

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyme Inc.,
Patentee.

Case No. PGR2025-00046
U.S. Patent No. 12,091,692

PETITIONER'S REPLY

TABLE OF CONTENTS

	Page
I. Introduction.....	1
II. Claim Construction and Scope.....	1
III. The Claims Are Unpatentable Under § 112.....	4
A. The Claims Define Structurally Heterogenous Genera.....	4
B. Determining the Properly Folded and Active PH20s in the Sequence Space is Impossible.....	7
C. Written Description.....	10
1. <i>The Disclosure Does Not Describe the Common Structural Features of Enzymatically Active PH20s.....</i>	<i>10</i>
(a) Sequence Identity Is Not a “Structural Feature”	11
(b) Enzymatically Active PH20s Must Possess Several Structural Features, Not One	12
(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
2. <i>Single Substitutions Provide No Structure-Function Correlation </i>	<i>19</i>
3. <i>Representative Species Not Described</i>	<i>20</i>
D. Enablement	22
1. <i>Multiple Concurrent Mutations Are Unpredictable</i>	<i>23</i>
2. <i>The α/β Barrel Motif Does Not Make Multiply-Modified PH20s Stable or Predictable</i>	<i>30</i>
3. <i>Dr. Petsko’s Tolerance Ratings Are Not Credible or Predictive of Combinations</i>	<i>32</i>
E. Halozyme’s § 112 Positions Conflict with the Disclosure.....	34
1. <i>Dr. Petsko Mischaracterizes How the Disclosure Proposes Making Multiply-Modified PH20s</i>	<i>35</i>

2.	<i>PH20₁₋₄₃₀ and PH20₁₋₄₃₁ Are Not “Inactive”</i>	35
3.	<i>Following Petsko’s Tolerance Ratings Leads POSAs Into Conflict with the Disclosure</i>	37
4.	<i>Wrong Substrate Binding Sites</i>	38
5.	<i>No Rescue Mutation Theory</i>	39
F.	No Credible Utility for Inactive PH20s	39
IV.	Obviousness	42
V.	Conclusion	47

TABLE OF AUTHORITIES**Page(s)****Cases**

<i>Ariad Pharms., Inc. v. Eli Lilly & Co.</i> , 598 F.3d 1336 (Fed. Cir. 2010) (“ <i>Ariad</i> ”)	10, 11
<i>Bicon, Inc. v. Straumann Co.</i> , 441 F.3d 945 (Fed. Cir. 2006) (“ <i>Bicon</i> ”)	2, 3
<i>Boston Sci. Corp. v. Johnson & Johnson</i> , 647 F.3d 1353 (Fed. Cir. 2011) (“ <i>Boston</i> ”)	14
<i>Duke Univ. v. Sandoz Inc.</i> , 160 F.4th 1305 (Fed. Cir. 2025) (“ <i>Duke</i> ”)	2, 11
<i>In re Fisher</i> , 421 F.3d 1365 (Fed. Cir. 2005) (“ <i>Fisher</i> ”)	42
<i>Idenix Pharm., LLC v. Gilead Scis., Inc.</i> , 941 F.3d 1149 (Fed. Cir. 2019) (“ <i>Idenix</i> ”)	20
<i>Juno Therapeutics, Inc. v. Kite Pharma, Inc.</i> , 10 F.4th 1330 (Fed. Cir. 2021) (“ <i>Juno</i> ”)	14
<i>In re McLeay</i> , No. 2023-2338, 2025 WL 516809 (Fed Cir. Feb. 18, 2025) (“ <i>McLeay</i> ”)	40
<i>Regents of the Univ. of Minn. v. Gilead Scis.</i> , 61 F.4th 1350 (Fed. Cir. 2023) (“ <i>Gilead</i> ”)	2, 10
<i>TIP Sys., LLC v. Phillips & Brooks/Gladwin, Inc.</i> , 529 F.3d 1364 (Fed. Cir. 2008) (“ <i>TIP</i> ”)	4

Other Authorities

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 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. Halozyme ignores failures that foreclose using PH20s as contraceptive vaccines. Finally, its experts endorsed Merck's expert's prior art-based methods that identified the obvious M313K PH20₁₋₄₄₇ 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 a "*structurally and functionally distinct genus*" of PH20s (*i.e.*, "properly folded" modified PH20 polypeptides),¹ or do they *also* include 10⁶⁰+ other PH20 sequences in the claim parameter's "sequence space" (*i.e.*, a genus weighing more than

¹ POR, 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).

Earth)?²

The Board can resolve the patentability issues in this proceeding without resolving this dispute: (i) 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 this disclosure does not;³ and (ii) the claims capture the obvious M313K PH20₁₋₄₄₇ mutant.

Regardless, the Board should reject Halozyme’s arguments,⁴ as they entirely ignore the claim term “PH20”—a clear legal error.⁵ When *all* claim terms are credited, the claims require “properly folded” modified PH20s.

Initially, Halozyme cannot dispute the preamble is limiting—*Halozyme itself* relies on the *preambular* phrase “modified PH20 polypeptide” for its construction.⁶ Halozyme’s expert (Dr. Simpson) also testified the term “PH20”

² EX1003, ¶¶ 131-132.

³ POR, 44-45; *Duke*, 1310; *Gilead*, 1356-57.

⁴ POR, 32-43; EX1130, 55:23-56:7, 90:1-16.

⁵ POR, 32-42; Pet., 17; EX1026, 50:31-32, 54:5-10; EX1130, 55:23-56:7, 57:9-58:4; *Bicon*, 950-51.

⁶ POR, 33-42.

provides context to “modified PH20 polypeptide,”⁷ while their expert Dr. Petsko provided that context: “*POSAs think of PH20 as a folded protein.*”⁸ Dr. Simpson also testified PH20’s definition in the disclosure⁹ led POSAs to view “PH20s” as being properly folded and active proteins.¹⁰ When both defined terms are credited, it compels reading the claims as requiring a “*properly folded* PH20 polypeptide with *at least one modification.*”

The Petition further explained that the disclosure portrays “active” and “inactive” mutants as mutually exclusive embodiments, while certain dependent claims restrict choices for the substitution at position 313 to amino acids that yield PH20s that retain activity.¹¹ POSAs thus read the claims *as a whole* as directed to properly folded PH20s, which, depending on the claim, either encompass or

⁷ EX1130, 57:9-58:4; *Bicon*, 952.

⁸ EX2070, ¶ 345.

⁹ EX1026, 50:31-32; EX1130, 60:14-61:12.

¹⁰ EX1130, 61:19-23; EX2070, ¶ 128-FN12; EX1133, ¶¶ 92-104; Halozyme’s experts use “polypeptide” interchangeably with “protein.” EX1133, ¶¶ 87-89; EX1131, 32:8-37:20; EX2068, ¶¶ 283, 353, 376; EX2070, ¶¶ 50, 434.

¹¹ Pet., 18-27, 35, 81-82, 85-87; EX1026, 253, 251:2-4; 272:3-5; EX1003, ¶¶ 101, 103-104, 109-116, 123, 135-144; EX1131, 146:14-148:8.

require active mutants.¹²

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"—Halozyme's experts *confirmed* it was correct ($\sim 10^{60}$ to $\sim 10^{113}$ sequences).¹³ The Petition also explained (and Halozyme's experts agree) the claims permit (i) modifications at any position, (ii) additions/deletions, and (iii) substitutions to any of 19 other amino acids.¹⁴

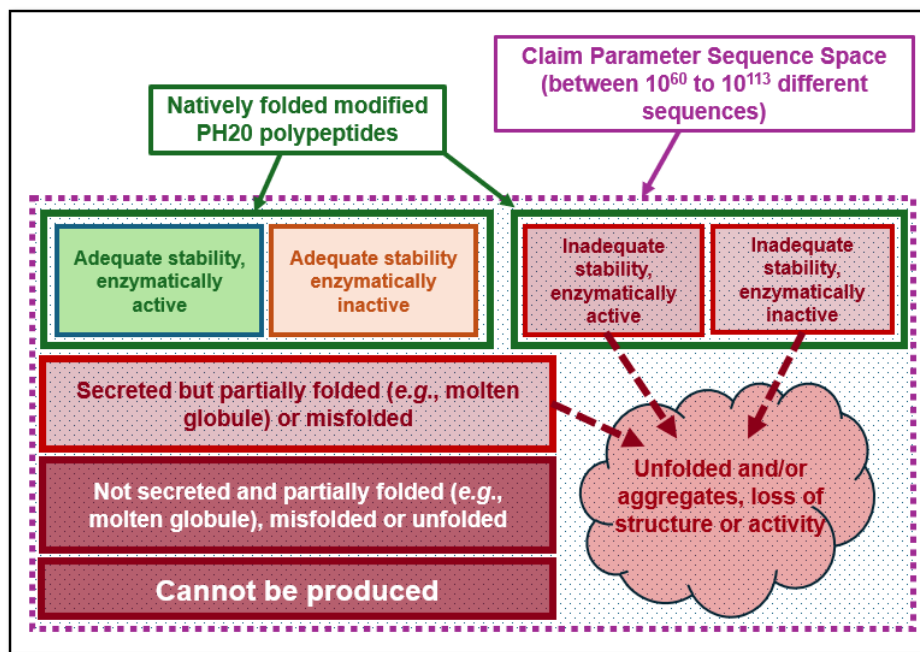
The sequence space thus reflects immense structural diversity with an unknowable subset of sequences that will properly fold into enzymatically active

¹² Pet., 24-27; EX1026, 90:33-34; EX1003, ¶¶ 136-139, 185-186; 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.

¹³ POR, 4; Pet., 20-21; EX1003, ¶¶ 129-131; EX1004, ¶¶ 174-178; EX1130, 90:1-16, 91:18-92:1; EX1131, 58:18-59:19, 61:6-8, 65:18-66:3; EX2070, ¶¶ 235-236.

¹⁴ Pet., 18-20; EX1003, ¶ 128; EX1026, 53:1-7, 68:18-34; EX1130, 90:25-91:5; EX1131, 54:24-55:6.

PH20s.¹⁵ All those “properly folded”¹⁶ active PH20s exist within one corner of the sequence space. Other sequences will never leave the cell (*e.g.*, cannot be made or are not secreted). Still others that are partially-folded, misfolded, or have the native fold will be secreted but are unstable, existing in unfolded and/or aggregated forms after secretion.¹⁷



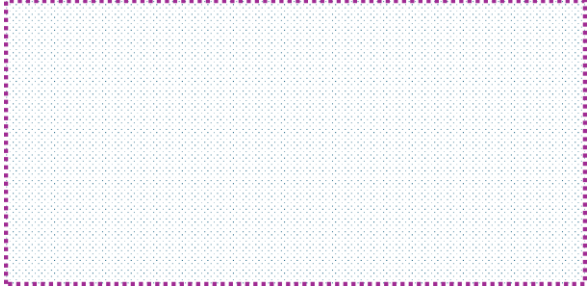
Halozyme’s experts contend the claims define a “structurally homogeneous” set of modified PH20s but disagree about what that set constitutes: Dr. Petsko says

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

¹⁶ POR, 5-6, 64-65; EX1131, 78:6-25; EX2068, ¶¶ 105-106; EX2070, ¶¶ 51, 128-FN12, 431.

¹⁷ EX1133, ¶¶ 77-80, 327-334; EX1131, 42:20-43:7; 47:7-19.

it is a subset of the proteins that have *folded*,¹⁸ while Dr. Simpson portrays it as *the entire sequence space*.¹⁹

<i>“structurally homogeneous” claimed PH20s</i>	
Dr. Petsko	Dr. Simpson
	

Halozyme embraces (rather than resolves) this confusion—it contends *both* sets of PH20s are “structurally homogeneous.”²⁰ But they plainly are not, as even active PH20s are structurally heterogeneous.²¹

¹⁸ 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.

¹⁹ EX2068, ¶ 33; EX1130, 89:16-90:16; EX1133, ¶¶ 52-57.

²⁰ POR, 64-65, 55, 7, 3-4.

²¹ Pet., 9-10; EX1003, ¶¶ 55-61, 66, 69, 149, 161; EX1133, ¶¶ 40-44, 70-80, 85-86.

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 $10^{60}+$ sequences meeting the claims' parameters.²² Halozyme's expert agreed: Dr. Petsko 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 approximate their number.²³ 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."²⁴ Critically, the disclosure does not (and could not) identify all 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, or the further sub-portion that will exhibit activity.²⁵ Dr. Hecht explained why directed evolution techniques

²² Pet., 45-46, 49-54, 65, 66-71; EX1003, ¶¶ 163-164, 171-182, 194-197, 200-201; EX1133, ¶¶ 112, 120, 123, 126.

