

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyme Inc.,
Patentee.

Case No. PGR2025-00039
U.S. Patent No. 12,104,185

PETITIONER'S REPLY

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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 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 claimed sequences will "properly fold" is impossible and admits "billions" will not. And the evidence uniformly confirms Merck's prior art-based reasons why the D320K PH20₁₋₄₄₇ mutant was obvious.

II. Claim Construction and Scope

Halozyme concedes the claims require use of modified PH20 polypeptides that are not only enzymatically active,¹ but also cause increased diffusion ("spreading").² The disclosure explains that "spreading" is a distinct activity

¹ POR, 30-31 ("claims require modified PH20s with at least some hyaluronidase activity").

² Halozyme declined the Board's invitation to explain why the claims do not "require a PH20 polypeptide with sufficient spreading/diffusion activity". ID, 31-FN12.

identified using a different assay.³ For the claimed methods, PH20s must exhibit both characteristics, which requires proper folding.⁴ But properly folded PH20s are a “*structurally and functionally distinct genus*” within (but not identified in) the claims’ immense sequence space.⁵

The claim language and disclosure support these conclusions. One Halozyme expert (Dr. Simpson) testified the claim term “PH20” *provides context* to “modified PH20 polypeptide.”⁶ Another (Dr. Petsko) provided that context: “*POSAs think of PH20 as a folded protein.*”⁷ Dr. Simpson likewise testified that PH20’s definition and use in the disclosure led POSAs to view “PH20s” as being properly folded and enzymatically active.⁸ Together, the terms “PH20” and

³ Pet., 22-25; EX1026, 83:24-26; 194:35-195:3; EX1003, ¶¶ 101-110, 180-183; EX1133, ¶ 105.

⁴ EX1133, ¶¶ 59, 87, 105, 109.

⁵ EX2068, ¶ 33; EX2070, ¶¶ 51, 58, 128-FN12; EX1130, 62:13-23; 68:6-69:5; EX1133, ¶¶ 55-58, 77-80; § III.C.1(b).

⁶ EX1130, 57:9-58:4. *Bicon*, 952.

⁷ EX2070, ¶ 345.

⁸ EX1026, 50:31-32; EX1130, 60:14-61:12, 61:19-23; EX2070, ¶ 128-FN12; EX1133, ¶¶ 91, 94; Halozyme’s experts use “polypeptide” interchangeably

“modified PH20 polypeptide” require a “*properly folded* PH20 polypeptide with *at least one modification*,”⁹ and POSAs read the claims *as a whole* as requiring properly folded, active PH20s that cause spreading.¹⁰

Halozyme’s admissions on activity render irrelevant their comments about “inactive” mutants, and their reading of “modified PH20 polypeptide” is legal error as it gives “PH20” no weight.¹¹

III. The Claims Are Unpatentable Under § 112

Halozyme recognizes that § 112 requires a POSA to “predictably distinguish between and make and use the *full scope of modified PH20s* in the claimed method.”¹² To do so here requires the disclosure to describe and enable the

with “protein.” EX1133, ¶¶ 87-89; EX1131, 32:8-37:20; EX2068, ¶¶ 283, 353, 376; EX2070, ¶¶ 50, 423.

⁹ EX1133, ¶¶ 87, 92-101.

¹⁰ Pet., 26-27, 65-66; EX1026, 90:33-34; EX1003, ¶¶ 134-136; EX1133, ¶¶ 105-110. *TIP*, 1375.

¹¹ POR, 30-34; EX1130, 55:23-56:7, 57:9-58:4; *Bicon*, 950-51.

¹² POR, 4, 54.

modified PH20s that are active and cause spreading within the claims' sequence space.¹³ It does neither.

A. The Claims Define Structurally Heterogenous Genera

Merck's description of the claims' "sequence space" is not a "parlor trick"—Halozyne's experts *confirmed* it was correct ($\sim 10^{49}$ to $\sim 10^{66}$ sequences).¹⁴ And it is undisputed that the claims permit (i) modifications at any position, (ii) additions/deletions, and (iii) substitutions to any of 19 other amino acids.¹⁵

The claims' sequence space contains immense structural diversity with an unknowable subset being sequences that properly fold into active PH20s that cause spreading.¹⁶ Active, spreading PH20s exist within a portion of one corner of the

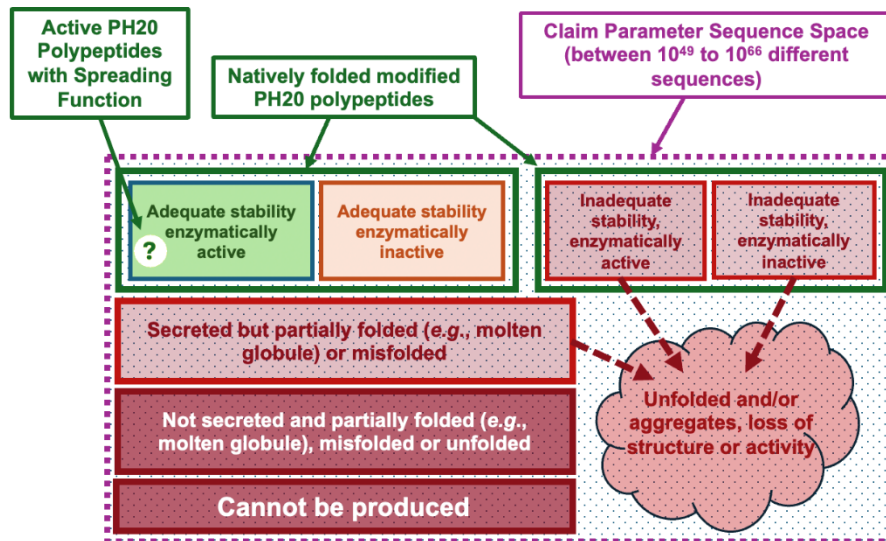
¹³ Pet., 32-37, 69-70, 73; *Duke*, 1310; *Gilead*, 1356-57.

¹⁴ POR, 4; Pet., 21-22; EX1003, ¶¶ 122-124; 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.

¹⁵ Pet., 19-20; EX1003, ¶ 121; EX1026, 53:1-7, 68:18-34; EX1130, 90:25-91:5; EX1131, 54:24-55:6.

¹⁶ EX1130, 92:2-94:14; EX1131, 61:15-62:5; EX1133, ¶¶ 77-80, 46.

sequence space.¹⁷ Many sequences will never leave the cell (*i.e.*, cannot be made or will not be secreted), while others will yield unstable PH20s that exist in unfolded and/or aggregated forms, including partially-folded, misfolded, or initially natively folded sequences.¹⁸



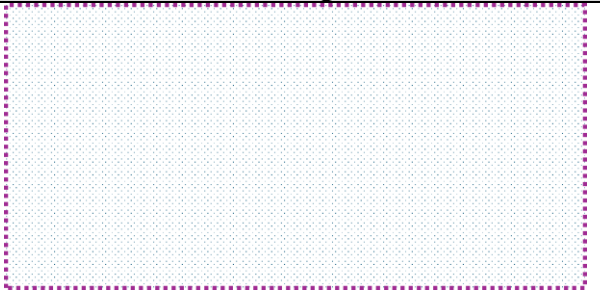
Halozyme’s experts contend the claims define a “structurally homogeneous” set of modified PH20s but disagree about what that set constitutes: Dr. Petsko says it consists of *folded* PH20s,¹⁹ while Dr. Simpson portrays it as *the entire sequence*

¹⁷ POR, 5, 55-56; EX1131, 78:6-25; EX2068, ¶¶ 105-106; EX2070, ¶¶ 51, 128-FN12, 420.

