ¶ 221.



Relying on Dr. Simpson's declaration, Halozyme contends US-457 describes $PH20_{1-430}$ and $PH20_{1-431}$ (SEQ ID NOs: 86 and 87) as "inactive mutants."[117] But US-457 and the disclosure ***explicitly*** label them "***active***,"[118] which Dr. Simpson ignored when she arbitrarily reclassified them.[119]

[117] POR, 30, 58-60; EX2068, ¶ 188.

[118] EX2165, ¶ 0362; EX1026, 79:25-31; EX1133, ¶¶ 215-216, 219.

[119] EX2068, ¶¶ 188, 330; EX1133, ¶¶ 212-219.

Terminus (precursor)	Terminus (mature)	pH 7.4	pH 5.5	Normalized Activity (pH 7.4)	Normalized Activity (pH 5.5)	Simpson Classification	US-457 Classification	Table
482	**447**	**2.03175**	**1.647**	**100%**	**100%**	**Active**	**Active**	**6**
465	**430**	0.441	0.468	22%	28%	Inactive	Active	6
466	**431**	0.000	0.212	0%	13%	Inactive	Active	6

3. Following Petsko's Tolerance Ratings Leads POSAs Into Conflict with the Disclosure

Halozyme uses Dr. Petsko's flawed positional tolerance table to contend the disclosure identifies multiply-modified active PH20s.[120] *See* § III.D.3. It does not. Regardless, the description does not propose selecting positions and substitutions based on ***a proportion*** of active mutants at a position. Where "tolerance" is used to inform changes, the disclosure instructs POSAs to ***not include*** inactivating substitutions in active PH20s.[121]

Dr. Petsko's tolerance table also induces POSAs to act ***contrary*** to the disclosure—it led Dr. Simpson to conclude a POSA ***would*** consider modifying positions 282, 299, 303, and 431, even though the disclosure ***expressly instructs otherwise***.[122]

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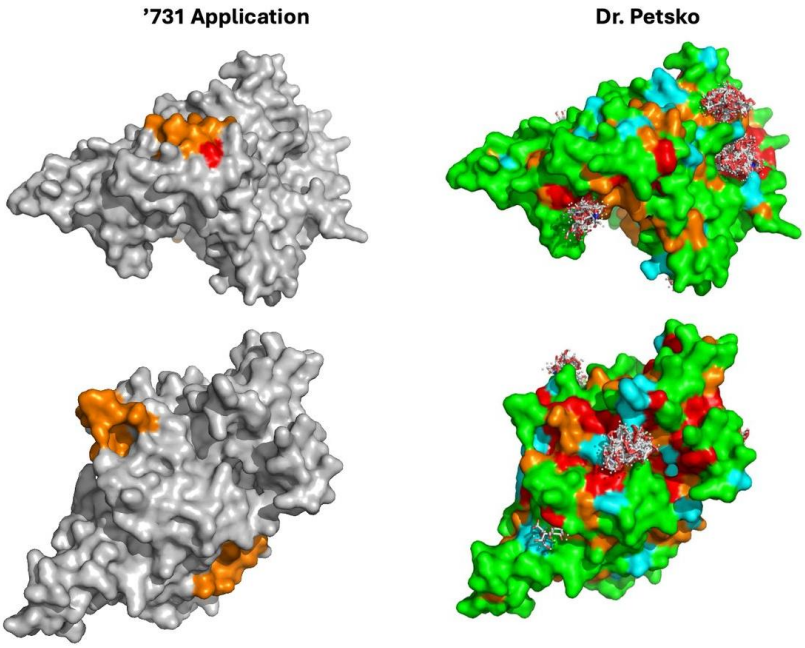
120 EX2070, ¶¶ 264, 274, 355-365; EX1133, ¶¶ 275-278.

121 EX1026, 91:30-92:20; EX1133, ¶¶ 206-207, 209.

122 EX1026, 91:30-92:20; EX1130, 191:5-16, 191:17-192:7, 192:8-194:6, 194:7-195:25; EX1133, ¶¶ 208-209.

4. Wrong Substrate Binding Sites

Based on an experiment he performed, Dr. Petsko theorizes that additional substrate binding sites exist on PH20.[123] Dr. Petsko's theories are not part of the disclosure, and his findings conflict with the disclosure's explanation that substrate binds within residues 170-200 (orange).[124]



[123] EX2070, ¶¶ 334-342. These opinions deserve no weight as counsel refused to produce Dr. Petsko's records. 37 C.F.R. § 42.65. *See* EX1125; EX1133, ¶¶ 223-230.