²³ EX1131, 63:19-64:17; EX1133, ¶¶ 121-122.

²⁴ EX2070, ¶ 347.

²⁵ Pet., 13-15, 71-78.

could not.²⁶ Drs. Petsko and Naismith confirmed his opinions.²⁷ For example, assays used in directed evolution techniques max out at a fraction of the smallest sequence space here: $\sim 10^9$ to $\sim 10^{12}$ mutants (*e.g.*, a PH20 with <5 modifications, exemplified below).²⁸

Total Change	Total Sequences	#
1	8	8.00E+00
2	65,216	6.52E+04
3	265,200,944	2.65E+08
4	717,280,588,032	7.17E+11
5	1,451,597,916,360,600	1.45E+15
6	2,344,623,824,689,060,000	2.34E+18
7	3,148,443,866,971,500,000,000	3.15E+21
8	3,615,319,817,748,530,000,000,000	3.62E+24
9	3,623,914,079,290,540,000,000,000,000	3.62E+27
10	3,221,265,000,415,160,000,000,000,000,000	3.22E+30
11	2,570,898,851,896,440,000,000,000,000,000,000	2.57E+33
12	1,860,869,196,059,100,000,000,000,000,000,000,000	1.86E+36
13	1,231,744,625,564,360,000,000,000,000,000,000,000,000	1.23E+39
14	750,798,590,910,646,000,000,000,000,000,000,000,000,000	7.51E+41
15	423,934,823,807,859,000,000,000,000,000,000,000,000,000,000	4.24E+44
16	222,877,670,746,184,000,000,000,000,000,000,000,000,000,000,000	2.23E+47
17	109,586,695,593,584,000,000,000,000,000,000,000,000,000,000,000,000	1.10E+50
18	50,590,638,415,623,600,000,000,000,000,000,000,000,000,000,000,000,000	5.06E+52
19	22,004,239,130,882,000,000,000,000,000,000,000,000,000,000,000,000,000,000	2.20E+55
20	9,044,953,769,534,580,000,000,000,000,000,000,000,000,000,000,000,000,000,000	9.04E+57
21	3,523,483,795,861,770,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000	3.52E+60

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 $\sim 1\text{-}3 \text{ \AA}$, or (iii) detect epistatic, physicochemical, or long-range effects.²⁹

²⁶ EX1003, ¶¶ 191-201.

²⁷ EX1133, ¶ 123; EX2070, ¶¶ 347, 349.

²⁸ EX1133, ¶¶ 124-127; EX1004, ¶¶ 175-178.

²⁹ EX1004, ¶¶ 166-168; EX1003, ¶ 240; EX1133, ¶¶ 130-132, 195, 260-263, 268, 270-274, 281-284.

Computational tools in the 2011-2012 timeframe also could not reliably model protein structures with 10, 15, or 20 changes from native.³⁰ And individual assessments are impossible.³¹

In 2011-2012, POSAs would need to perform experiments to identify modified PH20s with 5+ mutations that properly fold and exhibit activity.³² Doing so for even a tiny fraction of the claimed sequence space is impossible.

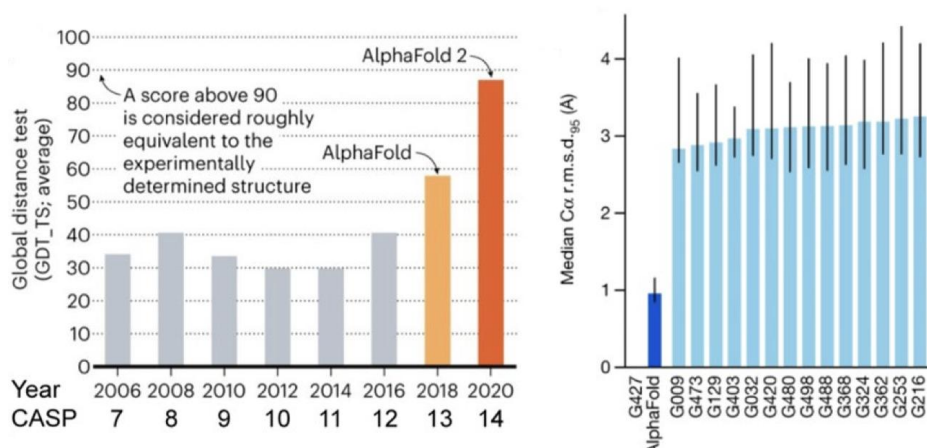


Figure 6. Left: progress of the CASP performance over the years for the best models and the most difficult targets.³⁸ Right: performance of AlphaFold2 relative to the top 15 entries by other groups in CASP14. Data are the median coordinate error and the 95% confidence interval of the median, estimated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

This evidence is dispositive on written description *and* enablement.³³ If a POSA cannot identify properly-folded (and active) PH20s within the claims'

³⁰ EX1027, 6-9; EX1133, ¶¶ 124, 128-129, 132-133, 257.

³¹ EX1133, ¶¶ 131-132.

³² EX1133, ¶¶ 131-132; EX1003, ¶¶ 163, 200-201; EX1004, ¶¶ 166-168.

³³ Pet., 27-28, 49-52, 71-78.

sequence space, the disclosure cannot demonstrate possession of them.

Impossibility also exceeds undue experimentation and establishes 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.*”³⁴ 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 active PH20s within the claim scope.³⁵ Halozyme disagrees.³⁶ But properly folded PH20s are the only PH20s in the sequence space that *could* have a common set of structural features, and the disclosure fails to identify what those structural features are and which of the 10⁶⁰+ sequences will fold to have them.

³⁴ *Ariad*, 1350; *Gilead*, 1356.

³⁵ Pet., 52-54; EX1003, ¶¶ 69, 146-152, 156, 160-164.

³⁶ POR, 46.

(a) *Sequence Identity Is Not a “Structural Feature”*

Halozyme and its experts contend the “91% sequence identity” requirement is a “common **structural** feature” of the claimed PH20 polypeptides.³⁷ It is not—it is a **mathematical** requirement (*i.e.*, are two sequences 91%+ identical?).³⁸

“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).³⁹

Common “structural features” are the **set** of those **physical** attributes “common to the members of the genus” (properly folded, active PH20s).⁴⁰

As a **claim element**, the 91% identity requirement defines the boundaries of the “sequence space”—the set of amino acid sequences within which the claimed PH20 polypeptides must be found.⁴¹ Each “primary sequence” is, **by definition**, up to 18% **different** than every other one.⁴²

³⁷ POR, 64-65; EX2068, ¶¶ 254, 358; EX1131, 65:18-66:17.

³⁸ EX1026, 66:32-67:9, 68:18-34; EX1133, ¶¶ 80, 83.

³⁹ EX1003, ¶ 152; EX1133, ¶¶ 83-86.

⁴⁰ *Duke*, 1311.

⁴¹ *Ariad*, 1349.

⁴² EX1133, ¶¶ 48-51.

(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 POSAs would recognize as an ‘alpha-beta barrel *fold*.’”⁴³ But Halozyme misleadingly portrays the α/β barrel *motif* as the *entire* tertiary structure of PH20s, including the catalytic site.⁴⁴ 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...”⁴⁵

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 can exhibit enzymatic activity.⁴⁶ The *tertiary* structure of human PH20, however, is not described in the disclosure—it was not reported until 2024.⁴⁷

Before 2011, the prior art identified at least three structural features shared

⁴³ POR, 12-13; EX2068, ¶¶ 33, 106, 289, 305; EX2070, ¶¶ 432, 51, 58, 101, 128, 345, 396, 400.

⁴⁴ POR, 55-56; EX2070, ¶ 51.

⁴⁵ EX1131, 69:2-5; EX1133, ¶¶ 153, 160.

⁴⁶ EX2070, ¶¶ 51, 128-FN12; EX1131, 78:6-25; 86:23-87:7; EX1003, ¶¶ 36, 62, 161, 237; EX1133, ¶¶ 17, 58-59, 96-97, 159.

⁴⁷ EX1126, 1068.

by 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;⁴⁸
- (ii) a “distorted” (non-canonical) PH20 α/β barrel motif;⁴⁹ and
- (iii) the Hyal-EGF domain (Leu336 to Asp416 in PH20).⁵⁰

Each is essential to active PH20s—mutations of active site residues⁵¹ or deletion of all or part of the Hyal-EGF domain “abolished” activity.⁵²

(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 PH20.⁵³ But the disclosure nowhere mentions a “PH20 α/β

⁴⁸ EX1026, 80:11-18; EX1010, 9437; EX1133, ¶¶ 96, 167.

⁴⁹ EX1008, 824, 829, 833; EX1006, 6913; EX1133, ¶¶ 140-150.

⁵⁰ EX1006, 6913; EX1010, 9441; EX1003, ¶¶ 84-91; EX1004, ¶¶ 96-99; EX1133, ¶¶ 189-192.

⁵¹ EX1003, ¶ 89; EX1133, ¶¶ 96, 304; EX2070, ¶ 128-FN12.

⁵² EX1003, ¶¶ 89-90, 95, 98, 100, 155-FN118, 176-179, 196; EX1133, ¶¶ 186-188; EX1010, 9439, 9441; EX1011, 813-14.

⁵³ POR, 46-49, 64-65; EX2068, ¶¶ 294-295, 305; EX2070, ¶¶ 51, 128, 396, 430.

barrel,” discusses this motif, or portrays it as a common structural feature of any set of modified PH20s.⁵⁴ It also does not (i) identify any amino acid sequences for the “distorted” PH20 α/β barrel motif or its elements,⁵⁵ (ii) explain how it differs from the canonical α/β barrel, or (iii) indicate that PH20’s active site is not in it.⁵⁶ *Any* of these omissions doom Halozyme’s attempt to retroactively import into the disclosure the label “ α/β barrel” as a “structural feature” of the claimed PH20s.⁵⁷

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.⁵⁸ It has a large gap, two irregular strands, and its shape is distorted (PH20: yellow, canonical: pink).⁵⁹

⁵⁴ EX1133, ¶¶ 165-170.

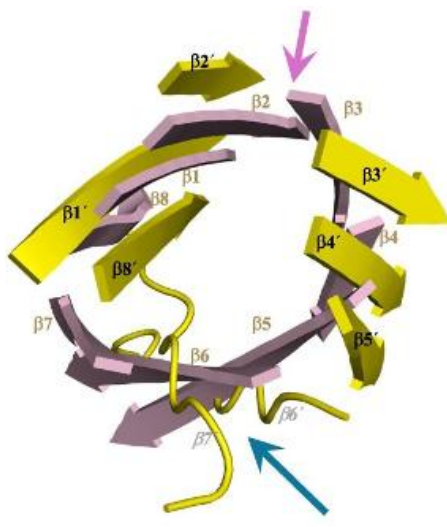
⁵⁵ EX1133, ¶¶ 151, 168.

⁵⁶ EX1133, ¶¶ 152-158, 165-167; EX1008, 824-825, 829, 833; EX1006, 6911-13; EX1033, 1027.

⁵⁷ *Juno*, 1339; *Boston*, 1366-67.

⁵⁸ EX1008, 833; EX1133, ¶¶ 141-147.

⁵⁹ 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 α/β motif because the two *are materially different*.⁶⁰

Second, the conserved features of the hyaluronidase active site that Dr. Petsko referenced *are not contained within* the PH20 α/β motif.⁶¹ The words “PH20 α/β barrel” thus cannot 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

⁶⁰ EX1133, ¶¶ 136-139, 144, 150-152; EX2070, ¶ 52.

⁶¹ EX1008, 829; EX1133, ¶ 149.

PH20.⁶² This is unknowable for the vast majority of the genus (*i.e.*, ***multiply-***modified PH20s).

Halozyme thus 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.

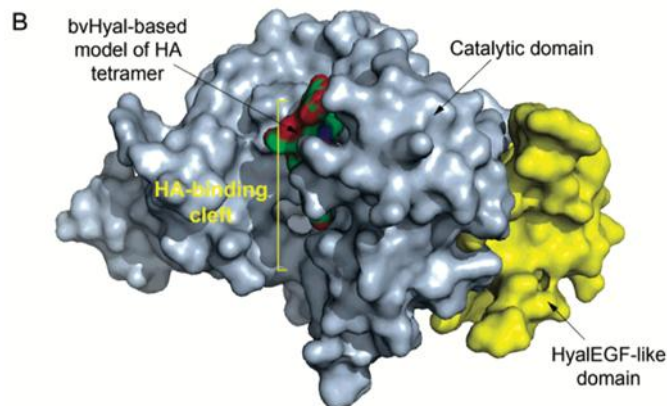
(d) No Description of the PH20 Hyal-EGF

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.⁶³ Before 2011, Chao reported the Hyal-EGF domain structure and that it is shared by human hyaluronidases (what Dr. Simpson portrayed as “a huge breakthrough in the field”).⁶⁴

⁶² EX1003, ¶¶ 42, 59; EX1133, ¶¶ 96-97.