¹⁸ EX1133, ¶¶ 77-80, 329-336; EX1131, 42:20-43:7; 47:7-19.

¹⁹ 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.

space.²⁰

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

Halozyme embraces this confusion—it contends *both* sets are “structurally homogeneous.”²¹ They plainly are not—even active PH20s are structurally heterogeneous.²²

B. Determining Which Modified PH20s in the Sequence Space Cause Spreading is Impossible

The Petition explained why it was impossible to determine which of the 10⁴⁹+ sequences within the claims’ sequence space can be used in the claimed methods.²³ Dr. Petsko testified it is impossible to calculate or experimentally

²⁰ EX2068, ¶ 33; EX1130, 89:16-90:16; EX1133, ¶¶ 52-57.

²¹ POR, 55, 57-58, 6-7.

²² Pet., 9-10; EX1003, ¶¶ 55-61, 66, 69, 149, 163; EX1133, ¶¶ 40-44, 60-61, 77-80.

²³ Pet., 47-48, 52-58, 62-65, 71-73; EX1003, ¶¶ 165-166; 173-184, 196-199, 202-203; EX1133, ¶¶ 113, 121, 124, 128.

determine the portion of the sequence space that will properly fold and be enzymatically active (much less cause “spreading”), and he could not approximate its size.²⁴ He also admits “billions” of sequences will not properly fold (*i.e.*, those with “substantial modifications to residues known to be invariant because they are involved in ... protein structure”).²⁵ But the disclosure does not identify which residues are involved in protein structure, while the claims encompass sequences with changes to any and all of them (§ 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.²⁶ Dr. Hecht explained why directed evolution techniques could not,²⁷ and Drs. Petsko and Naismith confirmed his opinions.²⁸ 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).²⁹

²⁴ EX1131, 63:19-64:17.

²⁵ EX2070, ¶ 347.

²⁶ Pet., 14-16, 74-82.

²⁷ EX1003, ¶¶ 193-203.

²⁸ EX1133, ¶ 124; EX2070, ¶¶ 347, 349.

²⁹ EX1133, ¶¶ 126-129; EX1004, ¶¶ 169-171.

Total Change	Total Sequences	#
1	1	1.00E+00
2	8,209	8.21E+03
3	33,615,865	3.36E+07
4	91,558,465,705	9.16E+10
5	186,596,321,227,165	1.87E+14
6	303,517,942,476,466,000	3.04E+17
7	410,458,053,168,718,000,000	4.10E+20
8	474,666,287,784,769,000,000,000	4.75E+23
9	479,176,644,423,119,000,000,000,000	4.79E+26
10	428,970,636,184,228,000,000,000,000,000	4.29E+29
11	344,807,556,668,326,000,000,000,000,000,000	3.45E+32
12	251,365,489,629,915,000,000,000,000,000,000,000	2.51E+35
13	167,577,568,481,621,000,000,000,000,000,000,000,000	1.68E+38
14	102,880,123,712,796,000,000,000,000,000,000,000,000,000	1.03E+41
15	58,509,635,827,633,600,000,000,000,000,000,000,000,000,000	5.85E+43
16	30,982,939,889,196,900,000,000,000,000,000,000,000,000,000,000	3.10E+46
17	15,344,374,245,979,500,000,000,000,000,000,000,000,000,000,000,000	1.53E+49

Rational design (*e.g.*, selecting 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.³⁰ Likewise, computational tools could not reliably model protein structures with 10+ changes from native.³¹ Evaluating even a sliver of the claims' sequence space this way is impossible.³²

³⁰ EX1004, ¶¶ 160-162; EX1003, ¶ 242; EX1133, ¶¶ 132-134, 262-265, 270, 272-276, 283-286.

³¹ EX1027, 6-9; EX1133, ¶¶ 126, 130, 134-135, 259.

³² EX1133, ¶¶ 131-134.

Consequently, in 2011-2012, POSAs would need to perform an impossible scale of experiments to identify which modified PH20s with 5+ mutations will properly fold and exhibit activity.³³

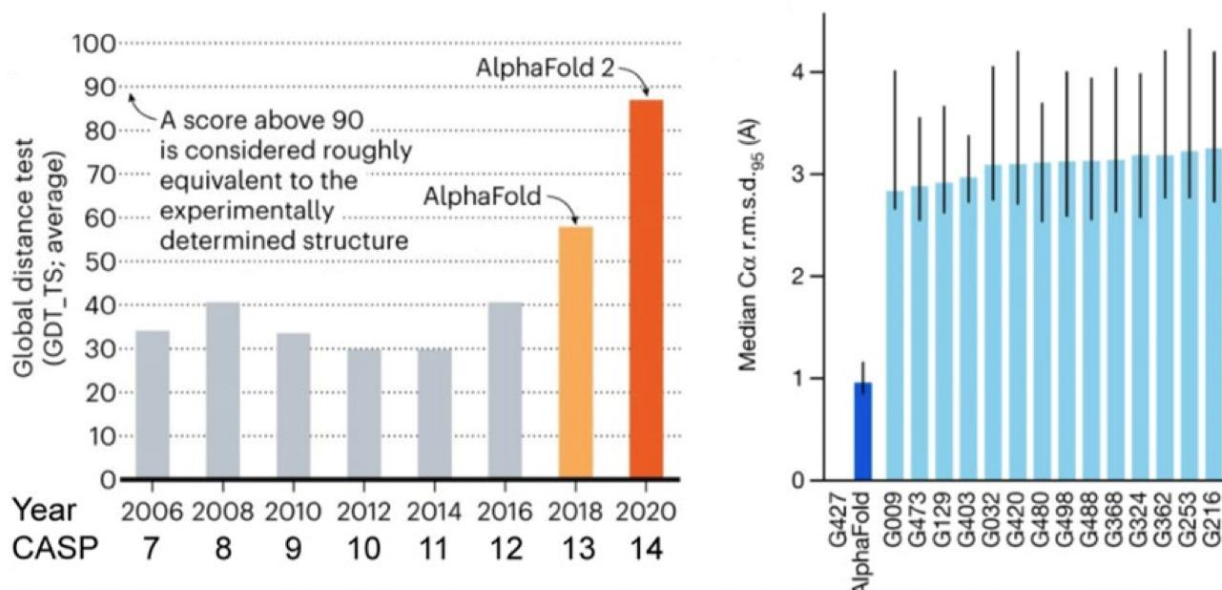


Figure 6. Left: progress of the CASP performance over the years for the best models and the most difficult targets.³⁸ Right: performance of AlphaFold2 relative to the top 15 entries by other groups in CASP14. Data are the median coordinate error and the 95% confidence interval of the median, estimated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

To be used in the claimed methods, modified PH20s must not only be active but “act as a spreading or diffusing agent” *in vivo*—activity is a prerequisite, but alone is insufficient (*see* § II).³⁴ But an unidentified portion of the 10⁴⁹+ D320 mutants in the claims’ sequence space ***lack*** activity and are ***incapable*** of

³³ EX1133, ¶¶ 133-134; EX1003, ¶¶ 165, 202-203; EX1004, ¶¶ 160-162.