[124] EX1026, 81:7-14; EX1133, ¶¶ 223-226, 227-230.

5. No Rescue Mutation Theory

Dr. Petsko contends a POSA could use the disclosure to identify mutations that would "rescue" a deleterious first mutation.[125] But the disclosure says nothing about rescue mutations and discovering them would entail impossible effort.[126]

F. No Credible Utility for Inactive PH20s

Halozyme concedes PH20s have no contraceptive utility in males.[127] The evidence in the record proves no utility for females.[128]

Halozyme's expert confirmed that contraceptive utility requires ***near 100% effectiveness*** and admitted modifications to PH20 were immaterial to his opinions.[129] But every attempt to use (unclaimed) PH20s for contraception ***failed***.[130] Impartial scientists pre-2012 thus concluded that "***PH-20 is not a useful***

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125 POR, 49; EX2070, ¶¶ 374-383.

126 EX1133, ¶¶ 210-211.

127 EX1026, 213:7-9; EX1129, 38:13-23; EX1134, ¶¶ 48-51.

128 Pet., 91-96.

129 EX1129, 57:16-58:15; 101:18-102:9, 104:9-20, 40:23-42:19; *see McLeay*, *3; EX1134, ¶¶ 15-16.

130 EX1003, ¶¶ 120-122; EX1134, ¶¶ 52-65; EX1129, 114:19-115:23; EX1189, 119, Table 3.

antigen for inclusion in immunocontraceptive vaccines."[131] Halozyme independently confirmed these experimental findings.[132] No claimed ***modified*** PH20 has ever been tested for contraceptive effect in any species.

Halozyme insists improper administration caused the failures, ignoring actual reasons the researchers gave.[133] Despite not being described for immunocontraception, Halozyme claims only mucosal immunization will work, ignoring that systemic immunization was used in the guinea pig experiment[134] and effectively delivers antibodies to the female reproductive tract (*e.g.*, HPV vaccines).[135]

Established immunological principles contradict Halozyme's remaining speculation:[136]

- Effective immunocontraception with PH20 requires antibodies that

131 EX1189, 119; EX1134, ¶¶ 64-67.

132 EX1122; EX1190, Abstract, 381; EX1134, ¶¶ 68-73.

133 POR, 77-78; EX1134, ¶¶ 59-62; EX1020, 181; EX1019, 332, 333.

134 POR, 77-78; EX1134, ¶ 58; EX2010, 544.

135 EX1134, ¶¶ 42-47, 64; EX1132, 110:1-14, 111:17-18; EX1120, 3-6; EX2114, 17.

136 POR, 73-76; EX1134, ¶¶ 22-41, 74-76.

block native PH20 epitopes associated with fertilization—inducing an antibody response alone is insufficient, and mechanisms deduced from generalized anti-sperm antibody research were not expected to play a significant role.[137]

- Polyclonal antibody responses target non-native regions of modified PH20s (even if native-like structures are preserved),[138] and are less likely to produce effective antibodies against native PH20s.[139]
- Sequence similarity alone cannot predict which modified PH20s present epitopes that induce production of effective antibodies against native PH20s in all species.[140]
- Adjuvants and boosters can magnify immune responses but cannot change its epitopic specificity.[141]

An impossible scale of trial-and-error testing is thus also implicated here.[142]

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137 EX1134, ¶¶ 61-62, 103-114; *cf.* EX2116, 172-175, 177.

138 EX1134, ¶¶ 85-91, 99-102; EX1170, 288-89, 311-13, 389.

139 EX1134, ¶¶ 92-98.

140 EX1134, ¶¶ 77-84; EX2013, 10075.

141 EX1134, ¶¶ 115-122.

142 EX1003, ¶¶ 123-124; EX1134, ¶¶ 17-21, 87, 105, 123-125.

Contraceptive utility was not credible for any PH20 polypeptide in 2011-2012; it was just an invitation for further research.[143]

G. Indefiniteness

The Petition explained—and Halozyme does not dispute—that the claims do not define "modified PH20 polypeptides" outside the "hyaluronidase domain" beyond requiring use of a "PH20," which includes neutral-active non-human PH20s and over 10^{500} other possible (not-yet-discovered) sequences that would need to be tested for neutral activity.[144] POSAs could not realistically determine whether all such sequences fall within the claims.[145]

IV. Obviousness

Merck explained that Halozyme's '429 Patent (with Chao) rendered obvious single-amino acid substitution ***mutants*** (plural) of $PH20_{1-447}$.[146] Dr. Hecht explained the '429 Patent "encouraged [POSAs] to make modified PH20 proteins

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143 *Fisher*, 1371; MPEP § 2107.01. Anti-PH20 monoclonal antibodies are not claimed and cannot establish practical utility for the modified PH20s being claimed. It also is an inchoate research plan.