⁶³ Pet., 38-42, 52-53, 64; EX1003, ¶¶ 88, 179, 196; EX1133, ¶¶ 185, 187, 190-193, 198.

⁶⁴ EX1130, 114:23-116:9; EX1003, ¶¶ 81-91; EX1004, ¶¶ 88-101; EX1006, 6915-6917 (Figs. 2, 4).



Despite this, there is no mention of the Hyal-EGF domain in the disclosure.⁶⁵ That omission is fatal to written description, because the Hyal-EGF domain is a “common structural feature” of at least the subset of enzymatically active PH20s being claimed.⁶⁶

Dr. Petsko strains to downplay Hyal-EGF’s importance to the structure and activity of PH20s.⁶⁷ But Zhang reported that deletion of 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.”⁶⁸

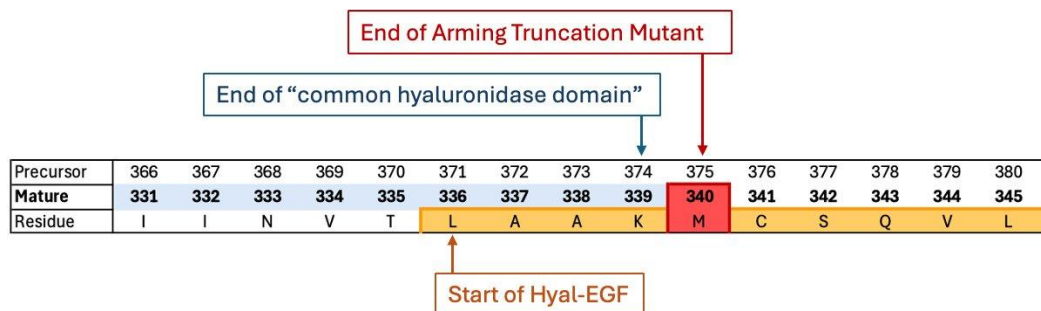
⁶⁵ EX1003, ¶¶ 88, 179, 196; EX1133, ¶¶ 185, 187, 190-193, 198.

⁶⁶ EX1003, ¶¶ 84-91, 95-100, 176-179, 196; EX1133, ¶¶ 163, 168, 185-189.

⁶⁷ EX2070, ¶¶ 209, 211.

⁶⁸ EX1010, 9439, 9441; EX1003, ¶¶ 89-91; EX1004, ¶¶ 94-99; EX2068, ¶ 143; EX1006, 6913; EX1133, ¶¶ 187-189.

The disclosure's reference to a "common core hyaluronidase domain" shared by PH20s (3-339 of PH20) does not identify the Hyal-EGF domain—it terminates 4-5 residues into it.⁶⁹ That "domain" also is not a "common structural feature" of active PH20s—mutants truncated at position 340 do not "properly fold"⁷⁰ and lack activity.⁷¹ Halozyme's experts do not contend otherwise.⁷²



Halozyme contends "a POSA's knowledge included possession" of homology models based on the bee venom hyaluronidase (bvH) and Hyal-1 structures published before 2011.⁷³ But written description is judged by the disclosure, not by a POSA's *mind*, and *this disclosure* describes no structural or homology models of any kind. Worse, Halozyme's indiscriminate reliance on the

⁶⁹ EX1026, 79:20-31.

⁷⁰ EX1133, ¶¶ 161-163.

⁷¹ EX1011, 813-814; EX1133, ¶¶ 192-193.

⁷² EX1133, ¶¶ 161-163.

⁷³ POR, 12.

bvH and Hyal-1 structures *ignores critical structural distinctions* between hyaluronidases, including that bvH *is* active without an EGF domain while Hyal-1 *is not*.⁷⁴ In Dr. Simpson's words, bvH "did not provide a complete picture of the structure for" human PH20.⁷⁵

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 91% identical" PH20s.⁷⁶

First, effects on PH20 folding and activity from single substitutions cannot predict effects of *combinations* of changes.⁷⁷ See § III.D.1. Even PH20s with modifications at positions Dr. Petsko labeled "100% tolerated" exhibited extensive activity variations, demonstrating that even single substitutions are unpredictable.⁷⁸

⁷⁴ EX1133, ¶¶ 163, 189-191.

⁷⁵ EX2068, ¶ 125.

⁷⁶ POR, 51.

⁷⁷ EX1003, ¶¶ 54-61, 147-150; EX1133, ¶¶ 115, 232-233, 252-259.

⁷⁸ EX1133, ¶¶ 264-269.

Second, listing options and leaving to a POSA the task of figuring out which combinations yield active PH20s does not describe species of multiply-modified PH20s.⁷⁹

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.⁸⁰ Both halves of the "structure-function" equation are missing here.

3. Representative Species Not Described

Halozyme points to 7 alleged "examples" of "M313 variants."⁸¹ None are described in its disclosure. Three are based on native *primate* sequences with known activity, while four were tested.⁸² None of the 7 illustrate the unpredictability of making 5+ changes to a native sequence.⁸³ They also are not representative—they do not reflect the types or physicochemical diversity of the

⁷⁹ *Idenix*, 1164-65.

⁸⁰ § III.D.3; Pet., 42-49, 52-54; EX1003, ¶¶ 67-76, 106-116, 150; EX1133, ¶¶ 151, 246-251, 307-309.

⁸¹ POR, 55-56; EX2070, ¶¶ 434-437.

⁸² EX1133, ¶¶ 114-119.

⁸³ EX1133, ¶¶ 114-119; EX1003, ¶¶ 54-61.

claimed modified PH20s, including truncations and mutants with changes beyond position 447 (for which no data is provided).⁸⁴

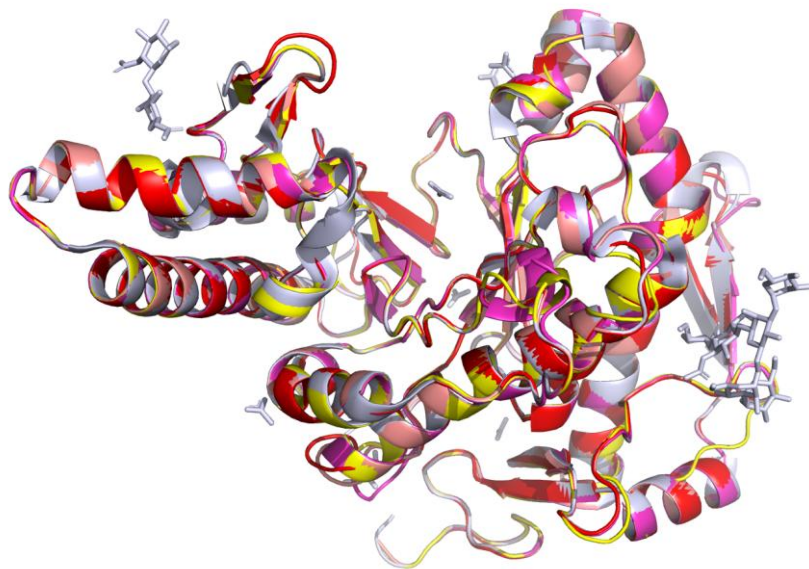
Halozyme's overlaid models of them can be ignored.⁸⁵ They all suffer from Dr. Petsko's flawed " α/β barrel" opinions (§ III.C.1(c)) and cannot reveal spatial differences <1.5 Å or any physicochemical or epistatic effects.⁸⁶ A comparable overlay of the 5 human hyaluronidases shows virtually identical structures despite their known functional differences.⁸⁷

⁸⁴ Pet., 36-42, 54-59, 69-70, 71-72; EX1003, ¶¶ 94, 147-150, 160-164, 171; EX1133, ¶¶ 77-80, 114-120, 221.

⁸⁵ POR, 46-50; EX2070, ¶¶ 434-437.

⁸⁶ EX1133, ¶¶ 197, 281-284.

⁸⁷ EX1133, ¶¶ 183-184.



D. Enablement

The scale of experimentation required to practice the full scope of claimed properly folded PH20s (including the portion that is enzymatically active) is beyond undue—it 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.⁸⁸ Even a project with 5 substitutions

⁸⁸ EX2070, ¶¶ 323-324, 351, 355-360, 364; EX1130, 93:20-24; EX1133, ¶¶ 198-202.

would require billions of days to practice.⁸⁹ In 2011-2012, a POSA could not use this plan to predict whether PH20s with 5+ changes will properly fold, or which of those exhibit activity.⁹⁰

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.⁹¹ Each can cause effects remote from the mutation that change how the protein reacts to subsequent changes.⁹² The unpredictable effects of combinations of mutations ("epistasis") prevent a POSA from predicting whether the vast majority of multiply-modified PH20s will "properly fold."⁹³

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

⁸⁹ EX1133, ¶¶ 131-132; Pet., 51, 76-77; EX1003, ¶¶ 201-202.

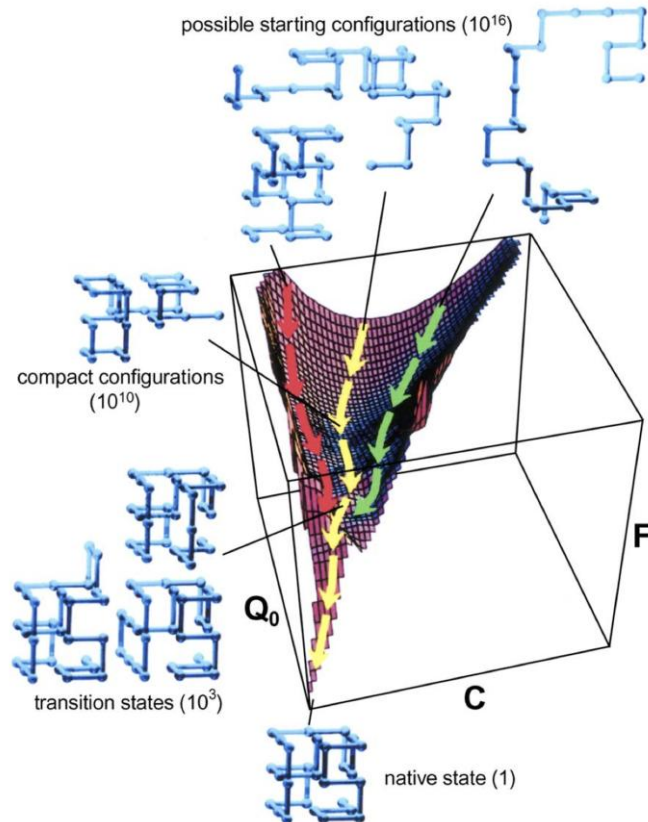
⁹⁰ EX1003, ¶¶ 61, 161-164, 194; EX1133, ¶¶ 260-263, 278, 317, 325.

⁹¹ Pet., 10-11, 52-54; EX1003, ¶¶ 54-61; EX1133, ¶¶ 232, 252-255, 262, 330, 222.

⁹² EX1133, ¶¶ 125-126, 255-259; EX1131, 79:15-22, 89:21-90:24; 270:9-17.

⁹³ EX1003, ¶¶ 61, 161-164; EX1133, ¶¶ 123, 252-259; EX1160, 383-85.