³⁴ ID, 31-FN12; Pet., 23-25, 65-67, 70-71, 76-78; EX1133, ¶ 105.

spreading.³⁵ To identify the PH20s that do, the disclosure instruct testing each in mice.³⁶ It does not, however, identify *any* structural features responsible for “activity” or “spreading” functions.³⁷

By 2011-2012, PH20 was reported to be involved in cell signaling and sperm-egg interactions.³⁸ Chao postulated a role for the Hyal-EGF domain in these functions, and thus POSAs would have believed that domain could play a role in “spreading.”³⁹ But the disclosure does not describe the Hyal-EGF domain, much less explain how it can be modified without affecting *both* activity *and* spreading functions.⁴⁰ And only one *unclaimed* PH20₁₋₄₄₇ mutant (“F204P”) was shown to have “spreading” functionality, and it is uncharacterized.⁴¹ Given the unpredictability of making unconstrained modifications to PH20, a POSA could

³⁵ EX2070, ¶ 347; EX1133, ¶ 105; EX1003, ¶¶ 165-175.

³⁶ EX1026, 194:35-195:11; EX1003, ¶ 180.

³⁷ Pet., 66-67; EX2070, ¶¶ 347-348.

³⁸ EX1003, ¶ 177; EX1079, 84; EX1006, 6916-17.

³⁹ Pet., 66-67; EX1006, 691; EX1003, ¶¶ 85-86, 89-90, 98, 178; EX1133, ¶¶ 105, 188-189, 191-193.

⁴⁰ EX1003, ¶ 88; EX1133, ¶¶ 105, 187, 190-193, 200.

⁴¹ EX1026, 316:21-317:25; Pet., 32, 65-67; EX1003, ¶¶ 176, 180-181, 198.

not have predicted which multiply-modified PH20s within the claims' sequence space cause spreading.⁴²

In *Teva*, the Federal Circuit found a claimed method of treating headaches not invalid under § 112 because there was no dispute that “all humanized anti-CGRP antagonist antibodies treat headaches,”⁴³ specifically crediting appellee's admission that “anti-CGRP antagonist antibodies *themselves* and methods of making them were well known, replete, or extensively described in the prior art.”⁴⁴ The opposite is true here: it is **undisputed** that (i) the sub-genus of modified PH20s within the claims' sequence space that are **both** active **and** cause spreading is **unknown** and **impossible to identify**, (ii) **no claimed** D320 mutants were shown to cause spreading, and (iii) the claims encompass (but do not identify) many PH20s that will not properly fold and cannot be used in the methods.⁴⁵

This evidence is dispositive on written description **and** enablement.⁴⁶ If a POSA cannot identify from the disclosure which modified PH20s can be used to

⁴² Pet., 66-67; EX1133, ¶¶ 113-135; EX1003, ¶¶ 181, 198.

⁴³ *Teva*, 13, 19-20, 23-24.

⁴⁴ *Teva*, 12-13.

⁴⁵ Pet., 76-77, 84; EX1003, ¶ 198; EX1133, ¶¶ 77-80, 105, 113, 125-126.

⁴⁶ Pet., 32, 52-56, 74-81.

increase delivery of a therapeutic agent, that disclosure cannot demonstrate possession of all such claimed methods. The impossibility of performing testing to identify those PH20s far exceeds undue experimentation. And, tellingly, Halozyme disclaimed (rather than defended) similar methods in related proceedings.⁴⁷

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.*”⁴⁸ 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 the common structural features of the modified PH20s used in the claimed methods.⁴⁹ In response, Halozyme contends it “characterizes the common structural features” of

⁴⁷ PGR2025-00030, claims 36-40; PGR2025-00033, claims 36-40; PGR2025-00042, claims 37-40; PGR2025-00046, claims 37-40.

⁴⁸ *Ariad*, 1350; *Gilead*, 1356.

⁴⁹ Pet., 56-58; EX1003, ¶¶ 69, 146-152, 158, 162-166.

the claimed genera of modified PH20 polypeptides.⁵⁰ Properly folded PH20s are the only PH20s in the claims' sequence space that could have common structural features, yet the disclosure entirely fails to identify what those common features are and which of the 10⁴⁹+ sequences will fold to have them.

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

Halozyme contends the "95% sequence identity" requirement is a "common structural feature" of the PH20s used by the claimed methods.⁵¹ It is not—it is a *mathematical* requirement (*i.e.*, are two sequences 95%+ identical?).⁵²

"Structural features" are *physical* attributes of *a* PH20 polypeptide (*e.g.*, a particular amino acid at a position or features of its tertiary structure).⁵³ Common "structural features" are the *set* of those *physical* attributes "common to the members of the genus" (properly folded, active PH20s).⁵⁴

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

⁵⁰ POR, 37.

⁵¹ POR, 55; EX2068, ¶ 254; EX1131, 65:18-66:17.

⁵² EX1026, 66:32-67:9, 68:18-34; EX1133, ¶¶ 80, 83.

⁵³ EX1003, ¶ 152; EX1133, ¶¶ 83-86.

⁵⁴ *Duke*, 1311.

the claimed PH20 polypeptides must be found.⁵⁵ Each “primary sequence” is, *by definition*, up to 10% *different* than every other one in the set.⁵⁶

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

Halozyme contends the active PH20s used in the claimed methods “all share a tertiary structure a POSA would recognize as an ‘alpha-beta barrel *fold*.’”⁵⁷ But Halozyme misleadingly portrays the α/β barrel *motif* as the *entire* tertiary structure of PH20s, including the catalytic site.⁵⁸ 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...”⁵⁹

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

⁵⁵ *Ariad*, 1349.

⁵⁶ EX1133, ¶ 48-51.

⁵⁷ POR, 11; EX2068, ¶¶ 33, 106, 289, 305; EX2070, ¶¶ 421, 51, 58, 101, 128, 345, 396, 400.

⁵⁸ POR, 45-47; EX2070, ¶ 51.

⁵⁹ EX1131, 69:2-5; EX1133, ¶¶ 155-159, 162.

enzymatic activity.⁶⁰ The *tertiary* structure of human PH20, however, is not described in the disclosure—it was not reported until 2024.⁶¹

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

- (i) the PH20 active site, which spatially positions catalytic residues D111, E113, and E249 and substrate binding residues R176, R246, and R252 correctly within a folded substrate-binding cleft;⁶²
- (ii) a “distorted” (non-canonical) PH20 α/β barrel motif;⁶³ and
- (iii) the Hyal-EGF domain (Leu336 to Asp416 in PH20).⁶⁴

Each is essential to active PH20s—mutations of active site residues⁶⁵ or deletion of

⁶⁰ EX2070, ¶¶ 51, 128-FN12; EX1131, 78:6-25; 86:23-87:7; EX1003, ¶¶ 36, 62, 163, 239; EX1133, ¶¶ 17, 58-59, 96-97, 105, 161.

⁶¹ EX1126, 1068.

⁶² EX1026, 80:11-18; EX1010, 9437; EX1133, ¶¶ 96, 169.

⁶³ EX1008, 824, 829, 833; EX1006, 6913; EX1133, ¶¶ 142-152.

⁶⁴ EX1006, 6913; EX1010, 9441; EX1003, ¶¶ 84-91; EX1004, ¶¶ 96-99; EX1133, ¶¶ 191-195.