144 Pet., 41-43, 49-52, 82-84 97-100; POR, 82-83; EX1004, ¶ 177.

145 EX1003, ¶¶ 131-133, 171-174; EX1133, ¶¶ 48-51, 79-FN64; Pet., 43.

146 Pet., 101-104.

having single amino acid substitutions in non-essential regions."[147]

Dr. Park described how POSAs would have identified these singly-substituted active mutants using techniques Halozyme's experts confirmed would have been used in 2011.[148] Without reviewing the disclosure, Dr. Park used those techniques to identify M313K as ***one of ~750 such substitutions*** suggested by the '429 Patent before 2011.[149] For example, he and Dr. Hecht identified M313K's favorable effects, which confirms a POSA's motivation to make that substitution.[150] Dr. Naismith found Dr. Park's analysis objective, rigorous, and unbiased.[151] Thus, per *KSR*, the '429 Patent motivated POSAs to identify single substitutions in non-essential regions of $PH20_{1-447}$ that ***predictably*** retain activity.

Halozyme attacks its own '429 patent, contending it doesn't identify "non-essential" regions or "provide any guidance on which sites to modify."[152] But

147 EX1003, ¶¶ 231-244, 247; EX1005, 16:14-26.

148 EX1004, ¶¶ 23-25, 33; EX1133, ¶¶ 347-349, 357, 360, Appendix B-8.

149 EX2176; EX1133, ¶ 344; EX1003, ¶ 270.

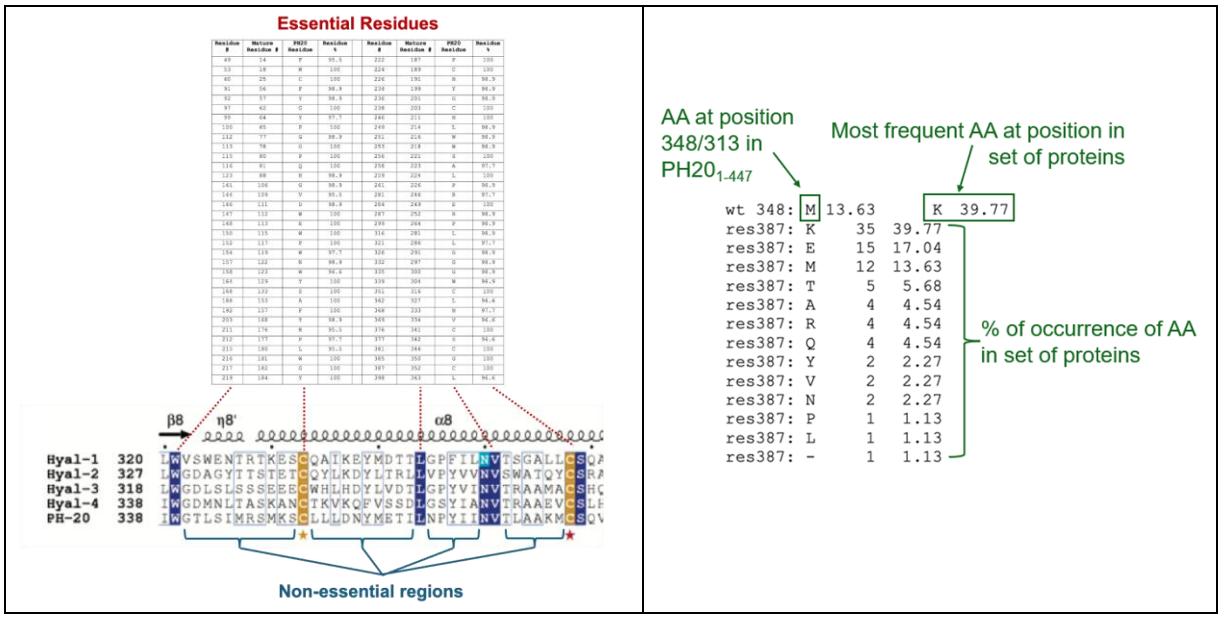
150 EX1004, ¶¶ 114-121; EX1003, ¶¶ 265-270; Pet., 108-111, 116-118.

