Paper No. 73
Filed: January 28, 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. PGR2025-00003
U.S. Patent No. 11,952,600

PETITIONER'S REPLY

Halozyme EX2034
Merck v. Halozyme
IPR2026-00312

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I. Introduction

Halozyme's response abandons its disclosure, invents new research plans, and disparages its earlier PH20 patents. Its experts propose conflicting pictures of claims coverage but concede "PH20" means a folded protein. Its newly identified "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. It ignores failures that foreclose using PH20s as contraceptive vaccines. Its experts endorsed Merck's expert's prior art-based methods that identified the obvious D320K $PH20_{1-447}$ mutant, and evidence refutes Halozyme's false "hindsight" narrative. The claims are unpatentable.

II. Claim Construction and Scope

The claim construction dispute is narrow: are the claims limited to a "***structurally and functionally distinct genus***" of PH20s (*i.e.*, "properly folded" and enzymatically active modified PH20 polypeptides),[1] or do they ***also*** include 10^{49}+ other PH20 sequences in the claim parameter's "sequence space" (*i.e.*, a

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

genus weighing more than Earth)?[2]

The Board can resolve patentability without resolving that dispute—as 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"[3] and D320K $PH20_{1-447}$ renders the claims obvious. Regardless, the Board should reject Halozyme's perspective,[4] as the claims ***as a whole*** require modified PH20s that are "properly folded and enzymatically active."

Because "PH20" and "modified PH20 polypeptide" are ***both*** defined terms,[5] Halozyme's assertions[6] warrant addressing their ***combined*** meaning.

Halozyme cannot dispute the preamble is limiting—its arguments rest on the ***preambular*** phrase "modified PH20 polypeptide."[7] Halozyme's expert (Dr. Simpson) testified that "PH20" ***provides context*** to "modified PH20 polypeptide."[8]

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2 EX1003, ¶¶ 122-123.

3 POR, 44.

4 POR, 42; EX1130, 55:23-56:7, 90:1-16.

5 Pet., 17; EX1026, 50:31-32, 54:5-10.

6 POR, 32-42.

7 POR, 32-42; POPR, 16-21.

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

Another Halozyme expert, Dr. Petsko, provided that context: "***POSAs think of PH20 as a folded protein***."[9] Dr. Simpson also testified PH20's definition[10] led POSAs to view "PH20s" as properly folded and enzymatically active proteins.[11] Giving effect to both defined terms, the preamble requires a "***properly folded*** PH20 polypeptide with ***at least one modification***."

The Petition explained ***other*** claim language restricts them to active PH20s:

- the disclosure portrays "active" and "inactive" mutants as mutually exclusive embodiments;
- paragraphs (a) and (b) impose 95%+ sequence identity and position 320 modification requirements; and
- paragraph (c) requires a 320 substitution that yields only "active

[9] EX2070, ¶ 345.

[10] EX1026, 50:31-32; EX1130, 60:14-61:12.

[11] EX1130, 61:19-23; EX2070, ¶ 128-FN12; EX1133, ¶¶ 92-101, 104; Halozyme's experts use "polypeptide" interchangeably with "protein." EX1133, ¶¶ 87-89; EX1131, 32:8-37:20; EX2068, ¶¶ 283, 353, 376; EX2070, ¶¶ 50, 423.

mutants." [12]

POSAs thus read the claims ***as a whole*** as being directed to properly folded, enzymatically active PH20s.[13]

Halozyme's exposition of defined terms ignores "PH20"[14] and gives it no weight—that is legal error.[15]

III. The Claims Are Unpatentable Under § 112

A. The Claims Define Structurally Heterogenous Genera

Merck's reading of the "sequence space" of the claims is not a "parlor trick"— Halozyme's experts ***confirmed*** it (~10^{49} to ~10^{66} sequences).[16] The Petition also explained (and Halozyme's experts agree) the claims permit (i)

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[12] Pet., 22-26; EX1026, 254-55, 251:2-4; 272:3-5; EX1003, ¶¶ 98, 100-101, 107; EX1131, 146:14-148:8.

[13] Pet., 25-26; EX1026, 90:33-34; EX1003, ¶¶ 127-129; 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.

[14] POR, 32-42.

[15] EX1130, 55:23-56:7, 57:9-58:4; *Bicon*, 950-51.

[16] Pet., 20-21; EX1003, ¶¶ 120-122; EX1004, ¶¶ 168-171; EX1130, 90:1-16, 91:18-92:1; EX1131, 58:18-59:19, 61:6-8, 65:18-66:3; EX2070, ¶¶ 235-236.

modifications at any position, (ii) additions/deletions, and (iii) substitutions to any of 19 other amino acids.[17]

The sequence space thus reflects immense structural diversity (sequence and form), of which an unknowable portion will properly fold into an enzymatically active PH20 (below).[18] Natively folded ("properly folded")[19] enzymatically active PH20s exist within one corner (*i.e.*, those with the same tertiary structure as wild-type human PH20). Other PH20 sequences: (i) never leave the cell (e.g., cannot be made or are not secreted), (ii) are secreted but are partially- or misfolded, or (iii) adopt the native fold but are unstable and unfold after secretion, existing in unfolded and/or aggregated forms.[20]

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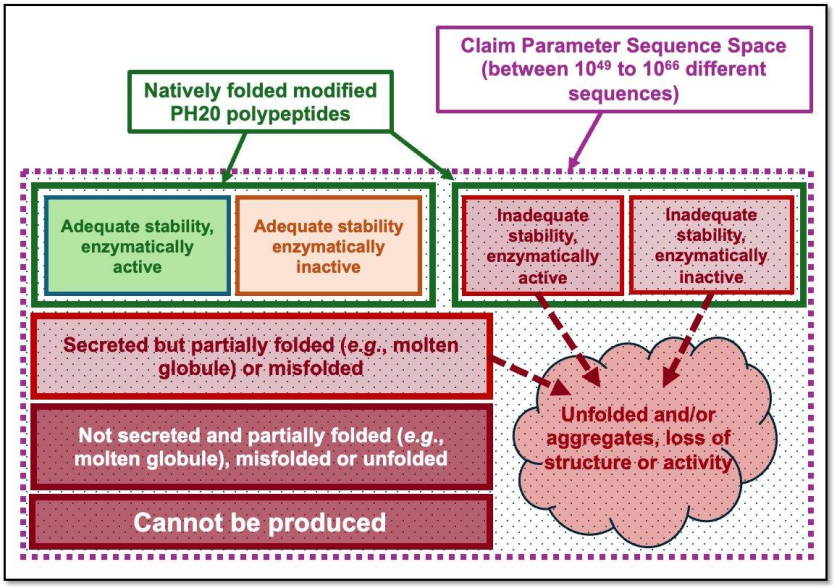
17 Pet., 19-20; EX1003, ¶ 119; EX1026, 53:1-7, 68:18-34; EX1130, 90:25-91:5; EX1131, 54:24-55:6.

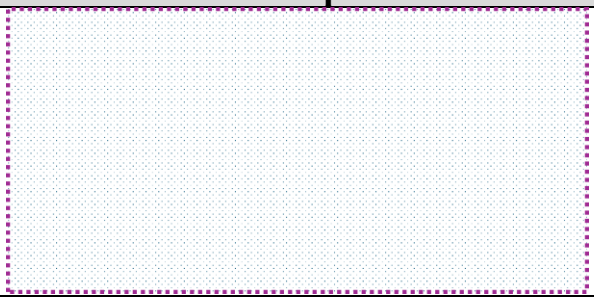
18 EX1130, 92:2-94:14; EX1131, 61:15-62:5; EX1133, ¶¶ 77-80.

19 POR, 5, 63; EX1131, 78:6–25; EX2068, ¶¶ 105–106; EX2070, ¶¶ 51,128-FN12, 420.

20 EX1133, ¶¶ 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 they disagree about what that set contains: Dr. Petsko says it is a subset of the proteins that have ***folded***,[21] while Dr. Simpson portrays it as ***the entire sequence space***.[22]

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

[21] 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.

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

Halozyme embraces (rather than resolves) this confusion—it contends ***both*** sets are "structurally homogeneous."[23] But the broader set plainly is not, even active PH20s are structurally heterogeneous.[24]

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

The Petition explained it was impossible to determine the enzymatically active species within the 10^{49}+ sequences meeting the claims' parameters.[25] Halozyme's expert Dr. Petsko agreed: he testified it is impossible to calculate or experimentally determine what portion of the sequence space will properly fold and be enzymatically active, and could not even approximate their number.[26] Dr. Petsko 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."[27] Critically, the disclosure does not (and could

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23 POR, 31, 3-4.