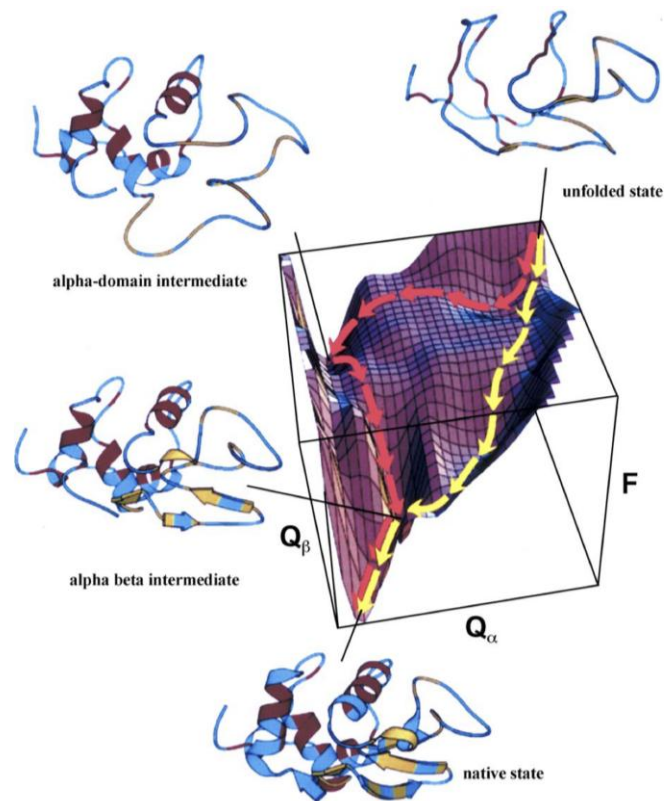
number of conformations (10^{27} for even a small protein) during its folding process, adopting energetically preferred ones as it proceeds:⁹⁴



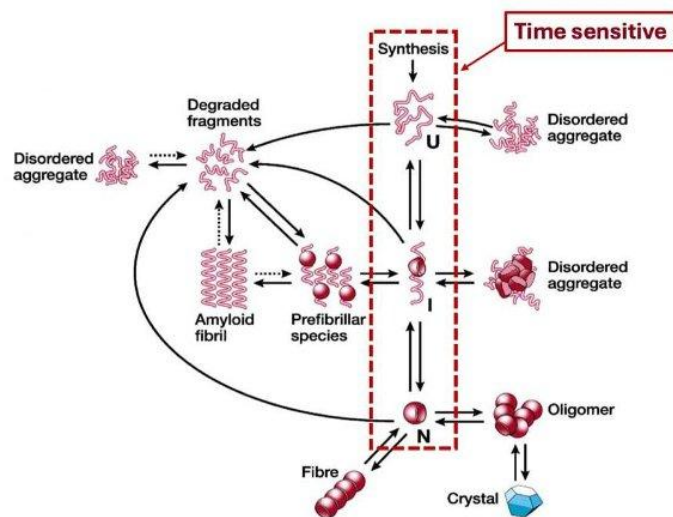
Intermediate conformations can get trapped in energetic “valleys,” preventing them from efficiently folding into the native state (red path below):⁹⁵

⁹⁴ Pet., 10-11; EX1003, ¶¶ 55-59; EX1133, ¶¶ 68-72; EX1136, 4-6.

⁹⁵ EX1133, ¶¶ 70-72; EX1136, 4-6.



The folding process must complete quickly, otherwise the protein will degrade:⁹⁶



⁹⁶ 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 a POSA cannot predict, which affects each sequence’s ability to fold and the protein’s stability.⁹⁷ 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:⁹⁸

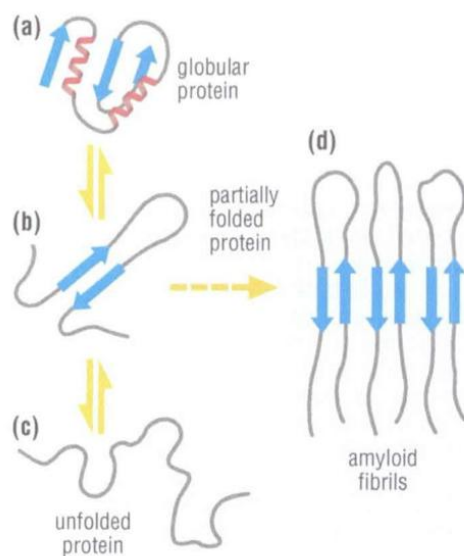


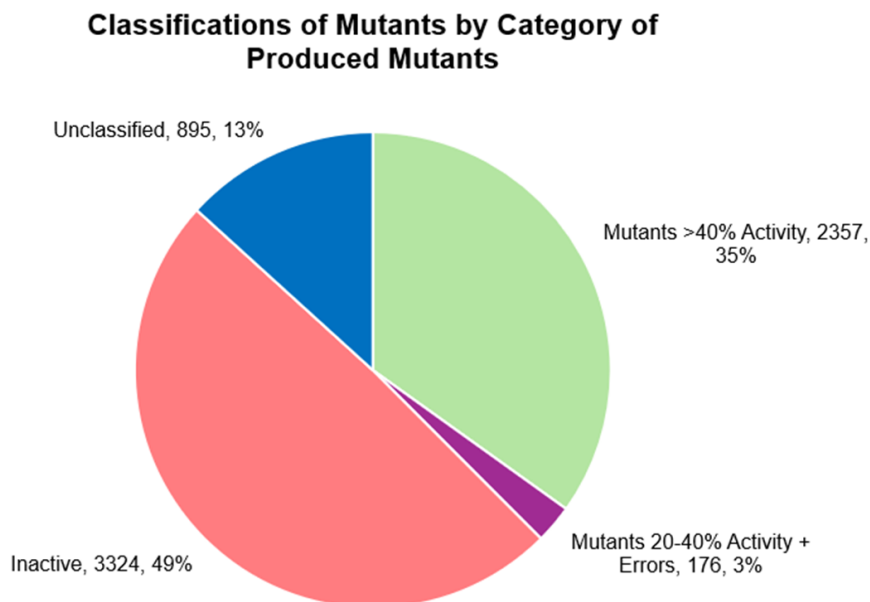
Figure 4-53 A possible mechanism for the formation of amyloid fibrils by a globular protein The correctly folded protein (a) is secreted from the cell. Under certain conditions, or because it contains a mutation, the protein unfolds partially (b) or completely (c); the unfolded forms can also refold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

⁹⁷ EX1003, ¶¶ 62-65; EX1133, ¶ 129; EX1131, 99:4-22, 102:1-9.

⁹⁸ EX2164, 160; EX1133, ¶¶ 73-76, 326; EX1003, ¶ 54; EX1131, 41:22-42:11.

And multiply-mutated PH20 sequences may adopt the **wrong** structure.⁹⁹

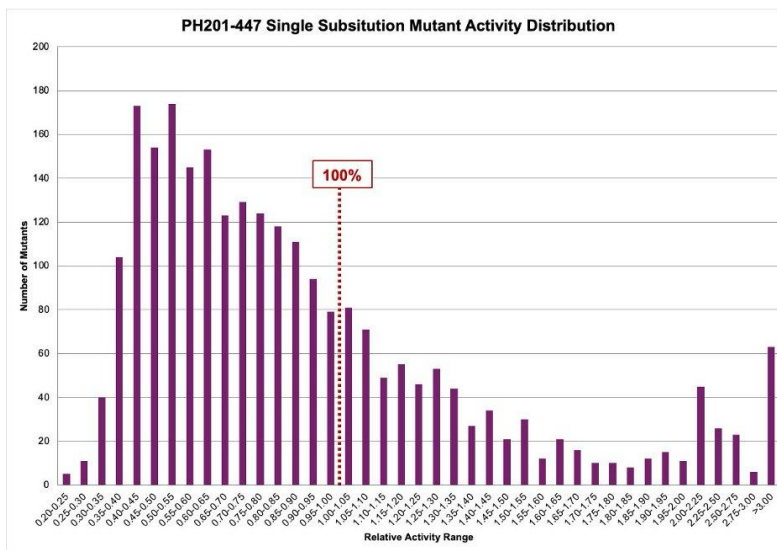
Halozyme's experts downplay unpredictability, contending a POSA could pick combinations of "tolerated" mutations using the disclosure's single-substitution data.¹⁰⁰ That ignores not just science but the data itself, which shows most single mutations were deleterious.¹⁰¹



⁹⁹ EX1003, ¶¶ 55-56; EX1133, ¶¶ 73-79.

¹⁰⁰ EX2070, ¶¶ 317-324, 355-359; EX2068, ¶¶ 311-314, 380-382.

¹⁰¹ Pet., 42-46; EX1003, ¶ 114; EX1133, ¶¶ 170-176, 236, 324-325; EX1146, 22381-82; EX1151, 743-744.

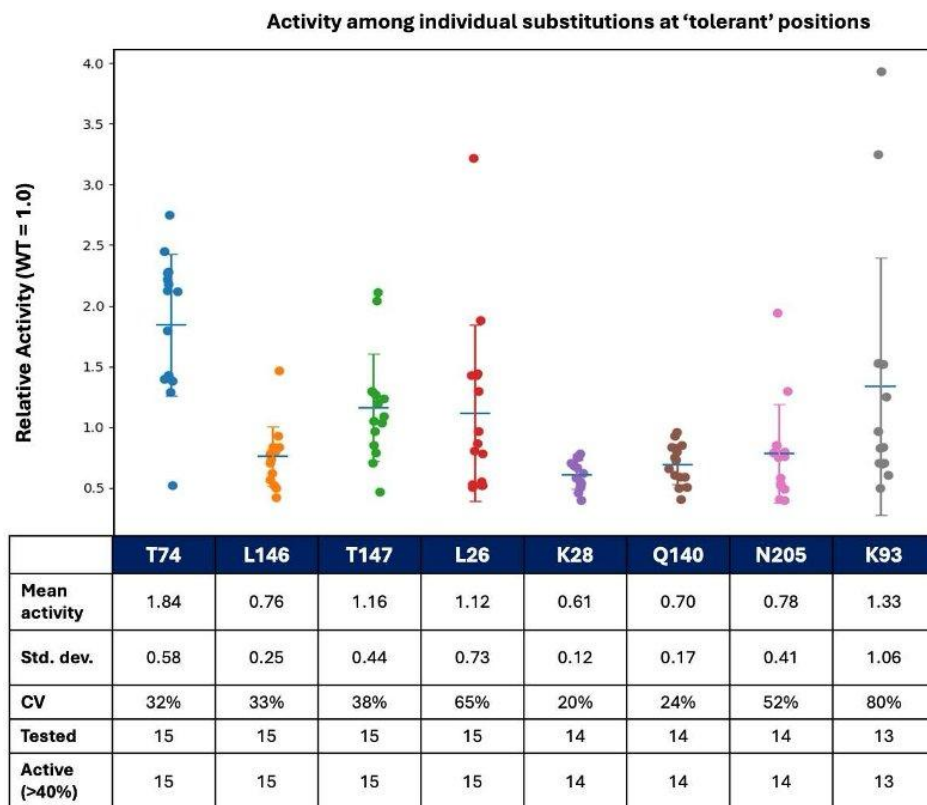


Even positions Dr. Petsko labeled as “100% tolerant” (the *most* predictable in his table) exhibit widely varying effects.¹⁰² This reflects that *each* substitution causes a *unique* effect on *the entire* PH20 protein structure not limited to its position.¹⁰³

		30 D	61 L	92 A	123 W	154 K	185 L
Posmon WT	31 E	62 G	93 K	124 K	155 Q	186 F	
1 L	32 P	63 Y	94 N	125 P	156 E	187 P	
2 N	33 L	64 Y	95 D	126 K	157 F	188 D	
3 F	34 D	65 P	96 I	127 D	158 E	189 C	
4 R	35 M	66 Y	97 T	128 V	159 K	190 Y	
5 A	36 S	67 I	98 F	129 Y	160 A	191 N	
6 P	37 L	68 D	99 Y	130 K	161 G	192 H	
7 P	38 F	69 S	100 M	131 N	162 K	193 H	
8 V	39 S	70 I	101 P	132 R	163 D	194 Y	
9 I	40 F	71 T	102 V	133 S	164 F	195 K	
10 P	41 I	72 G	103 D	134 I	165 L	196 K	
11 N	42 G	73 H	104 N	135 E	166 V	197 P	
12 V	43	74 T	105 L	136 L	167 E	198 G	
13 P	44 P	75 V	106 G	137 V	168 T	199 Y	
14 F	45 R	76 N	107 M	138 Q	169 I	200 N	
15 L	46 I	77 G	108 A	139 G	170 K	201 G	
16 W	47 N	78 G	109 V	140 Q	171 L	202 S	
17 A	48 A	79 I	110 I	141 R	172 G	203 C	
18 W	49 T	80 P	111 D	142 V	173 K	204 F	
19 N	50 G	81 Q	112 W	143 Q	174 L	205 N	
20 A	51 Q	82 K	113 E	144 L	175 L	206 Y	
21 P	52 G	83 I	114 E	145 S	176 R	207 E	
22 S	53 V	84 S	115 W	146 L	177 P	208 I	
23 E	54 T	85 L	116 R	147 T	178 N	209 K	
24 F	55 I	86 Q	117 P	148 E	179 H	210 R	
25	56 F	87 D	118 T	149 A	180 L	211 N	
26 L	57 Y	88 H	119 W	150 T	181 W	212 D	
27	58 V	89 L	120 A	151 E	182 G	213 D	
28 K	59 D	90 D	121 R	152 K	183 Y	214 L	
29	60 R	91 K	122 N	153 A	184 Y	215 S	

¹⁰² EX1133, ¶¶ 264-266.

¹⁰³ EX1133, ¶¶ 267-269.