⁶⁵ EX1003, ¶ 89; EX1133, ¶¶ 96, 306; EX2070, ¶ 128-FN12.

all or part of the Hyal-EGF domain “abolish[ed]” activity.⁶⁶ The disclosure provides no guidance on how multiple mutations impact these structural features.⁶⁷

(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 PH20.⁶⁸ 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.⁶⁹ It also does not identify any amino acid sequences for the PH20 α/β barrel motif or its elements.⁷⁰ Nor does it reference the “distorted” (α/β) barrel motif in human PH20, explain that it does not contain PH20’s active site, or explain how it differs from the canonical α/β structure.⁷¹ *Any* of these omissions doom Halozyme’s attempt to retroactively import into the

⁶⁶ EX1003, ¶¶ 90, 98; EX1133, ¶ 189; EX1010, 9439, 9441; EX1011, 813-14.

⁶⁷ Pet., 48, 57-61, 65-66.

⁶⁸ POR, 37-40, 55; EX2068, ¶¶ 294-295, 305; EX2070, ¶¶ 51, 128, 396, 419.

⁶⁹ EX1133, ¶¶ 167-172.

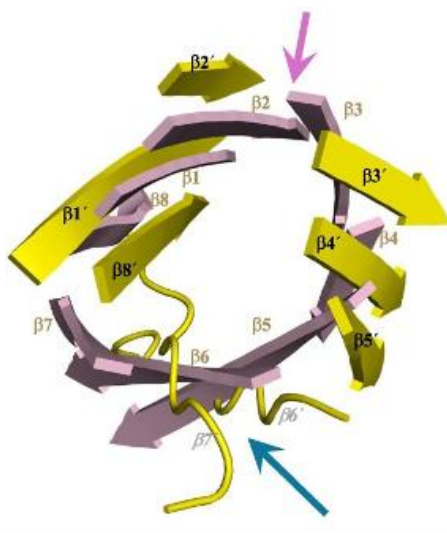
⁷⁰ EX1133, ¶¶ 153, 170.

⁷¹ EX1133, ¶¶ 154-160, 167-170; EX1008, 824-825, 829, 833; EX1006, 6911-13; EX1033, 1027.

disclosure the “ α/β barrel” label as a “structural feature” of the claimed PH20s.⁷²

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.⁷³ It has a large gap, two irregular strands, and its shape is distorted (PH20: yellow, canonical: pink).⁷⁴



A POSA thus could not have used knowledge of the *canonical* “ α/β barrel” motif to visualize the *structurally distinct* PH20’s α/β motif because the two *are*

⁷² *Juno*, 1339; *Boston*, 1366-67.

⁷³ EX1008, 833; EX1133, ¶¶ 143-149.

⁷⁴ EX1033, 1027-28; EX1133, ¶ 146.

materially different.⁷⁵ The conserved features of the hyaluronidase active site that Dr. Petsko referenced also *are not contained within* the PH20 α/β motif.⁷⁶ And the words “PH20 α/β barrel” do not describe the *structure* of the PH20 active site.

Knowledge of individual residues in the PH20 sequence necessary for catalysis does not describe the *structure* of the human PH20 active site. 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 PH20.⁷⁷ This is unknowable for the vast majority of the genus (*i.e.*, *multiply*-modified PH20s).

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

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

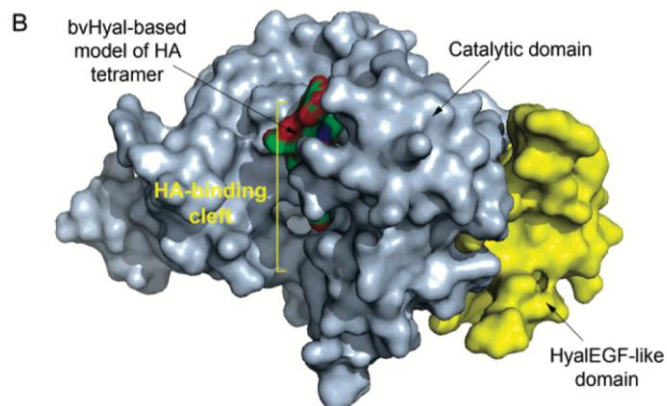
The disclosure contains no description of the Hyal-EGF domain or its sequence, despite its essential role in the structure and function of enzymatically

⁷⁵ EX1133, ¶¶ 137-141, 146, 152-154; EX2070, ¶ 52.

⁷⁶ EX1008, 829; EX1133, ¶ 151.

⁷⁷ EX1003, ¶¶ 42, 59; EX1133, ¶¶ 96-97.

active PH20s.⁷⁸ 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”).⁷⁹



The Petition explained the Hyal-EGF domain was a structural feature essential to folding and activity of PH20s.⁸⁰ But there is no mention in the disclosure of this domain.⁸¹ That omission is fatal to written description, because the Hyal-EGF domain is a “common structural feature” of the genera of active PH20s required for the claimed methods.⁸²

⁷⁸ EX1133, ¶¶ 187, 192, 195.

⁷⁹ EX1130, 114:23-116:9; EX1003, ¶¶ 88-91; EX1004, ¶¶ 97-99; EX1006, 6915-6917 (Figs. 2, 4); EX1010, 9439, 9441.

⁸⁰ Pet., 41-44, 56-57.

⁸¹ EX1003, ¶ 88; EX1133, ¶¶ 187, 190-193.

⁸² EX1003, ¶¶ 98-100, 178; EX1133, ¶¶ 167, 170, 190-193.

Dr. Petsko strains to downplay Hyal-EGF's importance to the structure and activity of PH20s.⁸³ But Zhang reported that deleting the Hyal-EGF "abolished" enzymatic activity and prevented secretion, while Dr. Simpson explained "the EGF-like motif is not a separate domain" but instead "packs tightly against the rest of the protein as a single domain."⁸⁴

The disclosure's reference to a "common core hyaluronidase domain" shared by PH20s (3-339 of PH20) also does not identify the Hyal-EGF domain—it terminates 4-5 residues into it (below).⁸⁵ That "domain" also is not a "common structural feature" of active PH20s—mutants truncated at position 340 do not "properly fold"⁸⁶ and lack activity.⁸⁷ Halozyme's experts do not contend otherwise.⁸⁸

⁸³ EX2070, ¶¶ 209, 211.

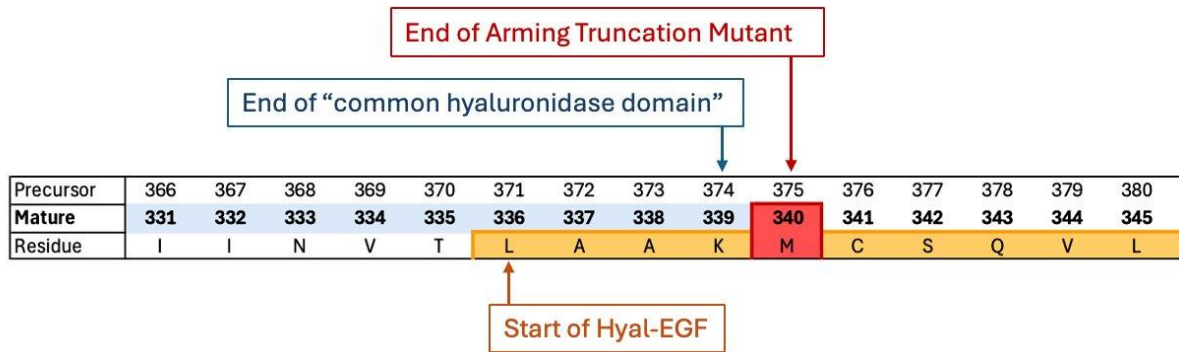
⁸⁴ EX2068, ¶ 143; EX1010, 6913; EX1133, ¶¶ 187-189.