24 Pet., 9-10; EX1003, ¶¶ 55-61, 66, 69, 142, 156; EX1133, ¶¶ 40, 85-86.

25 Pet., 44-45, 48-55, 60-61, 67-70; EX1003, ¶¶ 158-159; 167-172, 184-186, 189-190; EX1133, ¶ 112, 120, 123, 126.

26 EX1131, 63:19-64:17.

27 EX2070, ¶ 347.

not) identify all the residues involved in protein structure, while the claims ***expressly permit*** any change at any 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.[28] Dr. Hecht explained why directed evolution procedures could not.[29] Drs. Petsko and Naismith confirm his opinions.[30] 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, exemplified below).[31]

Total Changes	Total Sequences	#
1	4	4.0E+00
2	32,832	3.3E+04
3	134,430,624	1.3E+08
4	366,099,399,360	3.7E+11
5	746,019,051,045,840	7.5E+14
6	1,213,325,384,620,950,000	1.2E+18
7	1,640,618,140,904,970,000,000	1.6E+21
8	1,897,023,318,926,400,000,000,000	1.9E+24
9	1,914,807,912,541,340,000,000,000,000	1.9E+27
10	1,713,965,838,159,220,000,000,000,000,000	1.7E+30
11	1,377,514,344,128,570,000,000,000,000,000,000	1.4E+33
12	1,004,082,728,292,990,000,000,000,000,000,000,000	1.0E+36
13	669,304,811,967,966,000,000,000,000,000,000,000,000	6.7E+38
14	410,850,184,577,259,000,000,000,000,000,000,000,000,000	4.1E+41
15	233,627,022,815,683,000,000,000,000,000,000,000,000,000,000	2.3E+44
16	123,697,721,013,477,000,000,000,000,000,000,000,000,000,000,000	1.2E+47
17	61,253,565,224,361,100,000,000,000,000,000,000,000,000,000,000,000	6.1E+49

Picking and choosing combinations and using homology modeling also could not. *See* III.D. Homology models cannot (i) accurately model more than a

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28 Pet., 13-15, 70-77.

29 EX1003, ¶¶ 181-190.

30 EX1133, ¶ 123; EX2070, ¶¶ 347, 349.

31 EX1133, ¶¶ 124-127; EX1004, ¶¶ 169-171.

few substitutions, (ii) detect structural changes below ~1-3 Å, and (iii) detect epistatic, physicochemical or long-range effects.[32] Computational tools in the 2011-2012 timeframe also could not reliably model protein structures with 10, 15, or 20 changes from native.[33] And individual assessments are impossible.[34]

In 2011-2012, POSAs would need to perform experiments to know if modified PH20s with 5+ mutations would properly fold and exhibit activity. Performing that experimentation for the size of the sequence space is impossible.

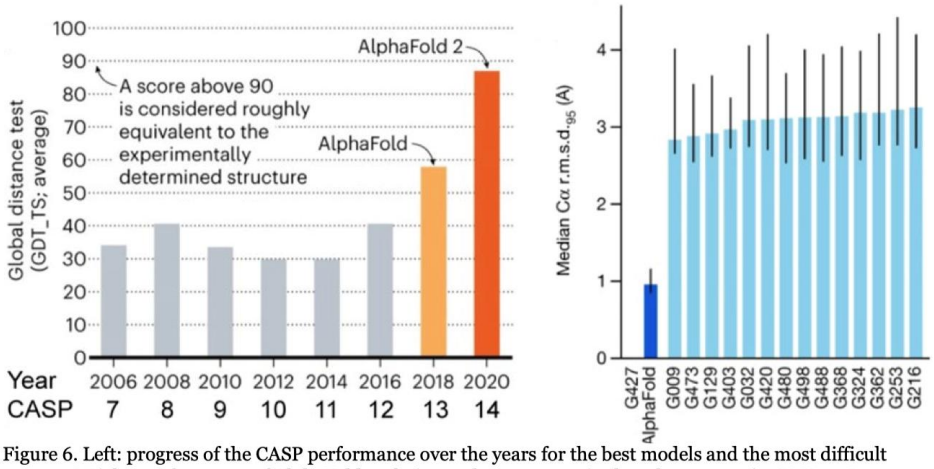

Figure 6. Left: progress of the CASP performance over the years for the best models and the most difficult targets.[38] Right: performance of AlphaFold2 relative to the top 15 entries by other groups in CASP14. Data are the median coordinate error and the 95% confidence interval of the median, estimated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

32 EX1004, ¶¶ 160-162; EX1003, ¶ 224; EX1133, ¶¶ 130-132, 260-263, 268, 270-274, 281-284.

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

34 EX1133, ¶¶ 131-132.

This evidence is dispositive to written description ***and*** enablement.[35] If a POSA cannot even identify the claimed genus of enzymatically active PH20s within the claims' sequence space, the disclosure cannot demonstrate possession of it. Impossibility is far more than undue experimentation, and demonstrates non-enablement.

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 common to the members of the genus ***so that one of skill in the art can 'visualize or recognize' the members of the genus***."[36] Visualizing or recognizing the members of the claimed genus here is impossible (§ III.B).

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

The Petition explained why the common disclosure did not describe common structural features of the claimed active PH20s.[37] In response, Halozyme contends the disclosure "characterizes the common structural features" of the

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35 Pet., 27, 48-52, 70-76.

36 *Ariad*, 1350.

37 Pet., 52-55; EX1003, ¶¶ 69, 139-145, 151, 155-159.

claimed genera of modified PH20 polypeptides.[38] It does not. Properly folded PH20s are the only "subgenus" of PH20s in the sequence space that could have a common set of structural features, but the disclosure fails to identify what they are and which of the 10^{49}+ sequences will fold to have them.

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

Halozyme and its experts contend the "95% sequence identity" requirement is a "common structural feature" of the claimed PH20 polypeptides.[39] It is not—it is a ***mathematical*** requirement (*i.e.*, are two sequences 95%+ identical).[40]

"Structural features" are ***physical*** attributes of ***a*** PH20 polypeptide molecule (*e.g.*, a particular amino acid at a position or features of its tertiary structure).[41] Common "structural features" are the ***set*** of those ***physical*** attributes "common to the members of the genus" (properly folded, active PH20s).[42]

As a ***claim element***, the 95% identity requirement defines the boundaries of the "sequence space"—the possible amino acid sequences within which the

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38 POR, 45.

39 POR, 63; EX2068, ¶ 254; EX1131, 65:18-66:17.

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

41 EX1003, ¶ 145; EX1133, ¶¶ 83-86.

42 *Duke*, 1311.

claimed PH20 polypeptides must be found.[43] Every "primary sequence" (complete amino acid sequence) ***by definition*** is up to 10% ***different*** than every other one in the sequence space.[44]

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

Halozyme and its experts contend the claimed active PH20s "all share a tertiary structure a POSA would recognize as an 'alpha-beta barrel ***fold***.'"[45] But Halozyme misleadingly portrays the α/β barrel ***motif*** as being the ***entire*** tertiary structure of PH20s, including the catalytic site.[46] 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…"[47]

A "properly folded" PH20 is one with the same tertiary structure (the native fold) of wild-type human PH20, and only "properly folded" PH20s exhibit

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43 *Ariad,* 1349.

44 EX1133, ¶ 51.

45 POR, 12; EX2068, ¶¶ 33, 106, 289, 305; EX2070, ¶¶ 421, 51, 58, 101, 128, 345, 396, 400.

46 POR, 54-55; EX2070 ¶ 51.

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

enzymatic activity.[48] The ***tertiary*** structure of human PH20, however, is not described in the disclosure—it was not reported until 2024.[49]

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

(i) the PH20 active site, which spatially positions catalytic residues D111, E113, and E249 and substrate binding residues R176, R246, and R252 correctly within a folded substrate-binding cleft;[50]

(ii) a "distorted" (non-canonical) PH20 α/β barrel motif;[51] and

(iii) the "hyal-EGF" domain (Leu336 to Asp416 in PH20).[52]

Each is essential to activity—mutations of active site residues[53] or deletion of all or

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48 EX2070, ¶¶ 51, 128-FN12; EX1131, 78:6-25; 86:23-87:7; EX1003, ¶¶ 36, 62, 156, 221; EX1133, ¶¶ 17, 58, 96-97, 159.

49 EX1126, 1068.

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

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

52 EX1006, 6913; EX1010, 9441; EX1003, ¶¶ 84-88; EX1004, ¶¶ 96-99; EX1133, ¶¶ 189-192.

53 EX1003, ¶ 87; EX1133, ¶¶ 96, 304; EX2070, ¶128-FN12.

part of the Hyal-EGF domain "abolished" activity.[54]

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

Halozyme anchors its "common structural feature" arguments on the "α/β barrel" motif in human PH20.[55] But the disclosure nowhere mentions a "PH20 α/β barrel," discusses this structural motif, or portrays it as a common structural feature of any set of modified PH20s.[56] It also does not identify any amino acid sequences for the PH20 α/β barrel motif or its elements.[57] Nor does it reference (much less explain) how the "distorted" (α/β) barrel motif in human PH20 differs from its canonical structure, or describe its relationship to PH20's active site.[58] ***Any*** of these omissions doom Halozyme's attempt to retroactively import into the disclosure the "α/β barrel" label as a definitional "structural feature" of the claimed modified

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54 EX1003, ¶¶ 87, 95; EX1133, ¶¶ 186-188; EX1010, 9439, 9441; EX1011, 813-14.

55 POR, 45-48, 63; EX2068, ¶¶ 294-295, 305; EX2070, ¶¶ 51, 128, 396, 419.

56 EX1133, ¶¶ 165-170.

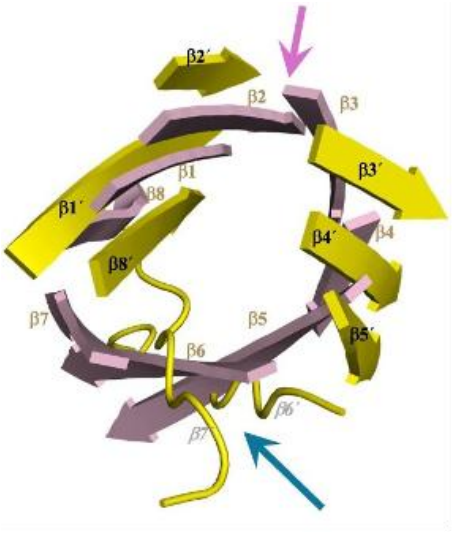
57 EX1133, ¶¶ 151, 168.