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.¹⁰⁴ A POSA thus could not predictably determine which combinations of such mutations might affect PH20's structure and activity.¹⁰⁵

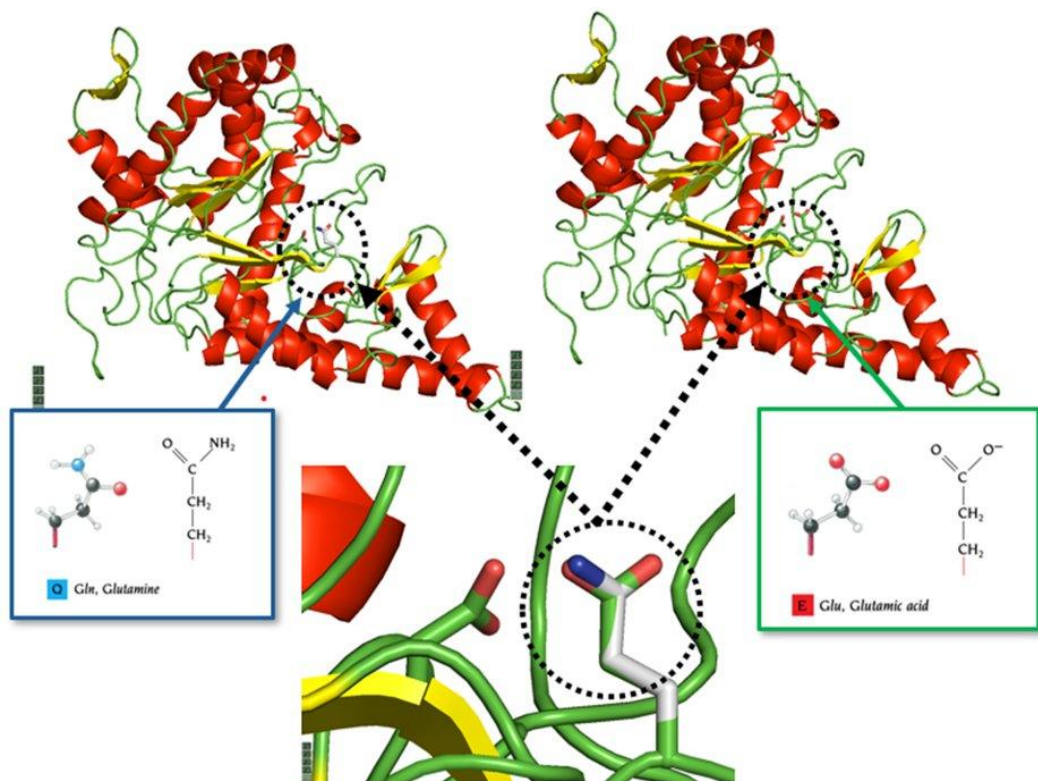
Position	WT	V	S	T	W
33	L	-	0.48	0.45	1.58
165	L	1.22	1.31	-	1.14
175	L	0.94	-	1.43	

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

¹⁰⁴ EX1133, ¶¶ 273-274.

¹⁰⁵ EX1133, ¶¶ 270-274; EX1003, ¶¶ 146-150.

And imperceptible differences in homology models can eliminate activity.¹⁰⁶



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

Halozyme contains the α/β barrel motif in PH20s makes it possible to predict combinations of changes to them.¹⁰⁷ A 2009 paper (EX1144) demonstrates the contrary.

¹⁰⁶ EX1133, ¶¶ 273-274, 281-284.

¹⁰⁷ POR, 51-54; 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.

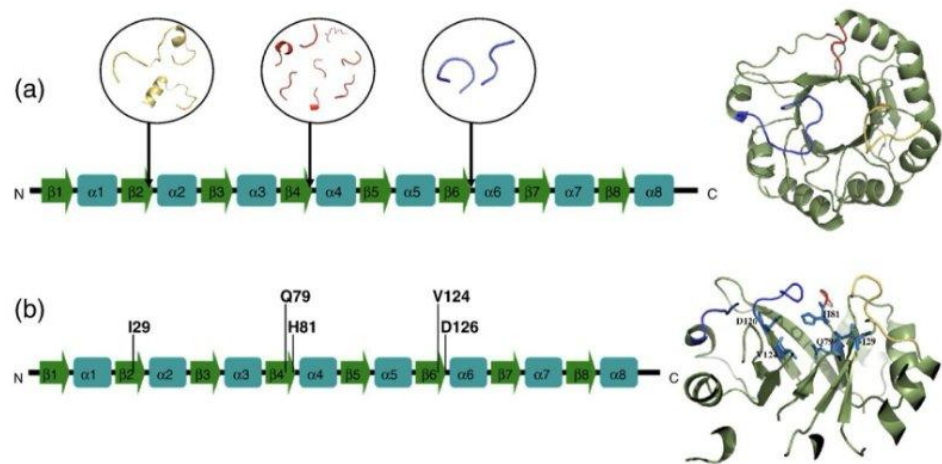


Fig. 1. Secondary-structure elements and tertiary structure (PDB code 1pii) of WT PRAI (ribbon diagram showing a view from the top of the central β -barrel). (a) The loops 2, 4, and 6 are shown in yellow, red, and blue, respectively. The circular insets show the loops to exchange in the PRAI-LoxP scaffold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

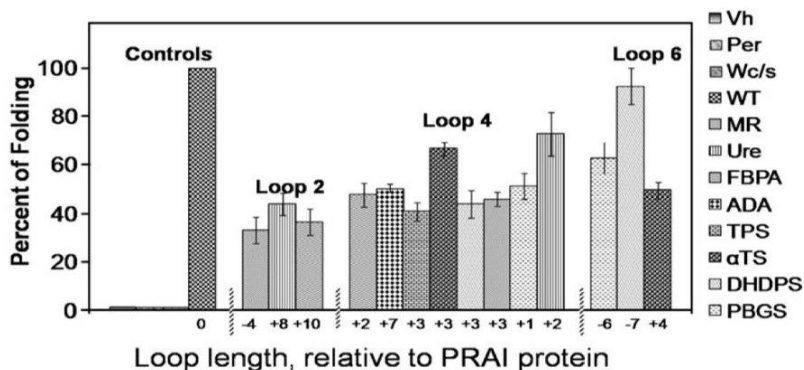
Table 1. Characteristics of the exchanged loops in the PRAI-LoxP scaffold

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
α TS (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
α TS (EC 4.2.1.20)	β/α loop 6	SRAGVTGAENRAALP	15
PRAI WT (5.3.1.24)	β/α loop 6	NGQGGSGQRF ^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*.¹⁰⁸



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 2011-2012.¹⁰⁹ 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.¹¹⁰

¹⁰⁸ EX1133, ¶¶ 177-182.

¹⁰⁹ POR, 51-54.

¹¹⁰ Pet., 45-46; EX1133, ¶¶ 75, 246-247; EX1131, 240:19-241:16.

Because mutations that impacted ***folding*** are not identified, the disclosure cannot provide “tolerance” insights.¹¹¹

Experimental design flaws and incomplete reporting of results independently render Dr. Petsko’s ratings unreliable:¹¹²

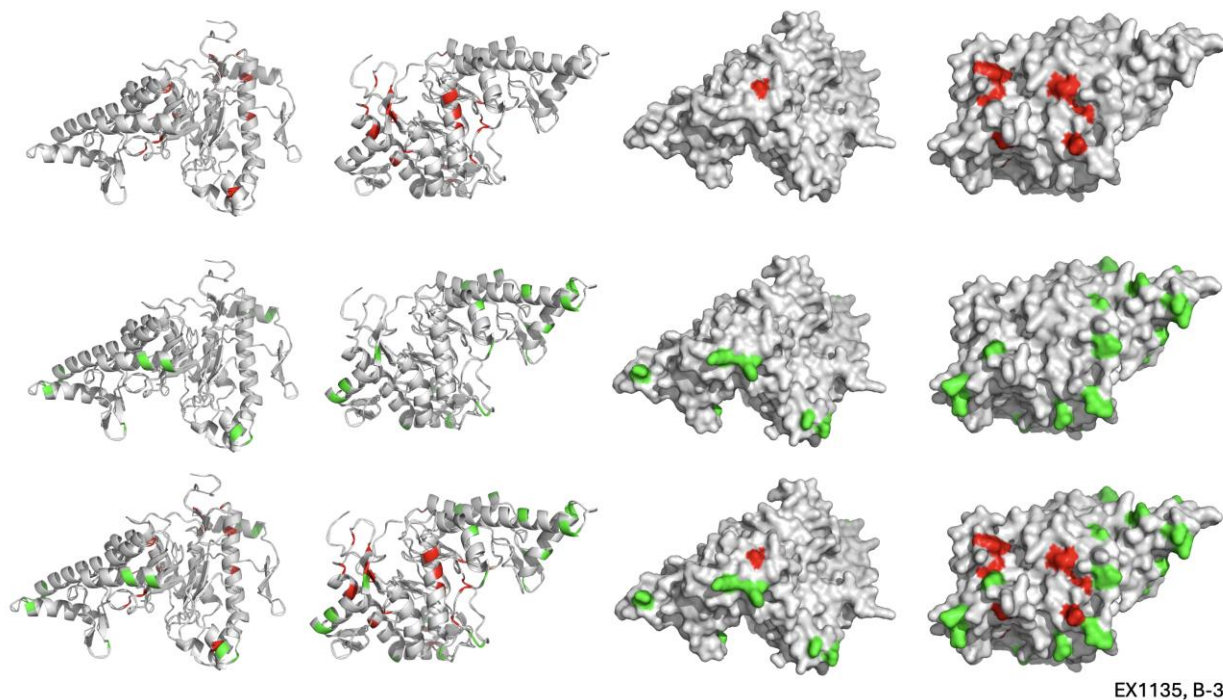
- inadequate numerical, structural context, and physicochemical interrogation of positions prevent reliable ratings of tolerance;
- no use of positive/negative controls in the primary assay, and no evidence of proteins in supernatants or their folded state;
- no activities reported for inactives, precluding 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.¹¹³

¹¹¹ EX1133, ¶ 247.

¹¹² Pet., 42-49; EX1003, ¶¶ 67-76, 99, 106-116; EX1133, ¶¶ 291-315, 246-248, 250, 175, 234-237.

¹¹³ 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 unpredictability of multiple mutations refute Halozyme's assertion that POSAs could predict effects of 5+ mutations on proper folding or activity of PH20s in 2011-2012.¹¹⁴

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

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

¹¹⁴ Pet., 76-77; EX1003, ¶ 240; EX1004, ¶ 167; 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 for doing so (albeit a research plan) uses directed evolution.¹¹⁵ Dr. Petsko also 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 (as the claims permit) the sequences can include mutations at invariant residues and require screening immense libraries to discover which ones do.¹¹⁶

2. PH20₁₋₄₃₀ and PH20₁₋₄₃₁ Are Not “Inactive”

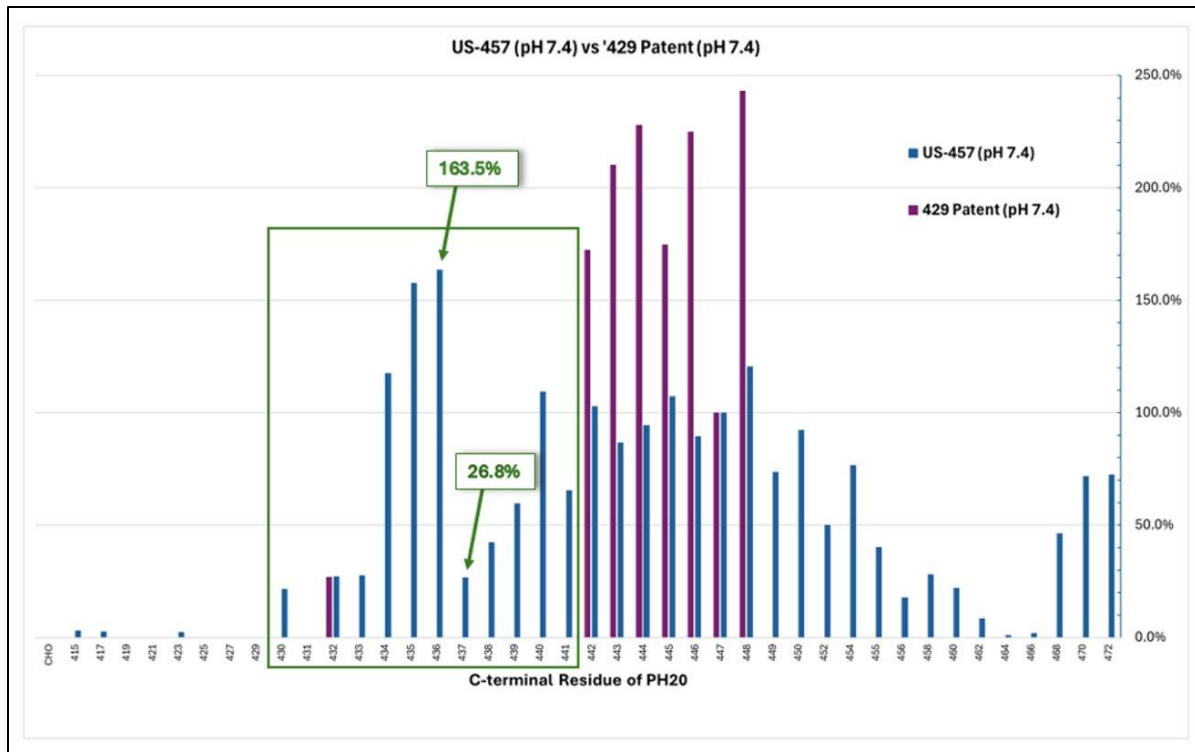
Halozyme also cited US-457 to criticize Dr. Hecht’s observation that the ’429 Patent reports unusual activity of C-terminal truncation mutants that vary by one residue.¹¹⁷ But US-457 shows the same phenomenon:¹¹⁸

¹¹⁵ Pet., 50-51; EX1026, 47:11-17, 141:30-33, 150:1-26; EX1003, ¶¶ 50-52, 183-188; EX1133, ¶¶ 204-205.