⁸⁵ EX1026, 79:20-31.

⁸⁶ EX1133, ¶¶ 163-165.

⁸⁷ EX1011, 813-814; EX1133, ¶¶ 194-195.

⁸⁸ EX1133, ¶¶ 163-165.



Halozyme contends “a POSA’s knowledge included possession” of homology models based on the bee venom hyaluronidase (bvH) and Hyal-1 structures published before 2011.⁸⁹ But written description is judged by the disclosure, not a POSA’s *mind*, and this disclosure describes *no* structural or homology models of any kind. Halozyme’s attempt to remedy these shortcomings also *ignores critical structural distinctions* between hyaluronidases, including that bvH *is* active without an EGF domain while Hyal1 *is not*.⁹⁰ In Dr. Simpson’s words, bvH “did not provide a complete picture of the structure for” human PH20.⁹¹

⁸⁹ POR, 11.

⁹⁰ EX1133, ¶¶ 165, 191-193.

⁹¹ EX2068, ¶ 125.

2. Single Substitutions Provide No Structure-Function Correlation

Halozyme contends examples of singly-substituted PH20s “provide structure/function correlations POSAs can use to identify the active 95% identical” multiply-modified PH20s.⁹² That is incorrect.

First, effects on PH20 folding and activity from single substitutions cannot predict effects of *combinations* of changes.⁹³ See § III.D.1. Even positions Dr. Petsko labeled “100% tolerated” varied extensively in activity, demonstrating the unpredictability of single substitutions.⁹⁴

Second, listing options and requiring a POSA to figure out which combinations yield active PH20s is not a description of any multiply-modified PH20—it is a research plan.⁹⁵

Finally, problems with the disclosure’s experimental data and their reporting negate the “functional” insights Halozyme contends exist, and the disclosure does

⁹² POR, 41-42.

⁹³ EX1003, ¶¶ 54-61, 147-150; EX1133, ¶¶ 116, 234-235, 254-261.

⁹⁴ EX1133, ¶¶ 266-271.

⁹⁵ *Idenix*, 1164-65.

not describe the PH20 tertiary structure that must be maintained, much less which combinations of changes maintain that structure.⁹⁶

3. Representative Species Not Described

Halozyme points to 7 supposed “examples” of “D320 modified PH20s.”⁹⁷ None are described in its disclosure or were actually made.⁹⁸ None address the unpredictability of making 5+ changes to a *native* PH20 sequence.⁹⁹ They also are not representative—they do not reflect the types or physicochemical diversity of modified PH20s being claimed, nor do they represent PH20s having C-terminal truncations of varying length and/or substitutions at positions past 447, for which no examples are provided.¹⁰⁰

Halozyme’s overlaid models can be ignored.¹⁰¹ They (i) all suffer from Dr.

⁹⁶ § III.D.3; Pet., 55-58; EX1003, ¶¶ 67-76, 105-106, 143; EX1133, ¶¶ 153, 248-253, 309-311.

⁹⁷ POR, 45-49; EX2070, ¶¶ 423-426.

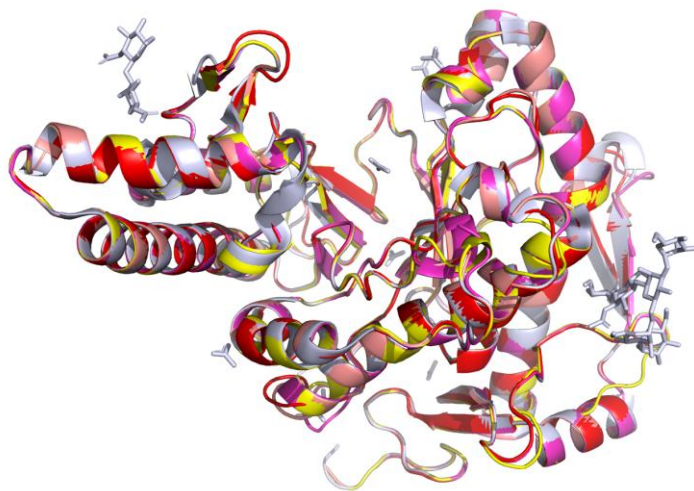
⁹⁸ EX1133, ¶¶ 115-120.

⁹⁹ EX1133, ¶¶ 115-120; EX1003 ¶¶ 55-59.

¹⁰⁰ Pet., 38-39, 43-44, 59-63, 75; EX1003, ¶¶ 94, 147-150, 162-166, 173; EX1133, ¶¶ 77-80, 115-120.

¹⁰¹ POR, 37-41; EX2070, ¶¶ 423-426.

Petsko’s flawed “ α/β barrel” opinions (§ III.C.1(c)) and (ii) cannot reveal spatial differences <1.5 Å or any physicochemical or epistatic effects.¹⁰² Notably, overlaying models of the 5 human hyaluronidases yields a virtually identical perception of identical structures despite their known functional differences.¹⁰³



D. Enablement

The scale of experimentation required to practice the full scope of claimed properly folded, active PH20s is beyond undue—it is impossible, rendering the claims non-enabled. *See* § III.B.

Halozyme now proposes a new research plan: use the data in the patent “as [a] starting point,” select unidentified combinations of substitutions using Dr.

¹⁰² EX1133, ¶¶ 199, 283-286.

¹⁰³ EX1133, ¶¶ 185-186.

Petsko's positional tolerance analysis (avoiding certain positions), and evaluate each mutant in a PH20 homology model.¹⁰⁴ But executing that plan with only 5 substitutions, a fraction of the claim scope, would require billions of days to practice.¹⁰⁵ In 2011-2012, a POSA could not use this new plan (which is nowhere described in the disclosure) to predict which PH20s with 5+ changes will properly fold and exhibit activity (and, further, which can be used in the claimed methods).¹⁰⁶

1. The Effects of Multiple Mutations Are Unpredictable

When *multiple* mutations are made together they can affect a protein's structure, capacity to fold, and stability differently than how each substitution alone does. Combinations can disrupt or alter secondary and higher order structures, change their relative positioning, and even form new motifs.¹⁰⁷ Combinations also can affect the folding process,¹⁰⁸ cause remote effects not

¹⁰⁴ EX2070, ¶¶ 323-324, 351, 355-360, 364; EX1130, 93:20-24; EX1133, ¶ 198.

¹⁰⁵ EX1133, ¶¶ 133-134; Pet., 56, 80-81; EX1003, ¶ 203.

¹⁰⁶ EX1003, ¶¶ 61, 163-166, 196; EX1133, ¶¶ 262-265, 280, 319, 327.

¹⁰⁷ Pet., 11-12, 56-58; EX1003, ¶¶ 55-61, 163; EX1133, ¶¶ 234, 254-257, 264, 332, 224.

¹⁰⁸ EX1003, ¶¶ 55, 59, 149, 163, EX1133, ¶¶ 97, 131.