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

PH20s.

Publications before 2011 also reveal why the words "α/β barrel" are incapable of doing what Halozyme contends.

First, the "unusual" α/β barrel motif in hyaluronidases is "only loosely associated" with the canonical α/β motif.[59] It has a large gap, two irregular strands, and its shape is distorted (PH20, yellow, canonical pink).[60]



A POSA could not have used knowledge of the ***canonical*** "α/β barrel" motif to visualize the ***distinct*** structure of PH20's α/β motif because the two ***are materially different***.[61]

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59 EX1008, 833; EX1133, ¶¶ 141-147.

60 EX1033, 1027-28; EX1133, ¶ 144.

61 EX1133, ¶¶ 136-139, 144, 150-152.

Second, the conserved features of the hyaluronidase active site that Dr. Petsko referenced ***are not contained within*** the PH20 α/β motif.[62]

The words "PH20 α/β barrel" cannot describe the ***structure*** of the PH20 active site.

Knowledge of the individual positions of the 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 PH20.[63] This is unknowable for the vast majority of the genus (*i.e.*, ***multiply***-modified PH20s).

Regarding the α/β barrel motif, Halozyme and its experts did not (i) describe its unique structural features in PH20, (ii) identify where it is described in the common 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 Petition explained the PH20 Hyal-EGF domain was a structural feature

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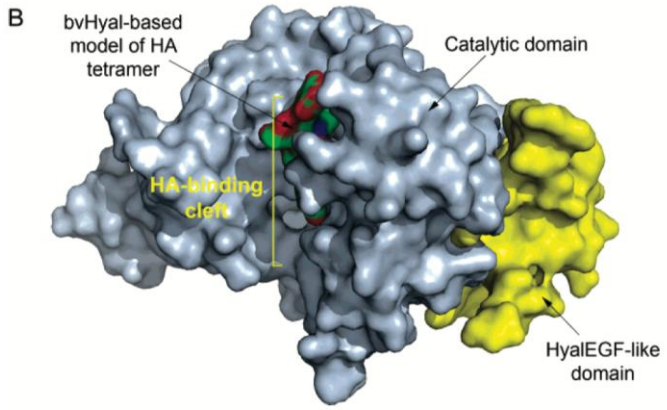
62 EX1008, 829; EX1133, ¶ 149.

63 EX1003, ¶¶ 42, 59; EX1133, ¶¶ 96-97.

essential to folding and activity of PH20s.[64] Chao reported the Hyal-EGF domain structure in 2007 (what Dr. Simpson portrays as "a huge breakthrough in the field"[65]), while Zhang demonstrated it is necessary for proper folding and activity.[66] But there is no mention anywhere in the disclosure of PH20's Hyal-EGF.[67]

This omission is fatal to written description, because the Hyal-EGF domain is a "common structural feature" of the claimed genus of active PH20s.



Dr. Petsko strains to downplay Hyal-EGF's importance to the structure and

64 Pet., 38-41, 52-53.

65 EX1130, 114:23-116:9.

66 EX1003, ¶¶ 86-88; EX1004, ¶¶ 97-99; EX1006, 6915-6917 (Figs. 2, 4); EX1010, 9439, 9441.

67 EX1003, ¶ 86; EX1133, ¶¶ 187, 190-193.

activity of PH20s.[68] But Zhang reported that deletion of 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."[69]

The common disclosure refers to a "common core hyaluronidase domain" shared by PH20 hyaluronidases (3-339 of PH20).[70] That does not identify the Hyal-EGF domain in PH20 (it terminates 4-5 residues into it), and is not a "common structural feature" of active PH20s because it cannot "properly fold."[71] Arming (EX1011) (cited in the disclosure) proves that—it reported a PH20 truncated at position 340 ***lacked activity***.[72] Halozyme's experts don't contend otherwise.[73]

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68 EX2070, ¶¶ 209, 211.

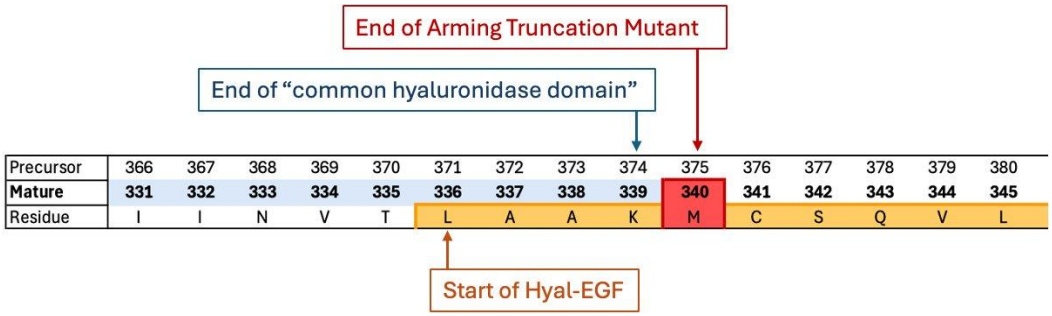
69 EX2068, ¶ 143; EX1010, 6913; EX1133, ¶¶ 187-189.

70 EX1026, 79:20-31.

71 EX1133, ¶¶ 161-163.

72 EX1011, 813-814; EX1133, ¶¶ 192-193.

73 EX1133, ¶¶ 161-163.



Halozyme contends "a POSA's knowledge included possession" of homology models based on the bee venom hyaluronidase (bvH) and Hyal1 structures published before 2011.[74] But written description is judged by the disclosure, not the ***mind*** of a POSA. This ***disclosure*** makes ***no mention*** of any PH20 structure or homology model. Worse, Halozyme's indiscriminate reliance on the bvH and Hyal1 structures ***masks critical structural distinctions*** not addressed in the disclosure, and particularly that without Hyal-EGF, bvH ***is*** active but Hyal1 ***is not***.[75] In Dr. Simpson's words, bvH "did not provide a complete picture of the structure for" human PH20.[76]

The disclosure contains no description of the "Hyal-EGF" domain or its sequence, despite its essential role in the structure and function of enzymatically

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74 POR, 11.

75 EX1133, ¶¶ 163, 189-191.

76 EX2068, ¶ 125.

active PH20s.[77]

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 95%" PH20s.[78]

First, effects on PH20 folding and activity from single-substitutions cannot predict effects of ***combinations*** of changes.[79] *See* § III.D.1. Even positions Dr. Petsko labeled "100% tolerated" exhibited extensive variation, demonstrating the unpredictability of single substitutions.[80]

Second, listing options and leaving to a POSA the task of figuring out which combinations yield active PH20s does not describe species of PH20s.[81]

Finally, problems with the experimental data and their reporting negate the "functional" insights Halozyme contends exist, and the disclosure does not

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77 EX1133, ¶¶ 185, 190, 193.

78 POR, 50.

79 EX1003, ¶¶ 54-61, 140-143; EX1133, ¶¶ 115, 232-233, 252-259.

80 EX1133, ¶¶ 264-269.

81 *Idenix*, 1164-65.

describe the PH20 tertiary structure that must be maintained.[82] Both halves of the "structure-function" equation are missing here.

3. Representative Species Not Described

Halozyme points to 7 alleged "examples" of "D320 modified PH20s."[83] None are described in its disclosure. Three are based on native ***primate*** sequences with known activity, while four were tested.[84] None of the seven illustrate the unpredictability of making 5, 10, or 15 changes to a native sequence.[85] They also are not representative—they do not reflect the types or physicochemical diversity of modified PH20s being claimed.[86]

Halozyme's overlaid models of them can be ignored.[87] They all suffer from Dr. Petsko's flawed "α/β barrel" opinions (§ III.C.1(c)), and cannot reveal spatial

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82 § III.D.3; Pet., 52-55; EX1003, ¶¶ 67-76, 105-106, 143; EX1133, ¶¶ 151, 246-251, 307-309.

83 POR, 54-55; EX2070, ¶¶ 423-426.

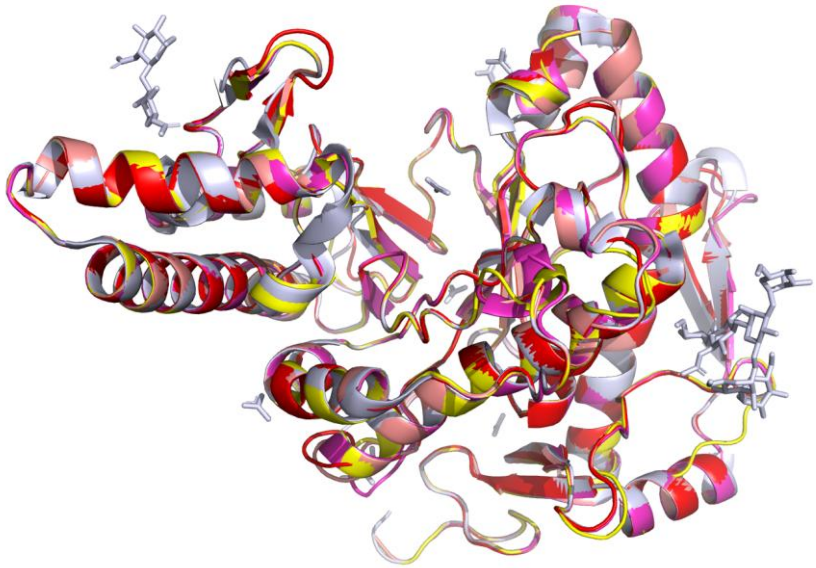
84 EX1133, ¶¶ 114-119.