¹¹⁶ EX2070, ¶ 347; EX1133, ¶ 203; EX1026, 140:15-150:26; EX1003, ¶¶ 183-196.

¹¹⁷ POR, 61.

¹¹⁸ EX1133, ¶ 221.



Citing Dr. Simpson, Halozyme contends US-457 describes PH20₁₋₄₃₀ and PH20₁₋₄₃₁ (SEQ ID NOs: 86 and 87) as “inactive mutants.”¹¹⁹ But US-457 *explicitly* labels them “*active*,”¹²⁰ which Dr. Simpson ignored when she arbitrarily reclassified its data.¹²¹

¹¹⁹ POR, 30, 59-61, EX2068, ¶ 188.

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

¹²¹ 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.¹²² 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 instructs POSAs to *not include* inactivating substitutions in active PH20s.¹²³

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*.¹²⁴

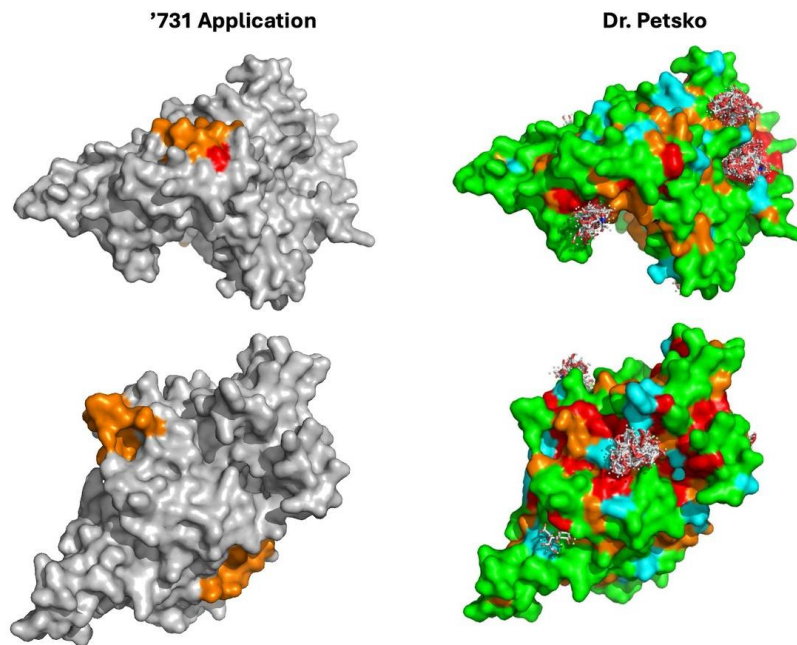
¹²² EX2070, ¶¶ 264, 274, 355-365; EX1133, ¶¶ 275-278.

¹²³ EX1026, 91:30-92:20; EX1133, ¶¶ 206-207, 209.

¹²⁴ 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 PH20.¹²⁵ Dr. Petsko's theories are not part of the disclosure, and conflict with the disclosure's explanation that substrate binds within residues 170-200 (orange).¹²⁶



¹²⁵ 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.

¹²⁶ EX1026, 81:7-14; EX1133, ¶¶ 223-226, 227-230.

5. No Rescue Mutation Theory

Dr. Petsko contends a POSA could somehow use the disclosure to identify and select mutations that would “rescue” a deleterious first mutation.¹²⁷ But the disclosure says nothing about rescue mutations and discovering them would entail the same impossible scale of effort to find active PH20s.¹²⁸

F. No Credible Utility for Inactive PH20s

Halozyme concedes PH20s have no contraceptive utility in males.¹²⁹ The Petition established that the evidence shows no utility for females.¹³⁰

Halozyme’s expert, Dr. Cherr, confirmed that contraceptive utility requires *near 100% effectiveness*.¹³¹ But *every* experiment testing PH20s for contraception *failed* (save one using unclaimed guinea pig PH20s).¹³² Impartial scientists pre-2012 thus concluded that “*PH-20 is not a useful antigen for inclusion in*

¹²⁷ POR, 50; EX2070, ¶¶ 374-383.

¹²⁸ EX1133, ¶¶ 210-211.

¹²⁹ EX1026, 213:7-9; EX1129, 38:13-23; EX1134, ¶¶ 48-51.

¹³⁰ Pet., 81-88.

¹³¹ EX1129, 57:16-58:15.

¹³² EX1003, ¶¶ 119-121; EX1134, ¶¶ 52-65; EX1129, 114:19-115:23; EX1189, 119, Table 3.

immunocontraceptive vaccines.”¹³³ Halozyme independently confirmed these experimental findings.¹³⁴ No claimed *modified* PH20 has ever been tested for contraceptive effect in any species. Moreover, Dr. Cherr admitted the claimed modifications are immaterial to his opinions.¹³⁵

Halozyme insists improper administration caused the failures, ignoring actual reasons the researchers gave.¹³⁶ It claims only mucosal immunization (which is not described in connection with immunocontraception in the disclosure) will work, ignoring that systemic immunization was used in the guinea pig experiment,¹³⁷ and that it effectively delivers antibodies to the female reproductive tract (*e.g.*, HPV vaccines).¹³⁸

Well-established immunological principles contradict Halozyme’s remaining

¹³³ EX1189, 119; EX1134, ¶¶ 64-67.

¹³⁴ EX1122; EX1190, Abstract, 381; EX1134, ¶¶ 68-73.

¹³⁵ EX1129, 101:18-102:9, 104:9-20, 40:23-42:19; *see McLeay*, *3; EX1134, ¶¶ 15-16.

¹³⁶ POR, 78-79; EX1134, ¶¶ 59-62; EX1020, 181; EX1019, 332, 333.

¹³⁷ POR, 78-79; EX1134, ¶ 58; EX2010, 544.

¹³⁸ EX1134, ¶¶ 42-47, 64; EX1132, 110:1-14, 111:17-18; EX1120, 3-6; EX2114, 17.

speculation.¹³⁹

- Effective immunocontraception with PH20 requires antibodies that 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.¹⁴⁰
- 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).¹⁴¹ Misfolded modified PH20s are even less likely to produce effective antibodies against native PH20s.¹⁴²
- Sequence similarity alone cannot predict which modified PH20s present epitopes that induce production of effective antibodies against native PH20s in all species.¹⁴³

¹³⁹ POR, 75-78; EX1134, ¶¶ 74-76, *see also* ¶¶ 22-41.

¹⁴⁰ EX1134, ¶¶ 61-62, 103-114; *cf.* EX2116, 172-175, 177.

¹⁴¹ EX1134, ¶¶ 85-91, 99-102; EX1170, 288-89, 311-13, 389.

¹⁴² EX1134, ¶¶ 92-98.

¹⁴³ EX1134, ¶¶ 77-84; EX1194, 10075.

- Adjuvants and boosters can magnify immune responses but cannot change its epitopic specificity.¹⁴⁴

An impossible scale of trial-and-error testing is thus also implicated here.¹⁴⁵

Contraceptive utility was not credible for any PH20 polypeptide in 2011-2012; it was just an invitation for further research.¹⁴⁶

IV. Obviousness

Merck explained that Halozyme's '429 Patent (with Chao) rendered obvious single-amino acid substitution *mutants* (plural) of PH20₁₋₄₄₇.¹⁴⁷ Dr. Hecht explained the '429 Patent "encouraged [POSAs] to make modified PH20 proteins having single amino acid substitutions in non-essential regions."¹⁴⁸

Dr. Park described how POSAs would have identified these singly-substituted active mutants using techniques Halozyme's experts confirmed would

¹⁴⁴ EX1134, ¶¶ 115-122.

¹⁴⁵ EX1003, ¶¶ 122-123; EX1134, ¶¶ 17-21, 87, 105, 123-125.

¹⁴⁶ *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.

¹⁴⁷ Pet., 90-93.

¹⁴⁸ EX1003, ¶¶ 217-219, 223-224; EX1005, 16:14-26.

have been used in 2011.¹⁴⁹ Without reviewing the disclosure, Dr. Park used those techniques to identify M313K as *one of ~750 such substitutions* suggested by the '429 Patent before 2011.¹⁵⁰ For example, he and Dr. Hecht identified M313K's favorable effects, which confirm a POSA's motivation to make that substitution.¹⁵¹ Dr. Naismith found Dr. Park's analysis objective, rigorous, and unbiased.¹⁵² Thus, per *KSR*, the '429 Patent motivated POSAs to identify single substitutions in non-essential regions of PH20₁₋₄₄₇ 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."¹⁵³ But Halozyme *patented all such singly-substituted PH20s*.¹⁵⁴

After extensive discovery and three depositions, Halozyme merely repeats the *identical* lawyer-directed hindsight theory initially raised in related

¹⁴⁹ EX1004, ¶¶ 22-24, 32; EX1133, ¶¶ 347-349, 357, 360, Appendix B-8.

¹⁵⁰ EX2176; EX1133, ¶ 344; EX1003, ¶ 246.

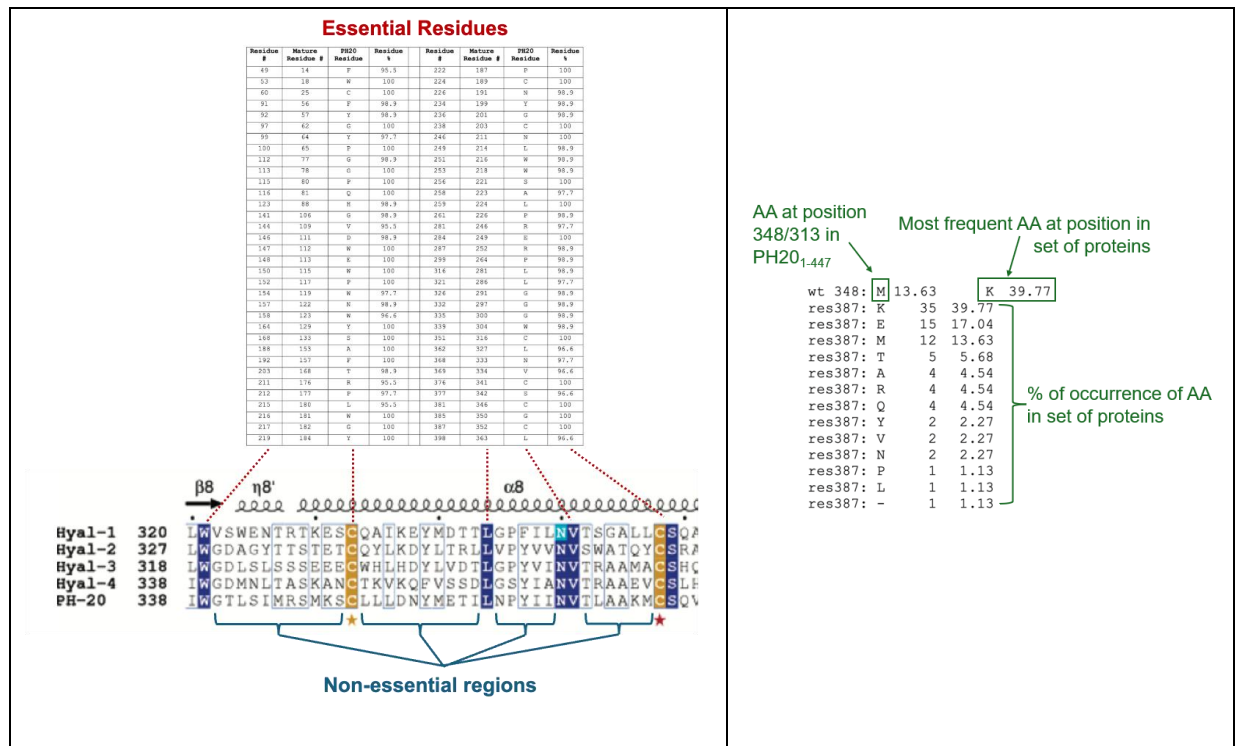
¹⁵¹ EX1004, ¶¶ 113-120; EX1003, ¶¶ 241-246; Pet., 99-102, 107-110.