151 EX1133, ¶¶ 338-343, 352-359; EX1003, ¶ 251.

152 POR, 89-90.

Halozyme ***patented all such singly-substituted PH20s.***[153]

After extensive discovery and three depositions, Halozyme repeats the ***identical*** lawyer-directed hindsight theory initially raised in related proceedings.[154] That evidence establishes that Dr. Park used his multiple-sequence alignment ("MSA")—not hindsight—to (i) identify ***which positions*** to evaluate (*i.e.*, the 379 residues ***between*** 68 "essential" positions),[155] and (ii) which substitutions at each position to assess—the frequently found residues at these non-essential positions.[156]



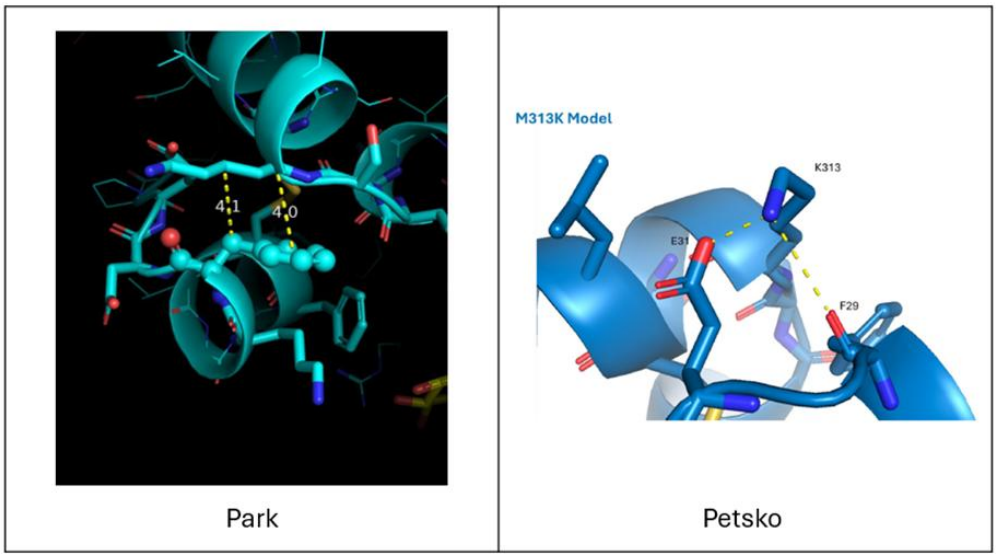
153 EX1005, claim 1.

154 POR, 84-85.

155 EX1004, ¶¶ 27-33.

156 EX1003, ¶¶ 249-250; EX1004, ¶¶ 42-44; Appendix D-1; EX1133, ¶ 342.

Dr. Park's objective and unbiased assessment found M313K tolerated. Notably, he and Dr. Petsko identified the same M313:F29 interaction:[157]



Halozyme's "hindsight" theory is refuted by Dr. Park's declaration—he testified he performed his analysis "in a manner that ***did not focus on any particular position***" and reviewed "***a lot of different types of substitutions***."[158] He also testified he assessed substitutions position-by-position, at least twice, using the frequently occurring amino acids ***from his MSA analysis***.[159]

EX2176 corroborates his testimony—it contains his observations and rating

[157] EX1004, ¶¶ 114-121; EX2070, ¶¶ 408-410; EX1133, ¶¶ 349-351.

[158] EX1004, ¶¶ 103-104.

[159] EX2078, 170:22-171:17.

for each substitution assessed at hundreds of positions.[160]

D	E	F	G	H	I	J	K	L	M	N
PH20 Mature Residue #	PH20 Residue	Alternative Residue	Residue %	Rating (1-3)	Comments	#neigh	fSASA	Factors		
								Hydrophobicity	Secondary Structure	Interactions
313	M	-	13.63			4	0.53			
313	-	K	39.77	3	gain: hydrophilic, hydrophobic contacts to F64	4	0.52	1		1
313	-	E	17.04	2	gain: hydrophilic but potential charge repulsion	4	0.55	1		1
313	-	T	5.68	2	loss: lower H propensity	4	0.42		1	
313	-	A	4.54	2	neutral	4	0.33			
313	-	R	4.54	3	gain: hydrophilic, hydrophobic contacts to F64	5	0.51	1		1
313	-	Q	4.54	2	gain: hydrophilic	4	0.48	1		1
313	-	Y	2.27	2	neutral: lower H propensity, increased hydrophobic contacts, hydrophobic exposed	5	0.51	1	1	1
313	-	V	2.27	2	neutral: lower H propensity, increased hydrophobic contacts	4	0.45			
313	-	N	2.27	2	neutral	5	0.4	1	1	1
313	-	P	1.13	2	gain: increased hydrophobic contacts, Ncap	5	0.44		1	1
313	-	L	1.13	2	neutral	4	0.45	1		1