85 EX1133, ¶¶ 114-119.

86 Pet., 55-60, EX1003, ¶¶ 140-143, 155-159; EX1133, ¶¶ 77-80, 114-119.

87 POR, 46-49; EX2070, ¶¶ 423-426.

differences <1.5 Å or any physicochemical or epistatic effects.[88] And comparable overlay of the 5 human hyaluronidases shows virtually identical structures despite their known functional differences.[89]



D. Enablement

The scale of experimentation required to practice the full scope of claimed properly folded, enzymatically active PH20s is beyond undue—it is impossible, which renders 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.

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88 EX1133, ¶¶ 197, 281-284.

89 EX1133, ¶¶ 183-184.

Petsko's positional tolerance analysis (avoiding certain positions) and evaluate each mutant in a PH20 homology model.[90] Even a project with 5 substitutions would require billions of days to practice.[91] In 2011-2012, a POSA could not use it to predict whether PH20s with 5, 10, or 15+ changes will properly fold and exhibit activity.[92]

1. Multiple Concurrent Mutations Are Unpredictable

When ***multiple*** mutations are made together they affect a protein's structure, capacity to fold, and stability differently than how each does alone.[93] Each can cause effects remote from the mutation that change how the protein reacts to subsequent changes.[94] The unpredictable effects of combinations of mutations ("epistasis") prevent a POSA from predicting whether the vast majority of multiply-modified PH20s will "properly fold."[95]

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90 EX2070, ¶¶ 323-324, 351, 355-360; EX1130, 93:20-24; EX1133, ¶ 198.

91 EX1133, ¶¶ 131-132; Pet., 52, 75-76; EX1003, ¶ 190.

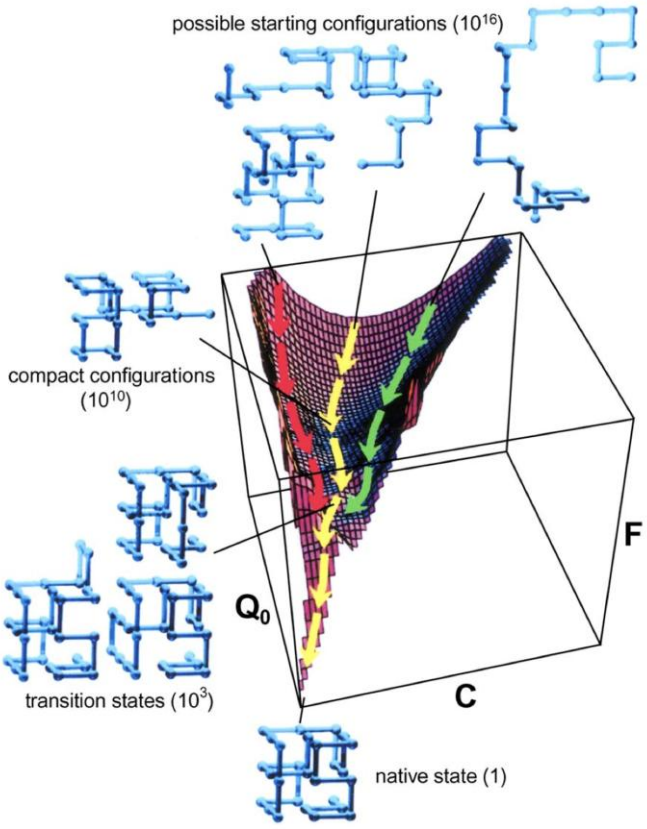
92 EX1003, ¶¶ 61, 156-159, 184; EX1133, ¶¶ 260-263, 278, 317, 325.

93 Pet., 10-11, 52-54; EX1003, ¶¶ 55-61; EX1133, ¶¶ 222, 232, 252-255, 262.

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

95 EX1003, ¶¶ 61, 156-159; EX1133, ¶¶ 123, 252-259; EX1160, 383-85.

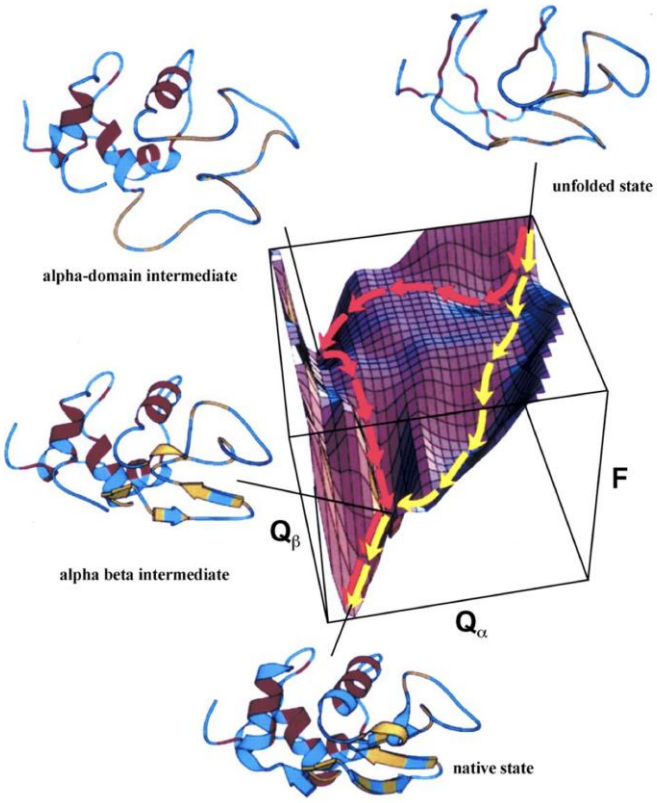
The complexity of folding illustrates why. After an amino acid sequence is synthesized, it must fold into the protein's native state. It samples a tremendous number of conformations (10^{27} for even a small protein) during its folding process, adopting energetically preferred ones as it proceeds (below).[96]



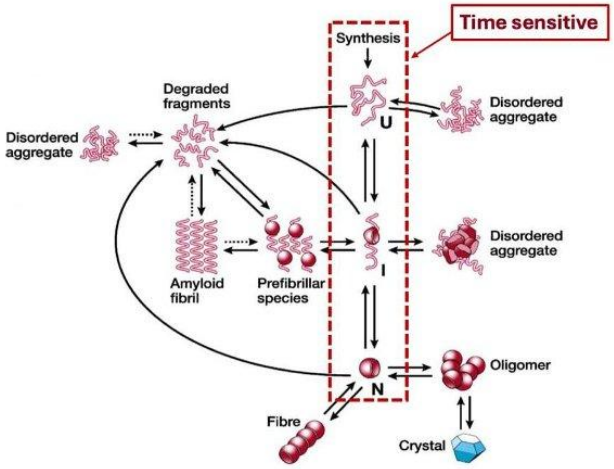
Intermediate conformations can get trapped in energetic "valleys," preventing them from efficiently folding into the native state (below).[97]

96 Pet., 10-11; EX1003, ¶¶ 55-59; EX1133, ¶¶ 68-72; EX1136, 4-6.

97 EX1133, ¶¶ 70-72; EX1136, 4-6.



Dr. Petsko also confirmed the folding process must complete quickly, otherwise the protein will be degraded.[98]



98 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 ways POSA cannot predict, which affects each sequence's ability to fold and the protein's stability.[99] Even ***one*** mutation can prevent folding, cause misfolding or incomplete folding, or adoption of a native fold but that unfolds outside the cell and forms aggregates—Dr. Petsko's textbook illustrates this.[100]

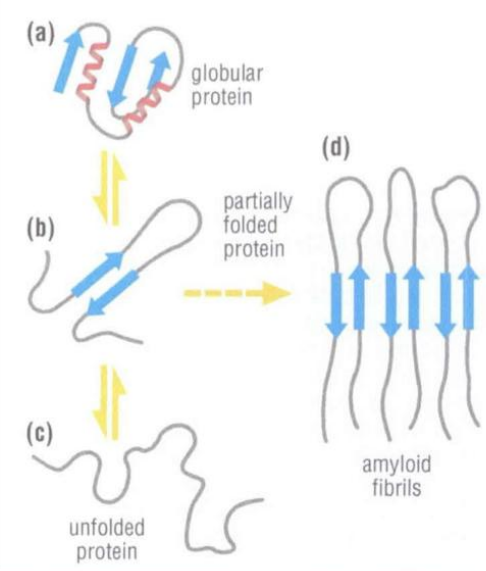


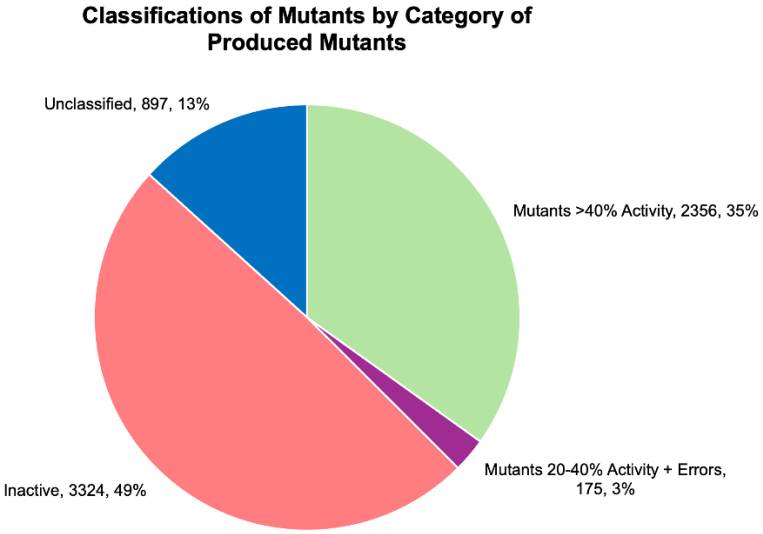
Figure 4-53 A possible mechanism for the formation of amyloid fibrils by a globular protein The correctly folded protein **(a)** is secreted from the cell. Under certain conditions, or because it contains a mutation, the protein unfolds partially **(b)** or completely **(c)**; the unfolded forms can 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.