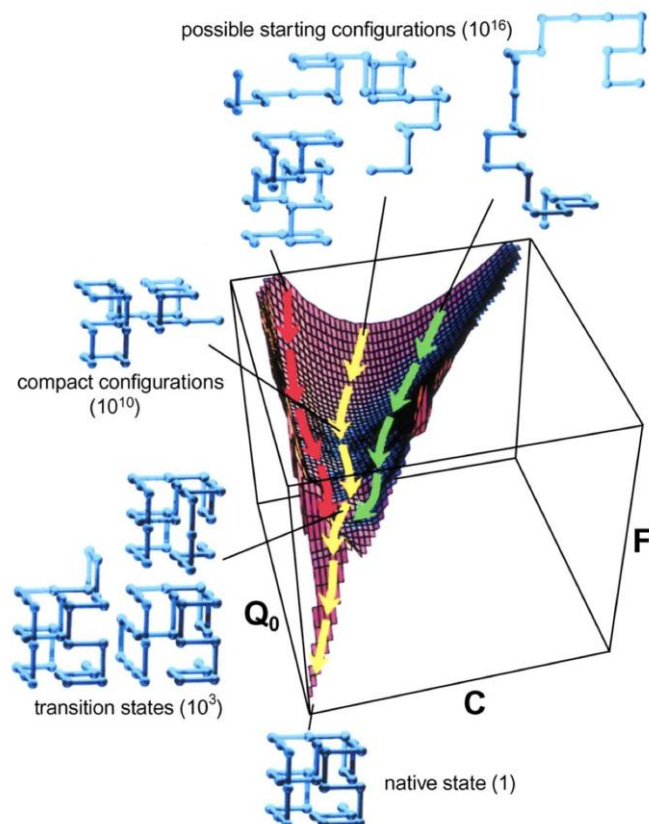
observed with individual changes (“epistasis”), and alter how the protein reacts to subsequent changes.¹⁰⁹ The unpredictable effects of combinations of mutations prevent a POSA from being able to predict whether the vast majority of the multiply-modified PH20s in the sequence space will “properly fold,” exhibit activity much less increase delivery of therapeutic agents.¹¹⁰

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.¹¹¹

¹⁰⁹ EX1133, ¶¶ 127-128, 257-261; EX1131, 79:15-22, 89:21-90:24; 270:9-17.

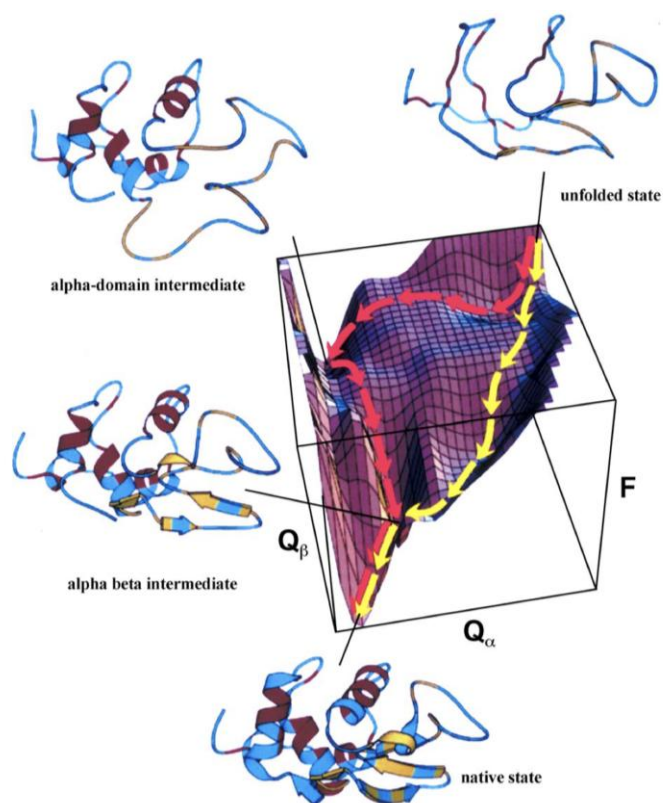
¹¹⁰ Pet., 75-78; EX1003, ¶¶ 61, 163-166, 176, 180-181, 198, 153-154; EX1133, ¶¶ 125, 254-261; EX1160, 383-85.

¹¹¹ Pet., 11-12; EX1003, ¶¶ 55-59; EX1133, ¶¶ 68-72; EX1136, 4-6.

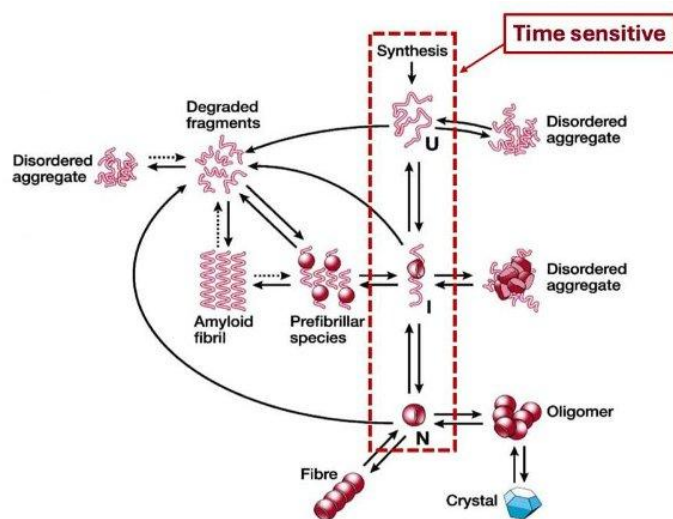


Intermediate conformations can get trapped in energetic “valleys,” preventing them from efficiently folding into the native state:¹¹²

¹¹² EX1133, ¶¶ 70-72; EX1136, 4-6.



The folding process also must complete quickly, otherwise the protein will degrade:¹¹³



¹¹³ EX1131, 43:15-23; EX1133, ¶¶ 64-77; EX1139, 351.

All these challenges exist for the *native* PH20 sequence evolutionarily selected due to its efficient folding and stability. Mutated sequences do not share those benefits—mutations alter the protein’s net free energy of stabilization in ways a POSA cannot predict, and affect each sequence’s ability to fold and its stability.¹¹⁴ Even *one* mutation can prevent folding, cause misfolding or incomplete folding, or instability that causes the PH20 to unfold outside the cell and form aggregates, as Dr. Petsko’s textbook illustrates:¹¹⁵