Moreover, Dr. Park testified he recorded his observations about M313K ***before*** counsel asked him to explain them in his declaration.[161]

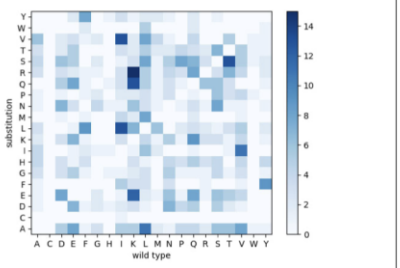
His "heat map" tracked the diversity of substitutions he assessed and prompted him to assess more substitutions.[162]

160 EX1004, ¶¶ 86-88; EX1133, ¶¶ 340-346.

161 EX2078, 320:10-20; EX2176, 38.

162 EX2078, 300:2-301:2, 322:20-324:3; EX2176.

	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1												Factors		
2	Hyal1 Residue#	Hyal1 Residue	PH20 Residue #	PH20 Mature Residue #	PH20 Residue	Alternative Residue	Residue %	Rating (1-3)	Comments	#neigh	fSASA	Hydrophobicity	Secondary Structure	Interactions
3	22	F	39	4	R	-	15.9				-			
4	22		39	4	-	T	15.9				-			
5	22		39	4	-	A	11.36				-			
6	22		39	4	-	Q	3.4				-			
7	22		39	4	-	S	3.4				-			
8	22		39	4	-	K	2.27				-			
9	22		39	4	-	G	1.13				-			
10	23	R	40	5	A	-	34.09			3	0.44			
11	23		40	5	-	R	15.9				-			
12	23		40	5	-	Q	2.27				-			
13	23		40	5	-	G	2.27				-			
14	23		40	5	-	T	1.13				-			
15	23		40	5	-	N	1.13				-			
16	24	G	41	6	P	-	34.09			5	0.49			
17	24		41	6	-	L	11.36				-			
18	24		41	6	-	A	4.54				-			
19	24		41	6	-	G	3.4				-			
20	24		41	6	-	D	3.4				-			
21	24		41	6	-	R	2.27				-			
22	24		41	6	-	W	2.27				-			
23	24		41	6	-	S	2.27				-			
24	24		41	6	-	H	1.13				-			
25	25	P	42	7	P	-	84.09				0.28			
26	25		42	7	-	T	2.27				-			
27	25		42	7	-	L	1.13				-			
28	26	L	43	8	V	-	25			6	0.23			
29	26		43	8	-	I	27.27	2	gain: increased hydrophobic contacts	6	-			1
30	26		43	8	-	L	25	2	neutral	6	-			
31	26		43	8	-	M	3.4				-			
32	26		43	8	-	T	2.27				-			
33	26		43	8	-	Q	2.27				-			
34	26		43	8	-	N	2.27				-			



Evidence shows Dr. Park assessed ~830 substitutions in non-essential regions of PH20 and found ~750 tolerated, without bias toward any position or substitution.[163]

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

Note:
Red - essential residues
Dark Green - >66% MSA options assessed
Green - 33 to 66% MSA options assessed
Light Green - <33% MSA options assessed
Unshaded - No MSA options assessed

Halozyme ignores, rather than refutes, this evidence.

163 EX1133, ¶¶ 340-343.

V. Conclusion

The challenged claims are unpatentable.