[99] EX1003, ¶¶ 62-65; EX1133, ¶ 129, EX1131, 99:4-22, 102:1-9.

[100] EX2164, 160; EX1133, ¶¶ 73-76; EX1003, ¶ 54; EX1131, 41:22-42:11.

Mutations cause many mutated PH20 sequences to adopt the ***wrong*** structure.[101]

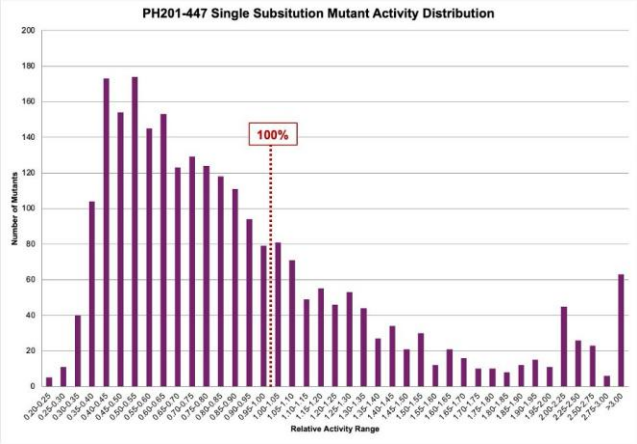
Halozyme's experts downplay unpredictability, contending a POSA could just pick combinations of "tolerated" mutations using the data in the disclosure.[102] That ignores not just science but the disclosure's data, which shows that most single mutations were deleterious.[103]



101 EX1003, ¶¶ 55-56; EX1133, ¶¶ 73-79.

102 EX2070, ¶¶ 317-324, 355-359; EX2068, ¶¶ 311-14, 380-82.

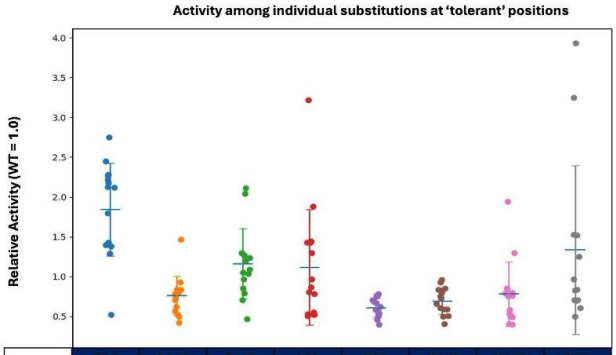
103 Pet., 42-44; EX1003, ¶ 105; EX1133, ¶¶ 170-176, 236.



Even positions Dr. Petsko labeled as "100% tolerant" (the *most* predictable in his table) exhibit widely varying effects.[104] That reflects that ***each*** substitution causes a ***unique*** effect on ***the entire*** PH20 protein structure not limited to its position.[105]

[104] EX1133, ¶¶ 264-66.

[105] EX1133, ¶¶ 267-69.



	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 many results in the disclosure or use those results to predictably mutate PH20s. For example, at many positions, residues with comparable size or chemistry show widely varying activities.[106]

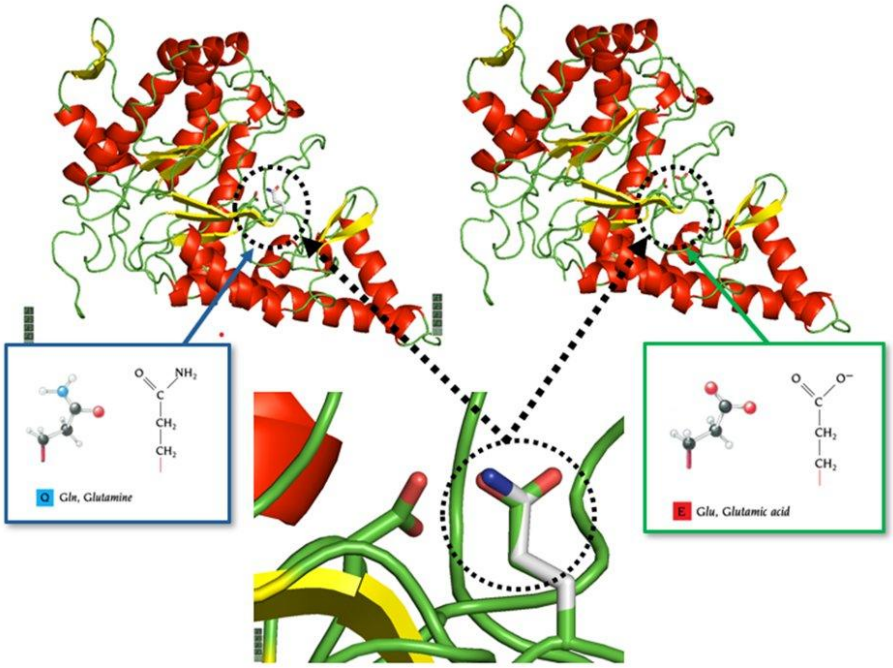
Position	WT	V	S	T	W
33	L	-	0.48	0.45	1.58
165	L	1.22	1.31	-	1.14
175	L	0.94	-	1.43	

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

And imperceptible differences in homology models can eliminate activity.[107]

106 EX1133, ¶¶ 273-74.

107 EX1133, ¶¶ 273-74, 281-284.



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.[108] A 2009 paper (EX1144) demonstrates the contrary.

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.

[108] POR, 54-56; EX2070, ¶¶ 52, 292.

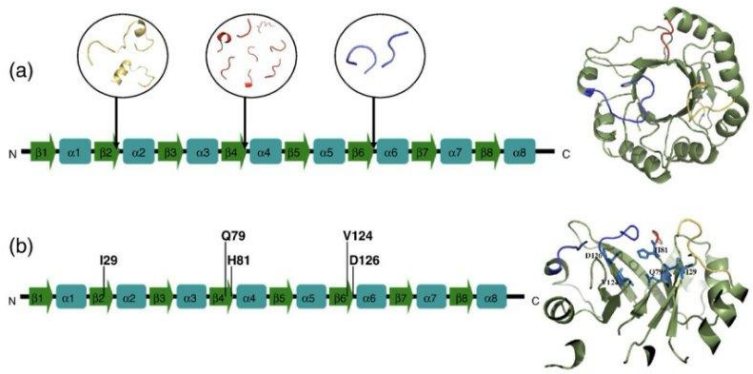


Fig. 1. Secondary-structure elements and tertiary structure (PDB code 1pii) of WT PRAI (ribbon diagram showing a view from the top of the central β-barrel). (a) The loops 2, 4, and 6 are shown in yellow, red, and blue, respectively. The circular insets show the loops to exchange in the PRAI-LoxP scaffold 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.

Like the present claims, the mutations involve ***4-17*** residues.

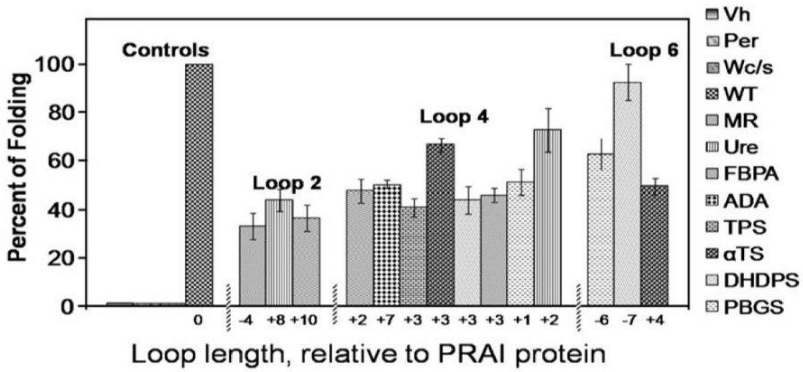
Table 1. Characteristics of the exchanged loops in the PRAI-LoxP scaffold

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	GGTGPAAGTHATTCTPG	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***.[109]

[109] EX1133, ¶¶ 177-182.



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

Halozyme contends Dr. Petsko's tolerance assessments render selection of combinations of changes in PH20s predictable in 2011-2012.[110] They cannot. § III.C.1.

First, the disclosure's "inactive mutant" dataset as reported is incapable of identifying inactivating mutations affecting ***folding***. Mutants showing <20% activity could have been: (i) not produced by the cell, (ii) not secreted, (iii) secreted but misfolded or partially folded, (iv) natively folded but due to instability unfolded, or (v) natively folded and stable, but had mutations that impaired substrate binding or catalysis.[111] No information in the disclosure enables POSAs

[110] POR, 55-56.

[111] Pet., 43-44; EX1133, ¶¶ 75, 246-47; EX1131, 240:19-241:16.

to determine ***which*** occurred for any inactive mutant, yet only mutations that impact ***folding*** could provide "tolerance" insights.[112]

Experimental design flaws and incomplete reporting of results independently render Dr. Petsko's ratings unreliable:[113]

- 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%) render classifications unreliable.