¹⁵² EX1133, ¶¶ 338-343, 352-359; EX1003, ¶ 227.

¹⁵³ POR, 88-89.

¹⁵⁴ EX1005, claim 1.

proceedings.¹⁵⁵ But the 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 *in between* the 68 “essential” positions),¹⁵⁶ and (ii) which substitutions at each position to assess—the frequently found residues at these non-essential positions.¹⁵⁷



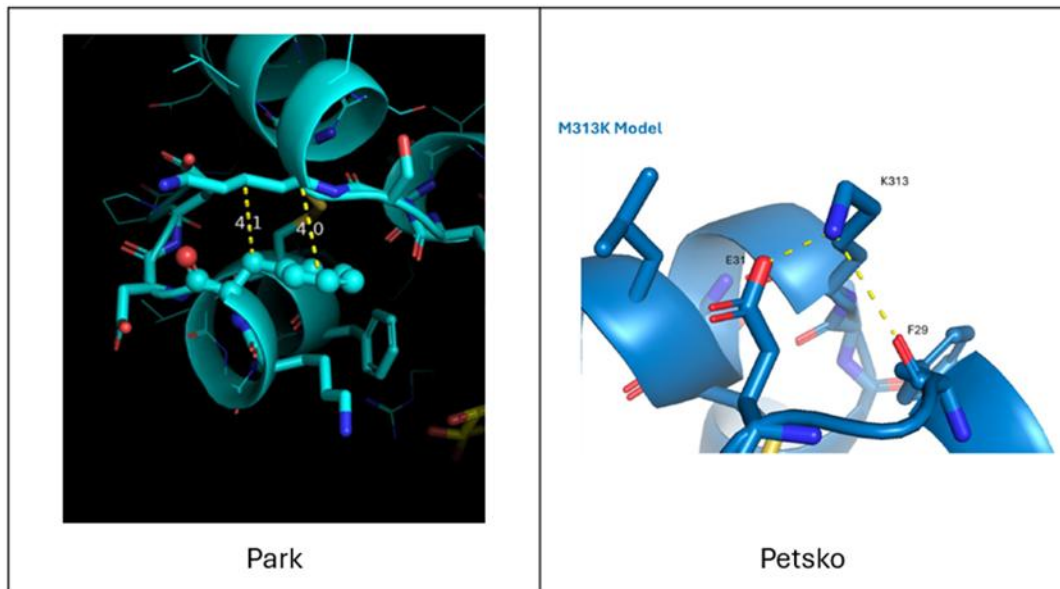
Dr. Park’s objective and unbiased assessment found M313K tolerated.

¹⁵⁵ POR, 84.

¹⁵⁶ EX1004, ¶¶ 26-32.

¹⁵⁷ EX1003, ¶¶ 225-226; EX1004, ¶¶ 41-43; Appendix D-1; EX1133, ¶ 342.

Notably, both he and Dr. Petsko identified the same M313:F29 interaction:¹⁵⁸



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.*”¹⁵⁹ He also testified he assessed substitutions position-by-position, at least twice, using the most frequently occurring amino acids *from his MSA analysis*.¹⁶⁰

EX2176 corroborates his testimony—it contains his observations and a tolerability rating for each substitution assessed at hundreds of positions.¹⁶¹

¹⁵⁸ EX1004, ¶¶ 113-120; EX2070, ¶¶ 408-410; EX1133, ¶¶ 349-351.

¹⁵⁹ EX1004, ¶¶ 102-103.

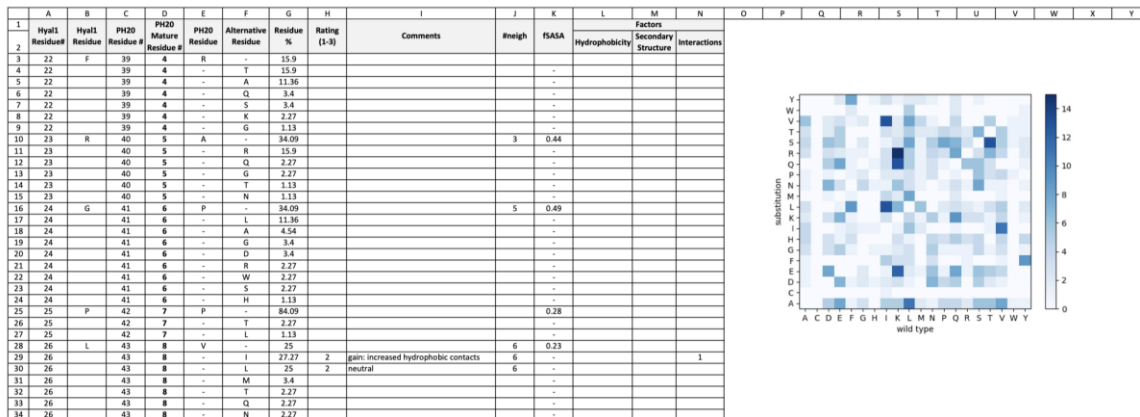
¹⁶⁰ EX2078, 170:22-171:17.

¹⁶¹ EX1004, ¶¶ 85-87; EX1133, ¶¶ 340-346.

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—the most prevalent residue in his MSA—*before* counsel asked him to explain them in his declaration.¹⁶²

Dr. Park’s “heat map” tracked the diversity of substitutions he assessed and prompted him to assess more substitutions.¹⁶³



¹⁶² EX2078, 320:10-20; EX2176, 38.

¹⁶³ EX2078, 300:2-301:2, 322:20-324:3; EX2176.

Evidence shows Dr. Park assessed ~830 substitutions in non-essential regions of PH20 and found ~750 tolerated, without bias toward any position or substitution.¹⁶⁴

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
5	A	43	S	81	Q	119	W	157	F	195	K	233	Q	271	I	309	I	347	Q
6	P	44	P	82	K	120	A	158	E	196	K	234	Q	272	V	310	M	348	E
7	P	45	R	83	I	121	R	159	K	197	P	235	S	273	F	311	R	349	Q
8	V	46	I	84	S	122	N	160	A	198	G	236	P	274	T	312	S	350	G
9	I	47	N	85	L	123	W	161	G	199	Y	237	V	275	D	313	M	351	V
10	P	48	A	86	Q	124	K	162	K	200	N	238	A	276	Q	314	K	352	C
11	N	49	T	87	D	125	P	163	D	201	G	239	A	277	V	315	S	353	I
12	V	50	G	88	H	126	K	164	F	202	S	240	T	278	L	316	C	354	R
13	P	51	Q	89	L	127	D	165	L	203	C	241	L	279	K	317	L	355	K
14	F	52	G	90	D	128	V	166	V	204	F	242	Y	280	F	318	L	356	N
15	L	53	V	91	K	129	Y	167	E	205	N	243	V	281	L	319	L	357	W
16	W	54	T	92	A	130	K	168	T	206	V	244	R	282	S	320	D	358	N
17	A	55	I	93	K	131	N	169	I	207	E	245	N	283	Q	321	N	359	S
18	W	56	F	94	K	132	R	170	K	208	I	246	R	284	D	322	Y	360	S
19	N	57	Y	95	D	133	S	171	L	209	K	247	V	285	E	323	M	361	D
20	A	58	V	96	I	134	I	172	G	210	R	248	R	286	L	324	E	362	Y
21	P	59	D	97	T	135	E	173	K	211	N	249	E	287	V	325	T	363	L
22	S	60	R	98	F	136	L	174	L	212	D	250	A	288	Y	326	I	364	H
23	E	61	L	99	Y	137	V	175	L	213	D	251	I	289	T	327	L	365	L
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

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

V. Conclusion

The challenged claims are unpatentable.

Dated: May 27, 2026

Respectfully Submitted,

/Jeffrey P. Kushan/

Jeffrey P. Kushan
 Reg. No. 43,401
 Sidley Austin LLP
 1501 K Street, N.W.
 Washington, D.C. 20005
 jkushan@sidley.com
 (202) 736-8914

¹⁶⁴ EX1133, ¶¶ 340-343.

Attorney for Petitioner

EXHIBIT LIST

No.	Exhibit Description
1001	U.S. Patent No. 12,091,692
1002	File History of U.S. Patent No. 12,091,692
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	Jedrzejewski 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 '692 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,” <i>Methods in Enzymology</i> , 388:176-186 (2004)
1017	Green, “Computer Graphics, Homology Modeling, and Bioinformatics,” <i>Protein Eng’g & Design</i> , 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,” <i>Curr. Opin. Biotechnol.</i> , (4):378-384 (2005)
1019	Hardy et al., “Assessment of contraceptive vaccines based on recombinant mouse sperm protein PH20,” <i>Reprod.</i> , 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,” <i>Am. J. Reprod. Immunol.</i> , (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,” <i>J. Biol. Chem.</i> , 277(33):30310-4 (2002)
1022	Primakoff et al., “Reversible Contraceptive Effect of PH-20 Immunization in Male Guinea Pigs,” <i>Biol Reprod.</i> , 56(5):1142-6 (1997)
1023	Tung et al., “Mechanism of Infertility in Male Guinea Pigs Immunized with Sperm PH-20,” <i>Biol. Reprod.</i> , 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,” <i>BioDrugs</i> , 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,” <i>FEBS Letters</i> , 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 & Moulton, “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 Res., 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 '692 Specifications
1046	Beasley & Hecht, "Protein Design: The Choice of <i>de Novo</i> 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, <i>DRUG: Hyaluronidase (human recombinant)</i> , 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 M313R Mutation
1073	Swiss Model Printout of PH20 Model with M313Y Mutation
1074	Swiss Model Printout of PH20 Model with M313P Mutation
1075	Swiss Model Printout of PH20 Model with M313L Mutation
1076	Declaration of Leif E. Peterson, II
1077-1078	[Reserved]
1079	Hunnicut 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	United States District Court – National Judicial Caseload Profile, navigable from: https://www.uscourts.gov/data-news/reports/statistical-reports/federal-court-management-statistics/federal-court-management-statistics-december-2024
1083	Table Showing Outcomes of Disputed Motions to Stay Pending IPRs in DNJ
1084	News Release: “Halozyme Raises 2025 Financial Guidance Ranges and Reports Strong First Quarter 2025 Results,” navigable from: https://www.prnewswire.com/news-releases/halozyme-raises-2025-financial-guidance-ranges-and-reports-strong-first-quarter-2025-results-302447541.html
1085	News Release: “Merck Breaks Ground on New \$1 Billion Biologics Center of Excellence in Wilmington, Delaware,” navigable from: https://www.merck.com/news/merck-breaks-ground-on-new-1-billion-biologics-center-of-excellence-in-wilmington-delaware/
1086	Halozyme Therapeutics, Inc. Q1 2025 Earnings Call Transcript (May 6, 2025)
1087-1112	[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)

No.	Exhibit Description
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)
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)

No.	Exhibit Description
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)
1149 [NEW]	Ten Have et al., “Cloning and characterization of the cDNA encoding the PH20 protein in the European red fox <i>Vulpes vulpes</i> ” Reprod. Fertil. Dev. 10(2):165-72 (1998)
1150 [NEW]	Chowpongpan 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)