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Respectfully Submitted,

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EXHIBIT LIST

No.	Exhibit Description
1001	U.S. Patent No. 12,264,345
1002	File History of U.S. Patent No. 12,264,345
1003	Declaration of Dr. Michael Hecht
1004	Declaration of Dr. Sheldon Park
1005	U.S. Patent No. 7,767,429
1006	Chao et al., "Structure of Human Hyaluronidase-1, a Hyaluronan Hydrolyzing Enzyme Involved in Tumor Growth and Angiogenesis," Biochemistry, 46:6911-6920 (2007)
1007	WO 2010/077297, published 8 July 2010
1008	Stern et al., "The Hyaluronidases: Their Genomics, Structures, and Mechanisms of Action," Chem. Rev. 106:818-839 (2006)
1009	Jedrzejas et al., "Structures of Vertebrate Hyaluronidases and Their Unique Enzymatic Mechanism of Hydrolysis," Proteins: Structure, Function and Bioinformatics, 61:227-238 (2005)
1010	Zhang et al., "Hyaluronidase Activity of Human Hyal1 Requires Active Site Acidic and Tyrosine Residues," J. Biol. Chem., 284(14):9433-9442 (2009)
1011	Arming et al., "In vitro mutagenesis of PH-20 hyaluronidase from human sperm," Eur. J. Biochem., 247:810-814 (1997)
1012	Bordoli et al., "Protein structure homology modeling using SWISS-MODEL workspace," Nature Protocols, 4(1):1-13 (2008)
1013	Frost, "Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration," Expert Opinion on Drug Delivery, 4(4):427-440 (2007)
1014	Brandon & Tooze, "Introduction to Protein Structure," Second Ed., Chapters 1-6, 11-12, 17-18 (1999)
1015	Table Associating Citations from the '345 Patent (EX1001) to Corresponding Citations in the '731 Application (EX1026)

No.	Exhibit Description
1016	Steipe, "Consensus-Based Engineering of Protein Stability: From Intrabodies to Thermostable Enzymes," Methods in Enzymology, 388:176-186 (2004)
1017	Green, "Computer Graphics, Homology Modeling, and Bioinformatics," Protein Eng'g & Design, Ch. 10, 223-237 (2010)
1018	Chica et al., "Semi-rational approaches to engineering enzyme activity: combining the benefits of directed evolution and rational design," Curr. Opin. Biotechnol., (4):378-384 (2005)
1019	Hardy et al., "Assessment of contraceptive vaccines based on recombinant mouse sperm protein PH20," Reprod., 127:325-334 (2004)
1020	Pomering et al., "Restricted Entry of IgG into Male and Female Rabbit Reproductive Ducts Following Immunization with Recombinant Rabbit PH-20," Am. J. Reprod. Immunol., (3):174-82 (2002)
1021	Baba et al., "Mouse Sperm Lacking Cell Surface Hyaluronidase PH-20 Can Pass through the Layer of Cumulus Cells and Fertilize the Egg," J. Biol. Chem., 277(33):30310-4 (2002)
1022	Primakoff et al., "Reversible Contraceptive Effect of PH-20 Immunization in Male Guinea Pigs," Biol Reprod., 56(5):1142-6 (1997)
1023	Tung et al., "Mechanism of Infertility in Male Guinea Pigs Immunized with Sperm PH-20," Biol. Reprod., 56(5):1133-41 (1997)
1024	Rosengren et al., "Recombinant Human PH20: Baseline Analysis of the Reactive Antibody Prevalence in the General Population Using Healthy Subjects," BioDrugs, 32(1):83-89 (2018)
1025	U.S. Patent No. 9,447,401
1026	U.S. Patent Application No. 13/694,731
1027	2024 Chemistry Nobel Prize Background
1028	[Reserved]
1029	Gmachl et al., "The human sperm protein PH-20 has hyaluronidase activity," FEBS Letters, 3:545-548 (1993)

No.	Exhibit Description
1030	Sills, "Retraction," Science, 319:569 (2008)
1031	Yue et al., "Loss of Protein Structure Stability as a Major Causative Factor in Monogenic Disease," J. Mol. Biol., 353:459-473 (2005)
1032	Wang & Moult, "SNPs, Protein Structure, and Disease," Hum. Mutation, 17:263-270 (2001)
1033	Marković-Housley et al., "Crystal Structure of Hyaluronidase, a Major Allergen of Bee Venom," Structure, 8:1025-1035 (2000)
1034	"Negative Results," Nature: Editorials, 453:258 (2008)
1035	Lins et al., "Analysis of Accessible Surface of Residues in Proteins," Protein Sci., 12:1406-1417 (2003)
1036	Hayden, "Chemistry: Designer Debacle," Nature, 453:275-278 (2008)
1037	Benkert et al., "Toward the Estimation of the Absolute Quality of Individual Protein Structure Models," Bioinformatics, 27:343-350 (2010)
1038	Schwede et al., "SWISS-MODEL: An Automated Protein Homology-Modeling Server," Nucleic Acids Rsch., 31:3381-3385 (2003)
1039	Alberts, "Molecular Biology of the Cell," Fifth Edition, Chapter 3 (2007).
1040	He et al., "NMR Structures of Two Designed Proteins with High Sequence Identity but Different Fold and Function," PNAS, 105:14412-14417 (2008)
1041	Alexander et al., "A Minimal Sequence Code for Switching Protein Structure and Function," PNAS, 106:21149-21154 (2009)
1042	Ruan et al., "Design and Characterization of a Protein Fold Switching Network," Nature Comm., 14 (2023)
1043	Sievers et al., "Fast, Scalable Generation of High-Quality Protein Multiple Sequence Alignments Using Clustal Omega," Molecular Sys. Biology, 7.1 (2011)
1044	Mihel, "PSAIA – Protein Structure and Interaction Analyzer," BMC Structural Biology, 8:21 (2008)