Correcting for these limitations and problems paints very different pictures than the ones Dr. Petsko presented.[114]

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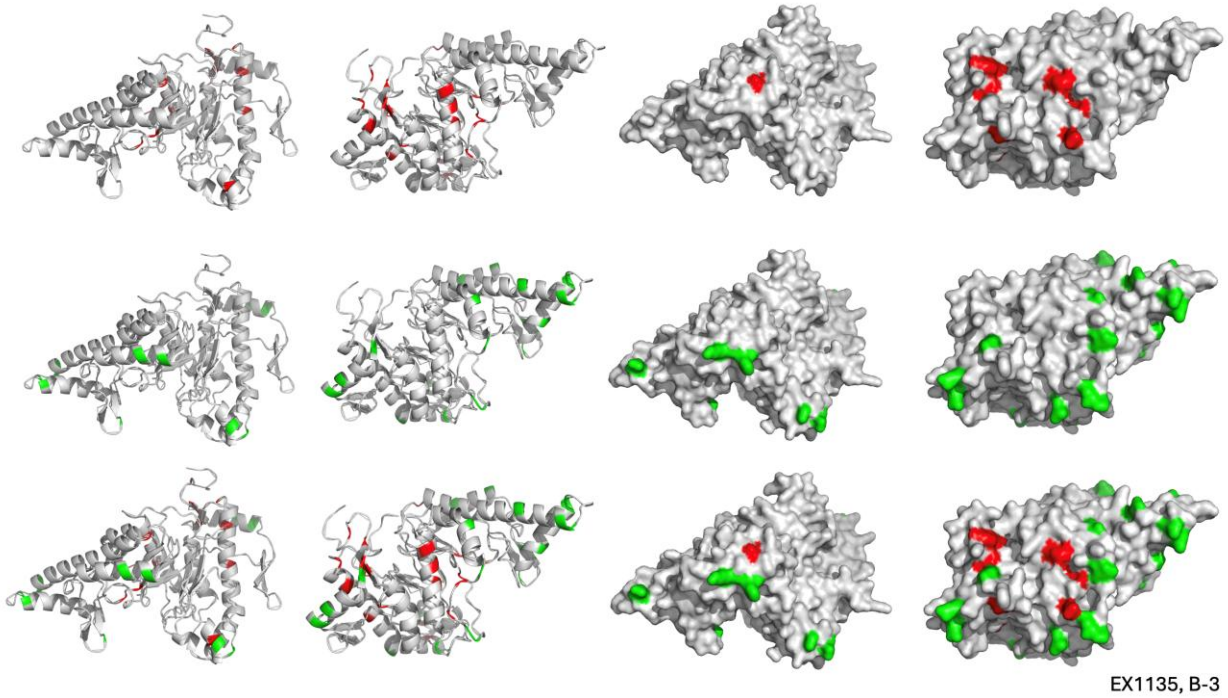
112 EX1133, ¶ 247.

113 Pet., 46-48; EX1003, ¶¶ 72, 76; EX1133, ¶¶ 294-315, 248, 250, 175, 235.

114 EX1133, ¶¶ 304-305, 316-321, 242, Appendix B (EX1135).



The unreliable and uninformative data, limits on homology modeling and experimental capabilities, and unpredictability of multiple mutations refute Halozyme's assertion that POSAs could predict effects of 5+ mutations on proper folding and activity of PH20s in 2011-2012.[115]

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

Much of what Halozyme presents for §112 support is not in the common disclosure, or conflicts with it.

[115] Pet., 75; EX1003, ¶ 224; EX1004, ¶ 161; EX1133, ¶¶ 257, 261, 281; EX1027, 6-11.

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

Halozyme and Dr. Petsko contend a skilled artisan would not use directed evolution techniques to produce multiply-modified PH20s. Their reading is contrary to the disclosure—the only ***specific*** procedure (albeit a research plan) it identifies uses directed evolution.[116] Also, contrary to Dr. Petsko (¶ 349), it proposes using results in the disclosure to identify positions to target.[117]

Dr. Petsko also confirms why Dr. Hecht was correct that method cannot enable the claimed multiply-modified PH20s—it will make "billions of sequences that… ***are not going to fold*** into PH20 proteins" because (as the claims permit) the sequences can include mutations at invariant residues.[118]

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[116] Pet., 48-49; EX1026, 47:11-18, 141:30-33, 150:1-26; EX1003, ¶¶ 50–52, 173–178; EX1133, ¶ 204.

[117] EX1026, 150:14-19; EX1003, ¶¶ 173–178.

[118] EX2070, ¶ 347; EX1133, ¶ 203.

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

Halozyme contends US-457 describes $PH20_{1-430}$ and $PH20_{1-431}$ (SEQ ID NOS:86 and 87) as "inactive mutants."[119] That is incorrect—US-457 ***explicitly*** labels them "***active***" (below), as does the common disclosure (464=429).[120]

To form her opinions, Dr. Simpson ignored the US-457's description and arbitrarily reclassified its data.[121] Halozyme cannot run away from its own disclosure.

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

Halozyme criticized Dr. Hecht's observation that the '429 Patent showed unusual activity for C-terminal truncation mutants varying by one residue, again citing US-457.[122] But US-457 shows the same phenomenon (below).[123]

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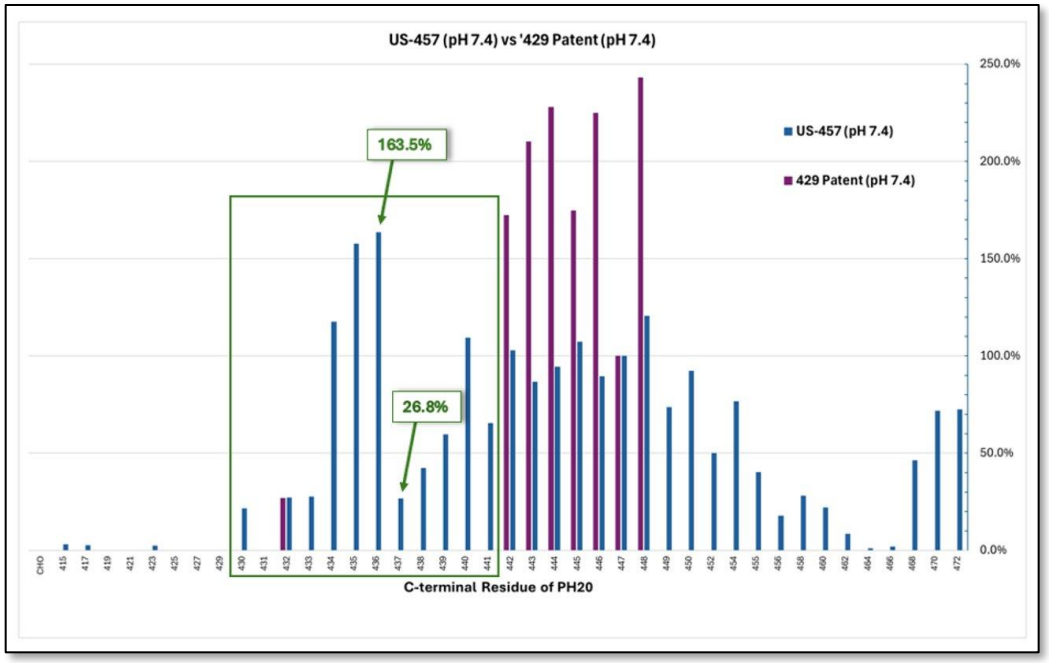
119 POR, 72, EX2068, ¶ 188.

120 EX2165, ¶ 0362; EX1026, 79:25-31; EX1133, ¶¶ 216, 219.

121 EX2068, ¶¶ 188, 330; EX1133, ¶¶ 212–219.

122 POR, 72.

123 EX1133, ¶ 221.



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.[124] *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. And where "tolerance" is used to inform changes, the disclosure simply instructs POSAs to ***not include*** inactivating substitutions in active PH20s.[125]

[124] EX2070, ¶¶ 264, 274, 355-365; EX1133, ¶¶ 275-278.

[125] EX1026, 91:30-92:20; EX1133, ¶¶ 206-207, 209.

Dr. Petsko's tolerance table also will induce POSAs to act ***contrary*** to the disclosure—it led Dr. Simpson to conclude that a POSA ***would*** consider modifying positions 282, 299, 303, and 431, even though the disclosure ***expressly instructs otherwise***.[126]

4. Wrong Substrate Binding Sites

Based on an experiment he performed, Dr. Petsko theorizes that additional substrate binding sites exist on PH20.[127] He cites no evidence they do, and his findings conflict with the disclosure's explanation that substrate binds within residues 170-200 (orange). [128] Dr. Petsko's theories are not part of the disclosure.

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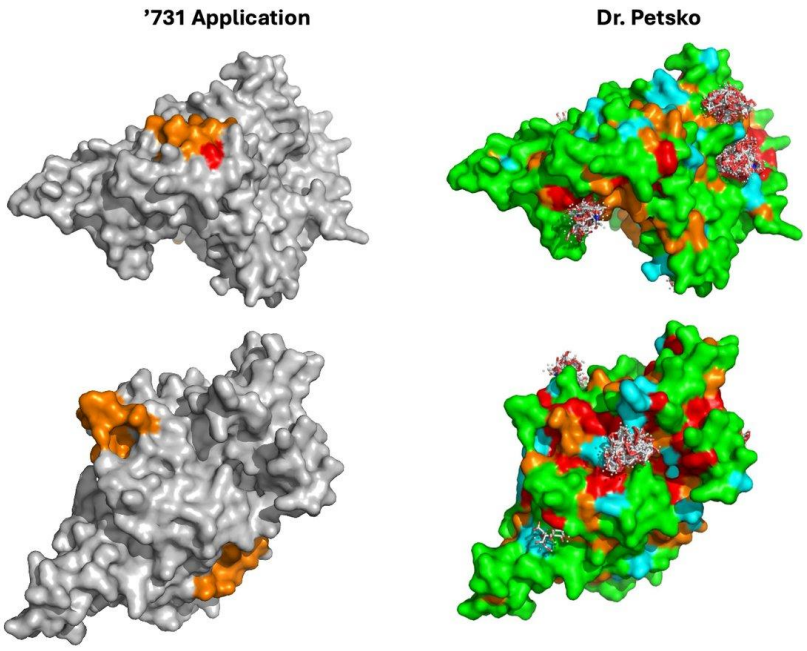
[126] EX1026, 91:30-92:20; EX1130, 191:5-16, 191:17-192:7, 192:8-194:6, 194:7-195:25; EX1133, ¶¶ 208-209.