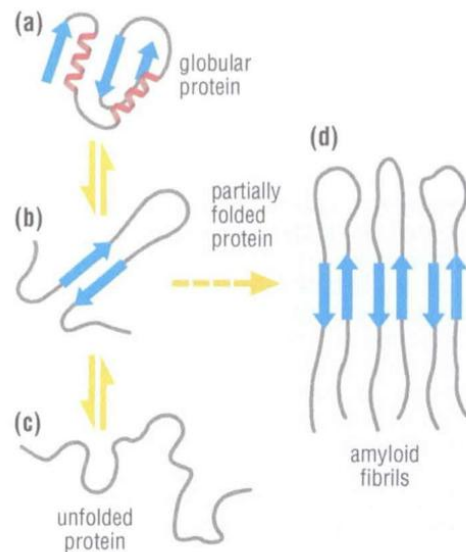


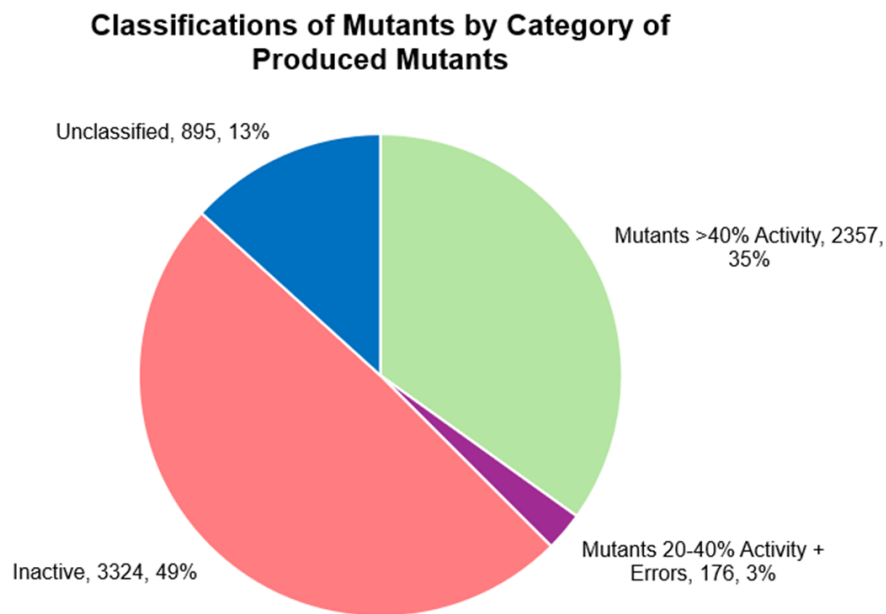
Figure 4-53 A possible mechanism for the formation of amyloid fibrils by a globular protein The correctly folded protein (a) is secreted from the cell. Under certain conditions, or because it contains a mutation, the protein unfolds partially (b) or completely (c); the unfolded forms can also refold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

¹¹⁴ EX1003, ¶¶ 62-65; EX1133, ¶ 131, EX1131, 99:4-22, 102:1-9.

¹¹⁵ EX2164, 160; EX1133, ¶¶ 73-76; EX1003, ¶ 54; EX1131, 41:22-42:11.

And multiply-mutated PH20 sequences may adopt the **wrong** structure.¹¹⁶

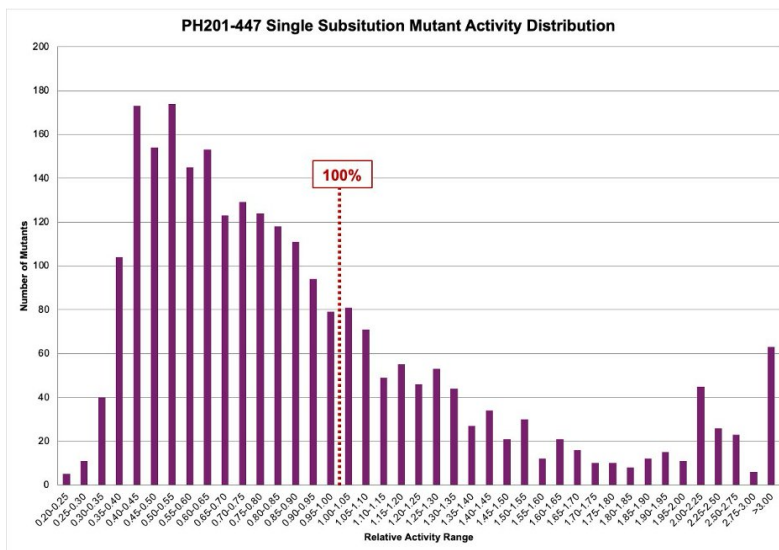
Halozyme's experts downplay this unpredictability. They contend a POSA could pick combinations of "tolerated" mutations using the data in the disclosure.¹¹⁷ That ignores not just the science but the data itself, which shows most single mutations were deleterious.¹¹⁸



¹¹⁶ EX1003, ¶¶ 55-56; EX1133, ¶¶ 73-79.

¹¹⁷ EX2070, ¶¶ 317-324, 355-359; EX2068, ¶¶ 311-14, 380-82.

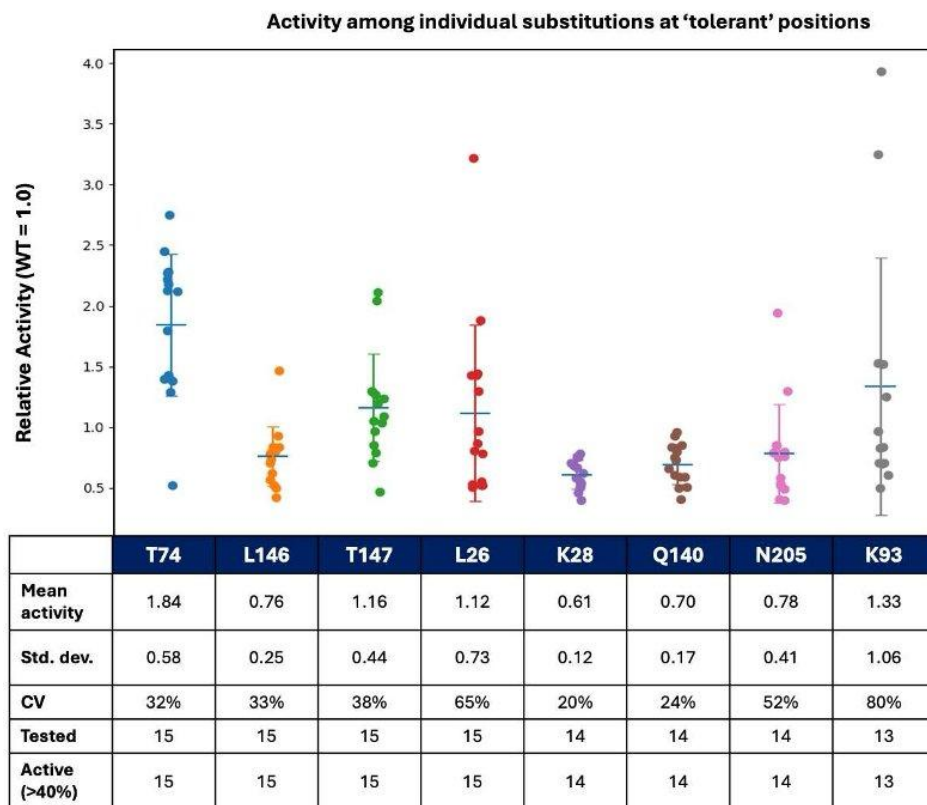
¹¹⁸ Pet., 45-47; EX1003, ¶ 108; EX1133, ¶¶ 172-178, 236-239, 326-327; EX1146, 22381-82; EX1151, 743-744.



Even positions Dr. Petsko labeled “100% tolerant” (the *most* predictable in his table) exhibit widely varying effects—*each* substitution causes a *unique* effect on *the entire* PH20 protein structure, rather than being limited to its position:¹¹⁹

	30 D	61 L	92 A	123 W	154 K	185 L
Position WT	31 E	62 G	93 K	124 K	155 Q	186 F
1 L	32 P	63 Y	94 R	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 V	104 N	135 E	166 V	197 P
12 V	43 G	74 T	105 L	136 L	167 E	198 G
13 P	44 P	75 Y	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 S	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 N	172 G	203 C
18 W	49 T	80 P	111 D	142 V	173 K	204 Y
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 L	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 K	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 L	60 R	91 K	122 N	153 A	184 Y	215 S

¹¹⁹ EX1133, ¶¶ 266-271.