No.	Exhibit Description
1045	Redline Comparison of the ’731 and ’345 Specifications
1046	Beasley & Hecht, “Protein Design: The Choice of *de Novo* Sequences,” J. Biological Chemistry, 272:2031-2034 (1997)
1047	Xiong et al., “Periodicity of Polar and Nonpolar Amino Acids is the Major Determinant of Secondary Structure in Self-Assembling Oligomeric Peptides,” PNAS, 92: 6349-6353 (1995)
1048	Hayden, “Key Protein-Design Papers Challenged,” Nature, 461:859 (2009)
1049	KEGG, *DRUG: Hyaluronidase (human recombinant)*, available at: https://www.genome.jp/entry/D06604
1050	Pace & Scholtz, “A Helix Propensity Scale Based on Experimental Studies of Peptides and Proteins,” Biophysical J. 75:422-427 (1998)
1051	U.S. Patent Application No. 61/631,313
1052	U.S. Patent Application No. 61/796,208
1053	Hom_pre2011
1054	Hom_pre2011_header
1055	Hom_pre2011_header_clean
1056	Hom_pre2011.fasta
1057	Ph20_pre2011.aln-clustal_num
1058	Ph20_pre2011 Alignment html
1059	Leisola & Turunen, “Protein Engineering: Opportunities and Challenges,” Appl. Microbiol. Biotechnol. 75:1225-1232 (2007)
1060	Hecht et al., “De Novo Proteins from Designed Combinatorial Libraries,” Protein Sci., 13:1711-1723 (2004)
1061	Rosengren et al., “Clinical Immunogenicity of rHuPH20, a Hyaluronidase Enabling Subcutaneous Drug Administration,” AAPS J., 17:1144-1156 (2015)
1062-1063	[Reserved]
1064	Collection of BLAST Webpages from the Internet Archive, navigable from:

No.	Exhibit Description
	https://web.archive.org/web/20111022151531/http://www.clustal.org/omega/
1065	Collection of Clustal Omega Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20111022151531/http://www.clustal.org/omega/
1066	Collection of SWISS-MODEL Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20110519141121/http://swissmodel.expasy.org/?pid=smh01&uid=&token=
1067	Collection of PyMol Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20110701072314/http://pymol.org/
1068	Declaration of Jeffrey P. Kushan
1069	Swiss Model Printout of PH20 Model
1070	Swiss Model Printout of PH20 Model with M313K Mutation
1071	Swiss Model Printout of PH20 Model with M313A Mutation
1072	Swiss Model Printout of PH20 Model with M131R Mutation
1073	Swiss Model Printout of PH20 Model with M131Y Mutation
1074	Swiss Model Printout of PH20 Model with M131P Mutation
1075	Swiss Model Printout of PH20 Model with M131L Mutation
1076	Declaration of Leif E. Peterson, II
1077-1078	[Reserved]
1079	Hunnicutt et al., "Sperm Surface Protein PH-20 Is Bifunctional: One Activity Is a Hyaluronidase and a Second, Distinct Activity Is Required in Secondary Sperm-Zona Binding," Biol. Reprod., 55(1):80-86 (1996)
1080	Bookbinder et al., "A Recombinant Human Enzyme for Enhanced Interstitial Transport of Therapeutics," J. Controlled Release, 114:230-241 (2006)
1081	Goldberg, "Protein degradation and protection of against misfolded or damaged proteins," Nature, 426:895-899 (2003)