[127] 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.

[128] EX1026, 81:7-14; EX1133, ¶¶ 223-224, 227-230.



5. No Rescue Mutation Theory

Dr. Petsko contends a POSA could somehow use its contents to identify and select mutations that would "rescue" a deleterious first mutation.[129] The disclosure says nothing about rescue mutations and discovering them would entail the same impossible scale of effort to find active PH20s.[130]

F. No Credible Utility for Inactive PH20s

Halozyme concedes PH20s have no contraceptive utility in males.[131] Evidence establishes no utility for females.

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129 POR, 49; EX2070, ¶¶ 374-383.

130 EX1133, ¶¶ 210-211.

131 EX1026, 213:7-9; EX1129, 38:13–23; EX1134, ¶¶ 49–51.

Halozyme's expert, Dr. Cherr, confirmed that contraceptive utility requires ***near 100% effectiveness***.[132] But ***every*** experiment testing PH20s for contraception ***failed*** (save one using unclaimed PH20s).[133] Impartial scientists pre-2012 concluded from this that "***PH-20 is not a useful antigen for inclusion in immunocontraceptive vaccines***," with the one guinea pig experiment being an outlier.[134] Halozyme independently confirmed these experimental findings.[135] No claimed ***modified*** PH20 has ever been tested for contraceptive effect in any species.[136]

Halozyme insists improper administration caused the failures, ignoring actual reasons researchers gave.[137] It claims only mucosal immunization will work, ignoring that the guinea pig experiment used systemic immunization,[138] and that it

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132 EX1129, 57:16–58:15.

133 EX1003, ¶¶ 110-12; EX1134, ¶¶ 57-65; EX1129, 114:19–115:23; EX1189, 119, Table 3.

134 EX1189, 119; *see also* EX1134 ¶¶ 64–67.

135 EX1122; EX1190, Abstract, 381; EX1134, ¶¶ 69–73.

136 EX1129, 101:18–102:9, 104:9–20; *see McLeay*, *3.

137 POR, 77; EX1134, ¶¶ 59–62; EX1020, 181; EX1019, 332, 333.

138 POR, 77; EX1134, ¶ 58; EX2010, 544.

effectively delivers antibodies to the reproductive tract (*e.g.*, HPV vaccines).[139]

Well-established immunological principles contradict Halozyme's remaining speculation:[140]

- Near-100% effective contraception requires antibodies that block native PH20 epitopes associated with fertilization—inducing an antibody response alone is insufficient.[141]
- Immunological principles applicable to all species cause polyclonal antibody responses to target non-native regions of modified PH20s (even if native-like structures are preserved).[142] Misfolded modified PH20s are even less likely to produce effective antibodies against native PH20s.[143]
- Sequence similarity alone cannot predict which modified PH20s present epitopes that induce production of effective antibodies against

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139 EX1134 ¶¶ 43–47, 64; EX1132, 110:1–14, 111:17–18; EX1120, 3–6; EX2114, 17.

140 POR, 74-76; EX1134, ¶ 76.

141 EX1134, ¶¶ 104–107, 113.

142 EX1134, ¶¶ 85–91, 101-102; EX1170, 288–89, 311–13, 389.

143 EX1134, ¶¶ 92–98.

native PH20s in all species.[144]

- Adjuvants and boosters can magnify immune responses but cannot change its epitopic specificity.[145]

An impossible scale of trial-and-error testing is thus implicated for the claimed modified PH20s.[146] Contraceptive utility was not a credible utility for any PH20 polypeptide in 2011-2012, it was just an invitation for further research.[147]

IV. Obviousness

Merck explained that Halozyme's '429 Patent (with Chao) rendered obvious single-amino acid substitution ***mutants*** (plural) of $PH20_{1-447}$.[148] As Dr. Hecht explained, the '429 Patent "encouraged [POSAs] to make modified PH20 proteins having single amino acid substitutions in non-essential regions…":[149]

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144 EX1134, ¶¶ 79–84; EX2013, 1075.

145 EX1134, ¶ 115-16.

146 EX1003, ¶ 113; EX1134, ¶¶ 19, 21, 87, 105, 124.

147 *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.

148 Pet., 85-88.

149 EX1003, ¶¶ 202-204, 208-209; EX1005, 16:14-26.

Halozyme attacks the '429 patent's support for singly-substituted $PH20_{1-447}$ mutants, arguing it doesn't identify "non-essential regions" or "provide any guidance on which sites to modify."[150] But they ***patented them all.***[151]

Merck turned to Dr. Park to determine how a POSA would (i) identify non-essential regions of PH20, and (ii) determine which substitutions at them retain activity. He devised a methodology to do that, using techniques Halozyme's experts confirmed would have used in 2011.[152] Dr. Naismith found Dr. Park's analysis objective, rigorous, and unbiased.[153]

The '429 Patent motivated POSAs to identify single-substitutions in non-essential regions of $PH20_{1-447}$ that would ***predictably*** retain activity. Without reviewing the common disclosure, Dr. Park identified D320K as ***one of ~750 such substitutions*** suggested by the '429 Patent before 2011.[154] ***Each*** would have been obvious under the rationale of *KSR*, and the identification of D320K's favorable

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150 POR, 87-88.

151 EX1005, claim 1.

152 EX1004, ¶¶ 22-24, 32; EX1133, ¶¶ 347-349, 357, 360, Appendix B-8.

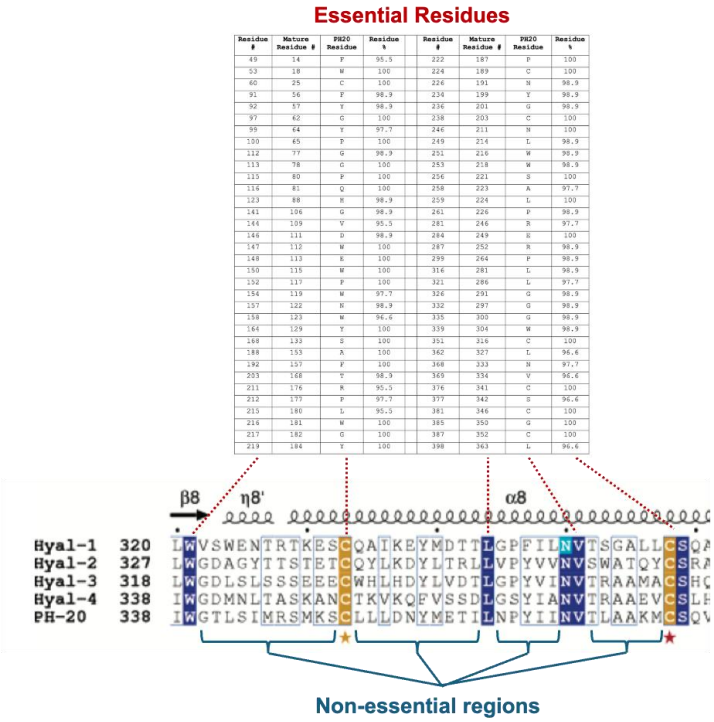
153 EX1133, ¶¶ 338-343, 352-359.

154 EX2176; EX1133, ¶ 344.

effects confirm a POSA's motivation to make that substitution.[155]

Halozyme reiterates its lawyer-directed hindsight theory first raised in its preliminary response.[156] After additional discovery and three depositions, Halozyme presents the ***identical*** theory.[157] The evidence refutes it.

Dr. Park identified ***which positions*** to evaluate using his MSA—the 379 residues ***in between*** the 68 "essential" positions ***the MSA*** identified.[158]



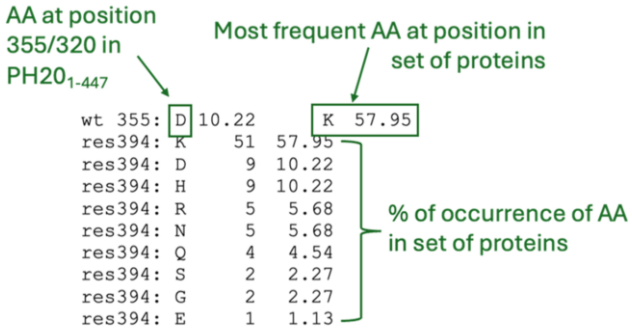
155 Pet., 85-88, 95-107.