No.	Exhibit Description
1154 [NEW]	Second Table Associating Citations from the '692 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)
1157 [NEW]	Chiti et al., "Rationalization of the effects of mutations on peptide and protein aggregation rates" Nature, 424:805-808 (2003)
1158 [NEW]	Wang et al., "Immunogenicity of protein aggregates-Concerns and Realities" Int. J. Pharmaceutics 431:1-11, (2012)
1159 [NEW]	Brachmann et al., "Genetic selection of intragenic suppressor mutations that reverse the effect of common p53 cancer mutations" EMBO Journal 17:1847-59 (1998)
1160 [NEW]	Poelwijk, Frank J., et al., "Empirical fitness landscapes reveal accessible evolutionary paths" Nature 445.7126 (2007): 383-386
1161 [NEW]	Primakoff, P. et al., "Purification of the guinea pig sperm PH-20 antigen and detection of a site-specific endoproteolytic activity in sperm preparations that cleaves PH-20 into two disulfide-linked fragments," Biology of Reproduction 38:921-934 (1988)
1162 [NEW]	Koch, C. et al., "A Comparison of the Immunogenicity of the Native and Denatured Forms of a Protein," APMIS 104:115-125 (1996)
1163 [NEW]	Leder, L. et al., "Genuine and Apparent Cross-Reaction of Polyclonal Antibodies to Proteins and Peptides," Eur. J. Biochem. 219:73-81 (1994)
1164	MERCK_PGR00355 - PTAB-PGR2021-00036-1 Merck-Genentech PGR
1165	MERCK_PGR00458 - PTAB-PGR2021-00036-16 Merck-Genentech PGR
1166	MERCK_PGR00462 - RE_2_25-cv-03179-ES-JRA_ HALOZYME, INC. v. MERCK SHARP & DOHME CORP.
1167	MERCK_PGR00094 - DNJ-2-25-cv-03179 Stipulation to Substitute Parties

No.	Exhibit Description
1168	MERCK_PGR00090 - DNJ-2-25-cv-03179 2025-07-14 [019] Corporate Disclosure Statement
1169 [NEW]	Declaration of Jeffrey P. Kushan (Petitioner's Reply)
1170 [NEW]	Murphy, K., "Janeway's Immuno Biology," (8th 2012), Chapters 1, 4, 8, 10, 11, 12, 15, and Appx I
1171 [NEW]	Yang, X. et al., "An Introduction to Epitope Prediction Methods and Software," Rev. Med. Virol., 19: 77–96 (2009)
1172 [NEW]	Bolland, S., "An Innate Path to Human B Cell Tolerance," Immunity, 29(5):667-9 (2008)
1173 [NEW]	Anderson, M. et al., "Projection of an Immunological Self Shadow Within the Thymus by the Aire Protein," Science, 298(5597):1395-401 (2002)
1174 [NEW]	Yewdell, J. et al., "Immunodominance in Major Histocompatibility Complex Class I-restricted T Lymphocyte Responses," Annu. Rev. Immunol., 17:51–88 (1999)
1175 [NEW]	Popova, L. et al., "Immunodominance of Antigenic Site B over Site A of Hemagglutinin of Recent H3N2 Influenza Viruses," PLoS One, 7(7):e41895 (2012)
1176 [NEW]	Gershoni, J. et al., "Epitope Mapping: The First Step in Developing Epitope-Based Vaccines," BioDrugs, 21(3):145-56 (2007)
1177 [NEW]	Rolland, M. et al., "Recognition of HIV-1 Peptides by Host CTL Is Related to HIV-1 Similarity to Human Proteins," PLoS One, 2(9):e823 (2007)
1178 [NEW]	Nelson, C. et al., "Peptides Determine the Lifespan of MHC Class II Molecules in the Antigen-Presenting Cell," Nature, 371(6494):250-2 (1994)
1179 [NEW]	Dormitzer, P. et al., "Influenza Vaccine Immunology," Immunol Rev., 239(1):167-77 (2011)
1180 [NEW]	Mantis, NJ., et al., "Secretory IgA 's Complex Roles in Immunity and Mucosal Homeostasis in the Gut," Mucosal Immunol., 4(6):603-11 (2011)

No.	Exhibit Description
1181 [NEW]	Siskind, G. and Eisen, H., “Effect of Variation in Antibody-Hapten Association Constant upon the Biologic Activity of the Antibody,” J Immunol., 95(3):436-41 (1965)
1182 [NEW]	Levine, B. and Levytska, V., “A Sensitive Hemagglutination Assay Method for Dinitrophenyl-Specific Antibodies. The Effect of Antibody Binding Affinity on Titers,” J Immunol., 98(3):648-52 (1967)
1183 [NEW]	Fauci, A. et al., “The Relationship between Antibody Affinity and the Efficiency of Complement Fixation,” J Immunol., 105(1):215-20 (1970)
1184 [NEW]	Laver, W. et al., “Epitopes on Protein Antigens: Misconceptions and Realities,” Cell 61:553-556 (1990)
1185 [NEW]	Lu, X. et al., “Anti-gp160 IgG and IgA Antibodies Associated with a Large Increase in Total IgG in Cervicovaginal Secretions from Human Immunodeficiency Virus Type I-Infected Women,” Journal of Infectious Disease, 167(5):1189-92 (1993)
1186 [NEW]	Kemp, T. et al., “Evaluation of Systemic and Mucosal Anti-HPV16 and Anti-HPV18 Antibody Responses from Vaccinated Women,” Vaccine, 26(29-30):3608-16 (2008)
1187 [NEW]	Montefiori, D. et al., “Magnitude and Breadth of the Neutralizing Antibody Response in the RV144 and Vax003 HIV-1 Vaccine Efficacy Trials,” Journal of Infectious Disease, 206(3):431-41 (2012)
1188 [NEW]	Cherr, G. et al., “The Dual Functions of GPI-Anchored PH-20: Hyaluronidase and Intracellular Signaling,” Matrix Biol., 20(8):515-25 (2001)
1189 [NEW]	Martin-Deleon, “Epididymal SPAM1 and its Impact on Sperm Function” Molecular and Cellular Endocrinology 250:114-121 (2006)
1190 [NEW]	Nolan et al., “The Safety of Recombinant Human Hyaluronidase PH20 in Nonclinical Models: An Overview of Toxicology, Pharmacology, and Impact of Anti-PH20 Antibodies,” Journal of Controlled Release, 374:369-383 (2024)

No.	Exhibit Description
1191 [NEW]	McCutcheon, J. et al., “HLA-B*0702 Antibody Epitopes are Affected Indirectly by Distant Antigen Residues,” <i>Hum Immunol.</i> , 36(2):69-75 (1993)
1192 [NEW]	Nobusawa, E. et al., “Comparison of Complete Amino Acid Sequences and Receptor-Binding Properties among 13 Serotypes of Hemagglutinins of Influenza A Viruses,” <i>Virology</i> , 182(2):475-85 (1991)
1193 [NEW]	CDC on H5N1 CDC Press Release: “Highly Pathogenic Avian Influenza A (H5N1) Virus Infection Reported in a Person in the U.S.” (Apr. 1, 2024)
1194 [NEW]	Lin, Y., et al., “Molecular cloning of the human and monkey sperm surface protein PH-20,” <i>Proc. Natl. Acad. Sci USA</i> 90:10071-10075 (November 1993) (EX2013 in Proceedings PGR2025-00003, -00004, -00006, -00009, -00017, -00024, -00030, -00033, and -00039)
1195 [NEW]	Zhang, H. et al., “Mouse Spam1 (PH-20) Is a Multifunctional Protein: Evidence for Its Expression in the Female Reproductive Tract,” <i>Biol Reprod.</i> , 69(2):446-54 (2003)
1196 [NEW]	Dunn, C. et al., “Transcription of the Human and Rodent SPAM1 / PH-20 Genes Initiates Within an Ancient Endogenous Retrovirus,” <i>BMC Genomics</i> , 6:47 (2005)
1197 [NEW]	Hirsch, C. et al., “The Ubiquitylation Machinery of the Endoplasmic Reticulum,” <i>Nature</i> , 458(7237):453-60 (2009)
1198 [NEW]	Singh, S., et al., “Solubilization and Refolding of Bacterial Inclusion Body Proteins,” <i>Journal of Bioscience and Bioengineering</i> 99:303-310 (2005)
1199 [NEW]	Li, M. et al., “Importance of Glycosylation and Disulfide Bonds in Hyaluronidase Activity of Macaque Sperm Surface PH-20,” <i>J Androl.</i> , 23(2):211-9 (2002)
1200	[Reserved]
1201 [NEW]	Rodriguez, L. et al., “Foot and mouth disease virus vaccines,” <i>Vaccine</i> 27:D90-D94 (2009)

No.	Exhibit Description
1202 [NEW]	Redwood, A. et al., “Viral Vectored Immunocontraception: Screening of Multiple Fertility Antigens using Murine Cytomegalovirus as a Vaccine Vector,” Vaccine, 25(4):698-708 (2007)
1203 [NEW]	Russell, M. et al., “Complement-Fixing Properties of Human IgA Antibodies. Alternative Pathway Complement Activation by Plastic-Bound, but not Specific Antigen-Bound, IgA,” Scand J Immunol., 30(2):175-83 (1989)
1204 [NEW]	Nikolova E. et al., “All Forms of Human IgA Antibodies Bound to Antigen Interfere with Complement (C3) Fixation Induced by IgG or by Antigen Alone,” Scand J Immunol., 39(3):275-80 (1994)
1205 [NEW]	Goodey, N. et al., “Allosteric Regulation and Catalysis Emerge via a Common Route,” Nat Chem Biol. 4(8):474-82 (2008)
1206-1223	[Reserved]
1224	Declaration of Kelly Grez – Protective Order Material
1225	Transcript of the Deposition of Kelly Grez, March 26, 2026
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)
1239	Press Release: “Merck and Schering-Plough to Merge” (Mar. 9, 2009)
1240	State of New Jersey, Certificate of Long Form Standing with Officers and Directors, Merck Sharp & Dohme LLC (Feb. 18, 2026)

No.	Exhibit Description
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
1244	Merck & Co., Inc., Form 851 – Affiliations Schedule for Tax Year Ending Dec. 31, 2024
2010	Primakoff, P., et al., “Fully effective contraception in male and female guinea pigs immunized with the sperm protein PH-20,” Nature 335:543-546 (October 6, 1988)
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
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
2077	Transcript of the Deposition of Dr. Sheldon Park, August 7, 2025
2078	Transcript of the Deposition of Dr. Sheldon Park, August 21, 2025
2108	Hunnicut, G. 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,” Biology of Reproduction, 55:80-86 (1996)
2114	Frayne, J. et al., “The potential use of sperm antigens as targets for immunocontraception; past, present and future,” Journal of Reproductive Immunology, 43:1-33 (1999)
2116	Chamley, L. et al., “Antisperm antibodies and conception,” Seminars in Immunopathology, 29:169-184 (2007)

No.	Exhibit Description
2119	Myles, D. et al., "Localized Surface Antigens of Guinea Pig Sperm Migrate to New Regions Prior to Fertilization," The Journal of Cell Biology, 99:1634-1641 (1984)
2120	Chan, C. et al., "Identification of Linear Surface Epitopes on the Guinea Pig Sperm Membrane Protein PH-20," Life Sciences, 64(22):1989-2000 (1999)
2137	Lipman, N. et al., "Monoclonal Versus Polyclonal Antibodies: Distinguishing Characteristics, Applications, and Information Resources," ILAR Journal, 46(3):258-268 (2005)
2164	Petsko, G., et al., Protein Structure and Function, New Science Press (2004)
2165	U.S. Patent Application Publication No. 2010/0143457 A1 to Wei et al., published June 10, 2010
2166	Petsko Patent Analysis Data
2167	Huang, C. et al., "Effect of sublingual administration with a native or denatured protein allergen and adjuvant CpG oligodeoxynucleotides or cholera toxin on systemic TH2 immune 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 5,587 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 27, 2026

Respectfully Submitted,

/Jeffrey P. Kushan/

Jeffrey P. Kushan

Reg. No. 43,401

Sidley Austin LLP

1501 K Street, N.W.

Washington, D.C. 20005

jkushan@sidley.com

(202) 736-8914

Attorney for Petitioner

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on this 27th 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:

Eldora L. Ellison, eellison-PTAB@sternekessler.com
R. Wilson Powers III, tpowers-PTAB@sternekessler.com
Jennifer Meyer Chagnon, jchagnon-PTAB@sternekessler.com
David H. Holman, dhholman-PTAB@sternekessler.com
Tyler C. Liu, tliu-PTAB@sternekessler.com
David J. Kappos, dkappos@cravath.com
Aubrey Haddach, ahaddach@halozyme.com
Louis P. Panzica, Jr., lpantzica-PTAB@sternekessler.com
Joshua A. Mack, jmack@halozyme.com
Lauren N. Martin, laurenmartin@quinnemanuel.com
Mark H. Snyder, msnyder@halozyme.com
Pratibha Khanduri, pkhanduri-PTAB@sternekessler.com
PTAB@sternekessler.com

Dated: May 27, 2026

Respectfully Submitted,

/Jeffrey P. Kushan/

Jeffrey P. Kushan
Reg. No. 43,401
Sidley Austin LLP
1501 K Street, N.W.
Washington, D.C. 20005
jkushan@sidley.com
(202) 736-8914
Attorney for Petitioner