No.	Exhibit Description
1082-1086	[Reserved]
1087	Vembar et al., "One step at a time: endoplasmic reticulum-associated degradation," Nat. Rev. Mol. Cell Biol., 9:944-958 (2008)
1088-1112	[Reserved]
1113	Declaration of Sue Wang
1114	Declaration of Brian M. Goldberg
1115	Declaration of Katherine A. Helm
1116-1118	[Reserved]
1119 [NEW]	Csoka, A. et al., "The Six Hyaluronidase-Like Genes in the Human and Mouse Genomes" Matrix Biology 20:499-508 (2001)
1120 [NEW]	Huo, Z. et al., "Systemic and Mucosal Immune Responses to Sublingual or Intramuscular Human Papilloma Virus Antigens in Healthy Female Volunteers," PLoS ONE 7(3):e33736 (2012)
1121	[Reserved]
1122 [NEW]	Printz, M. et al., "Risk Factors, Hyaluronidase Expression, and Clinical Immunogenicity of Recombinant Human Hyaluronidase PH20, an Enzyme Enabling Subcutaneous Drug Administration," AAPS 24(6):110 (2022)
1123-1124	[Reserved]
1125 [NEW]	Emails re: AutoDock Vina (Sept. 9, 2025 - Oct. 27, 2025)
1126 [NEW]	Im, S. et al., "Cryo-EM Structure of Human Hyaluronidase PH-20," Proteins: Structure, Function, and Bioinformatics 93:1067-1073 (2025)
1127-1128	[Reserved]
1129 [NEW]	Transcript of the Deposition of Dr. Gary Cherr, Ph.D., November 12, 2025
1130 [NEW]	Melanie Ann Simpson, Ph.D. Deposition Transcript

No.	Exhibit Description
1131 [NEW]	Gregory Petsko, Ph.D. Deposition Transcript
1132 [NEW]	Transcript of the Deposition of Dr. James Moon, Ph.D., November 18, 2025
1133 [NEW]	Declaration of James Naismith, Ph.D.
1134 [NEW]	Declaration of Dr. Garnett Kelsoe
1135 [NEW]	Dr. Naismith Analysis Spreadsheet
1136 [NEW]	Dobson, "Principles of protein folding, misfolding and aggregation" Semin. Cell. Dev. Biol. 15(1):3-16 (2004)
1137 [NEW]	Dobson, "Protein folding and misfolding" Nature. 18;426(6968):884-90 (2003)
1138 [NEW]	Dobson, "Experimental investigation of protein folding and misfolding" Methods 34(1):4-14 (2004)
1139 [NEW]	Chiti & Dobson, "Protein Misfolding, Functional Amyloid, and Human Disease" Annu. Rev. Biochem. 75:333–66 (2006)
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1167	MERCK_PGR00094 - DNJ-2-25-cv-03179 Stipulation to Substitute Parties
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1224	Declaration of Kelly Grez – Protective Order Material
1225	Transcript of the Deposition of Kelly Grez, March 26, 2026

No.	Exhibit Description
1226	Kelly Grez Deposition Transcript Errata
1227-1233	[Reserved]
1234	MSD Netherlands Capital B.V., Preliminary Prospectus Supplement (May 14, 2024)
1235	Merck & Co., Inc., Form 8-K (Nov. 4, 2009)
1236	Jennifer_Zachary WD_Redacted – Protective Order Material
1237	Merck & Co., Inc. Subsidiaries (Dec. 31, 2024)
1238	State of New Jersey, Certificate of Long Form Standing with Officers and Directors, Merck & Co., Inc. (Feb. 18, 2026)
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1240	State of New Jersey, Certificate of Long Form Standing with Officers and Directors, Merck Sharp & Dohme LLC (Feb. 18, 2026)
1241	Company Statement: "Merck Sues Merck KGaA, Darmstadt, Germany for Improper Use of "Merck"" (Jan. 15, 2016)
1242	ZacharyJennifer ADP_Redacted – Protective Order Material
1243	Table Comparing the Boards of Directors for Merck & Co., Inc. and Merck Sharp & Dohme LLC
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2068	Declaration of Melanie A. Simpson, Ph.D. in Support of Patent Owner's Response

No.	Exhibit Description
2070	Declaration of Gregory A. Petsko, Ph.D. in Support of Patent Owner's Response
2072	Declaration of Gary N. Cherr, Ph.D. in Support of Patent Owner's Response
2074	Declaration of James J. Moon, Ph.D. in Support of Patent Owner's Response
2076	Transcript of the Deposition of Michael Hecht, Ph.D., August 26, 2025
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2166	Petsko Patent Analysis Data
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2176	Park Analysis Spreadsheet

CERTIFICATE OF COMPLIANCE

I hereby certify that this brief complies with the type-volume limitations of 37 C.F.R. § 42.24, because it contains 5,596 words (as determined by the Microsoft Word word-processing system used to prepare the brief), excluding the parts of the brief exempted by 37 C.F.R. § 42.24.

Dated: May 7, 2026

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on this 7th day of May, 2026, I caused to be served a true and correct copy of the foregoing and any accompanying exhibits by e-mail on the following counsel of record for Patent Owner:

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