156 POPR, 58.

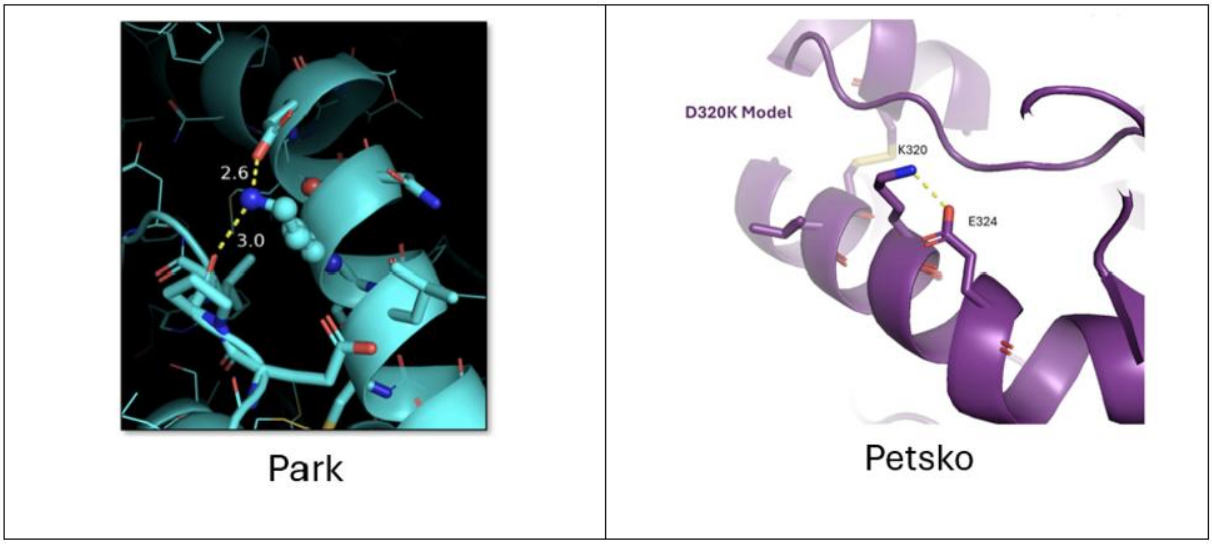
157 POR, 82.

158 EX1004, ¶¶ 26-32.

The MSA also dictated which substitutions Dr. Park assessed—the most frequently occurring ones at each non-essential position.[159]



Dr. Park's objective and unbiased assessment found D320K tolerated, and identified a D320:E324 interaction; Dr. Petsko repeated that assessment and reached the same conclusion.[160]



Halozyme's "hindsight" theory is refuted by Dr. Park's declaration—he

[159] EX1003, ¶¶ 210-211; EX1004, ¶¶ 41-43; Appendix D-1; EX1133, ¶ 342.

[160] EX1004, ¶¶ 116-123; EX2070, ¶ 403; EX1133, ¶¶ 349-351.

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.***"[161]

At depositions, Dr. Park testified he assessed substitutions position-by-position, at least twice, using the most frequently occurring amino acids ***from his MSA analysis***.[162]

EX2176 corroborates his testimony—it contains his observations and a tolerability rating for each substitution assessed at hundreds of positions.[163]

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
320	D	-	10.22			9	0.17			
320	-	K	57.95	3	gain: increased van der Waals, possible salt bridge, better H propensity	9	0.16	1		1
320	-	H	10.22	2	gain: increased van der Waals	9	0.16			1
320	-	R	5.68	3	gain: increased van der Waals, possible salt bridge, better H propensity	8	0.26		1	1
320	-	N	5.68	2	neutral	9	0.1			
320	-	Q	4.54	2	gain: higher H propensity, hbond	9	0.16		1	1
320	-	S	2.27	2	loss: lower H propensity, lost van der Waals	7	0.11		1	1
320	-	G	2.27	1	loss: Gly destabilizes helix	8	0.16		1	1
320	-	E	1.13	2	neutral	9	0.16			

Dr. Park testified he recorded his observations about D320K ***before*** counsel asked him to explain them in his declaration.[164]

Dr. Park's "heat map" tracked the diversity of substitutions he assessed and

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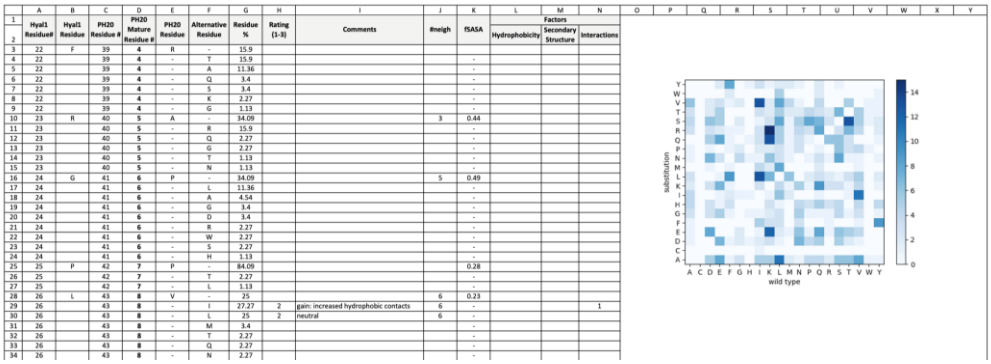
161 EX1004, ¶¶ 102-103.

162 EX2078, 170:22-171:17.

163 EX1004, ¶¶ 85-87; EX1133, ¶¶ 340-346.

164 EX2078, 320:10-20; EX2176, 39.

prompted him to assess more substitutions.[165]



	Hyal1 Residue#	Hyal1 Residue	PH20 Residue #	PH20 Mature Residue #	PH20 Residue	Alternative Residue	Residue %	Rating (1-3)	Comments	#neigh	fSASA	Factors: Hydrophobicity	Factors: 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.[166]

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 has no answer for this evidence, so it ignores it.

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

166 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. 11,952,600
1002	File History of U.S. Patent No. 11,952,600
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	Jedzrejas 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 '600 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 ’600 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 D320K Mutation
1071	Swiss Model Printout of PH20 Model with D320H Mutation
1072	Swiss Model Printout of PH20 Model with D320R Mutation
1073	Swiss Model Printout of PH20 Model with D320S Mutation
1074	Declaration of Leif E. Peterson
1075-1112	[Reserved]
1113	Declaration of Sue Wang
1114	Declaration of Brian M. Goldberg
1115	Declaration of Katherine A. Helm
1116	Declaration of Christine M. Engen
1117	Declaration of Amit Bhatla
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)

No.	Exhibit Description
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
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)

No.	Exhibit Description
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)
1140 [NEW]	Dobson, "Protein misfolding, evolution and Disease" Trends Biochem. Sci. (9):329-32 (1999)
1141 [NEW]	Goldsmith & Tawfik, "Directed enzyme evolution: beyond the low-hanging fruit" Curr. Opin. Struct. Biol. 22(4):406-12 (2012)
1142 [NEW]	Farber & Petsko, "The evolution of alpha/beta barrel enzymes" Trends Biochem. Sci. 15(6):228-34 (1990)
1143 [NEW]	Nagano et al., "One Fold with Many Functions: The Evolutionary Relationships between TIM Barrel Families Based on their Sequences, Structures and Functions" J. Mol. Biol. 30;321(5):741-65 (2002)
1144 [NEW]	Ochoa-Levya et al., "Protein Design through Systematic Catalytic Loop Exchange in the (beta/alpha)8 Fold" J. Mol. Biol. 10 387(4):949-64 (2009)
1145 [NEW]	AutoDock Vina Tutorial 2011
1146 [NEW]	Pal et al., "Comprehensive and Quantitative Mapping of Energy Landscapes for Protein-Protein Interactions by Rapid Combinatorial Scanning" J. Biol. Chem. 4;281(31):22378-22385 (2006)
1147 [NEW]	Van Rossum et al., "Reporter-based screening and selection of enzymes" FEBS J. 280:2979-96 (2013)
1148 [NEW]	Reed et al., "Use of Coefficient of Variation in Assessing Variability of Quantitative Assays" Clin. Diagn. Lab Immunol. 9(6):1235-9 (2002)

No.	Exhibit Description
1149 [NEW]	Ten Have et al., "Cloning and characterization of the cDNA encoding the PH20 protein in the European red fox Vulpes vulpes" Reprod. Fertil. Dev. 10(2):165-72 (1998)
1150 [NEW]	Chowpongpang et al., "Cloning and characterization of the bovine testicular PH-20 hyaluronidase core domain" Biotechnol. Lett. 26(15):1247-52 (2004)
1151 [NEW]	Fowler et al., "High-resolution mapping of protein sequence-function relationships" Nature Methods 7, 741–746 (2010)
1152 [NEW]	Ringe & Petsko, "Q&A: What are pharmacological chaperones and why are they interesting?" J. Biol. 8:80 (2009)
1153 [NEW]	Petsko, "Herding CATS" Sci. Transl. Med. 24;3(97):97 (2011)
1154 [NEW]	Second Table Associating Citations from the '600 Patent (EX1001) to Corresponding Citations in the '731 Application (EX1026)
1155 [NEW]	Calloni et al., "Investigating the Effects of Mutations on Protein Aggregation in the Cell" J. Biol. Chem. 10607-13 (2005)
1156 [NEW]	Chiti et al., "Studies of aggregation of mutant proteins in vitro provided insights into genetics of amyloid diseases" PNAS 99:16419-26 (2002)
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1167	MERCK_PGR00094 - DNJ-2-25-cv-03179 Stipulation to Substitute Parties
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2068	Declaration of Melanie A. Simpson, Ph.D. in Support of Patent Owner's Response
2070	Declaration of Gregory A. Petsko, Ph.D. in Support of Patent Owner's Response

No.	Exhibit Description
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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	responses and mucosal immunity in mice," Annals of Allergy, Asthma, and Immunology, 99:443-452 (November 2007)
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 5,584 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: January 28, 2026

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on this 28th day of January, 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, to replace the original versions served and filed on January 20, 2026:

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