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.¹²⁰ A POSA thus could not predictably determine how combinations of these mutations might affect PH20's structure and activity.

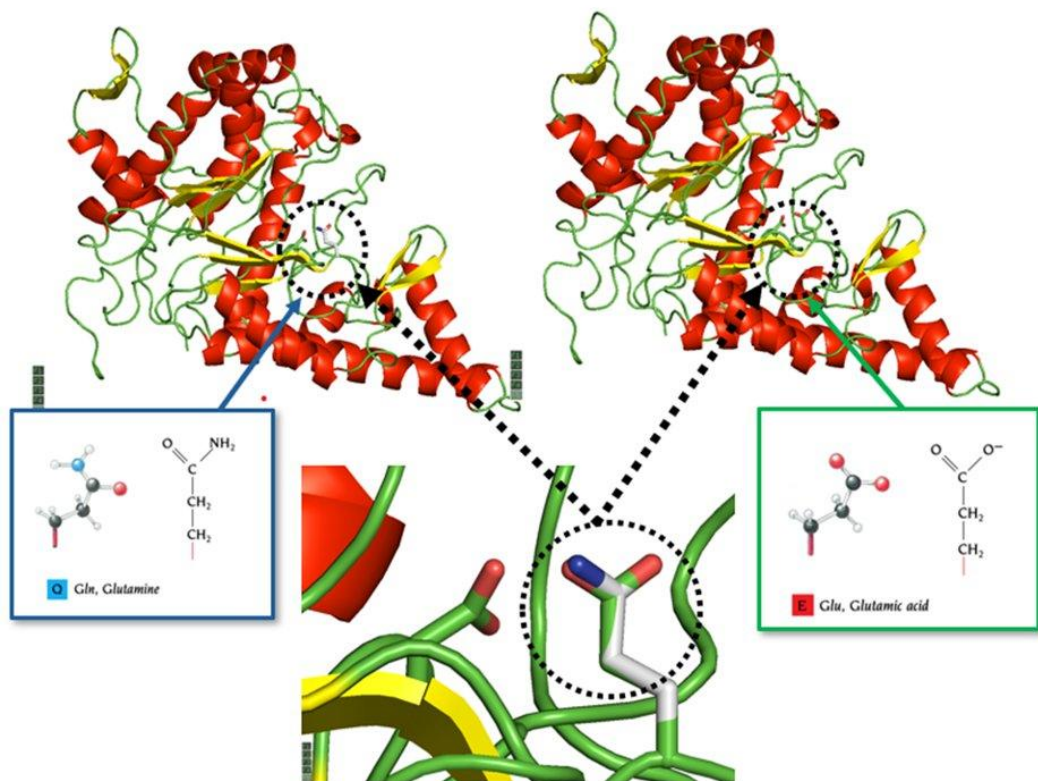
Position	WT	V	S	T	W
33	L	-	0.48	0.45	1.58
165	L	1.22	1.31	-	1.14
175	L	0.94	-	1.43	

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 changes that are imperceptible within homology models can eliminate

¹²⁰ EX1133, ¶¶ 275-276.

activity.¹²¹



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 for POSAs to predict how combinations of changes will impact the structure and functions of PH20s.¹²² A 2009 paper (EX1144) demonstrates the contrary.

¹²¹ EX1133, ¶¶ 275-276, 283-286.

¹²² POR, 45-48; EX2070, ¶¶ 52, 292.

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

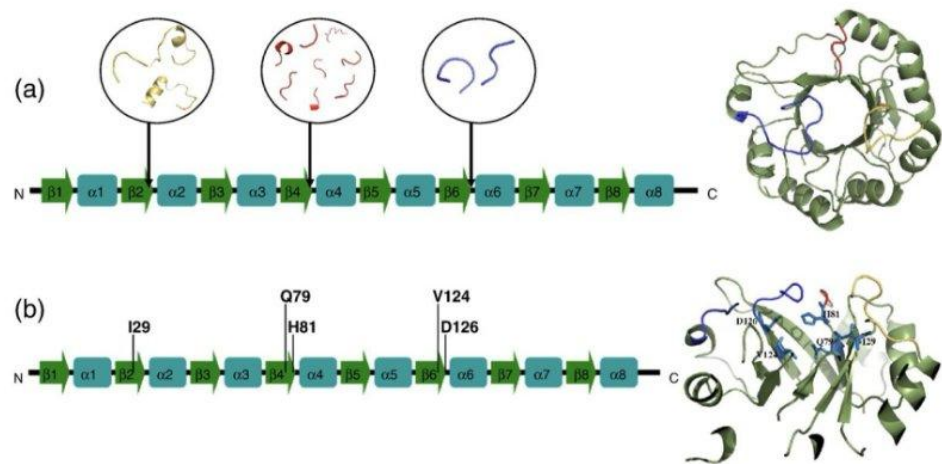


Fig. 1. Secondary-structure elements and tertiary structure (PDB code 1pii) of WT PRAI (ribbon diagram showing a view from the top of the central β -barrel). (a) The loops 2, 4, and 6 are shown in yellow, red, and blue, respectively. The circular insets show the loops to exchange in the PRAI-LoxP scaffold 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 altered 4-17 residues—comparable to changes permitted by the claims.

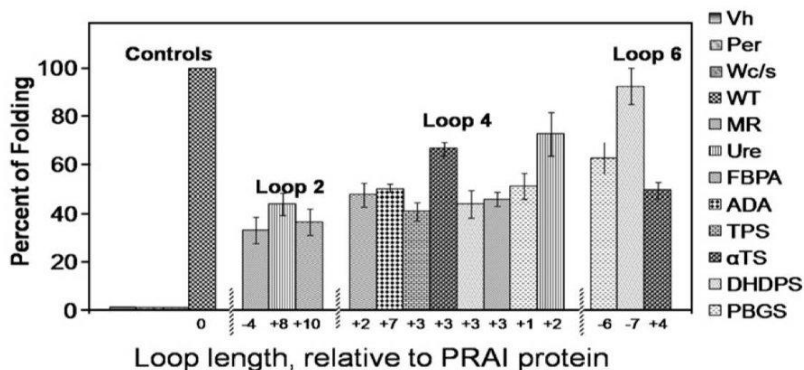
Table 1. Characteristics of the exchanged loops in the PRAI-LoxP scaffold

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	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
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	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 mutants *did not fold*.¹²³



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

Halozyme contends Dr. Petsko's tolerance assessments rendered selection of combinations of changes in PH20s predictable in 2011-2012.¹²⁴ 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) unfolded after initial native folding due to instability, or (v) natively folded and stable, but the mutation impaired substrate binding or

¹²³ EX1133, ¶¶ 179-184.

¹²⁴ POR, 46-48.

catalysis.¹²⁵ Because mutations that impacted ***folding*** are not identified, the disclosure cannot provide “tolerance” insights.¹²⁶

Experimental design flaws and incomplete reporting of results independently render Dr. Petsko’s ratings unreliable.¹²⁷

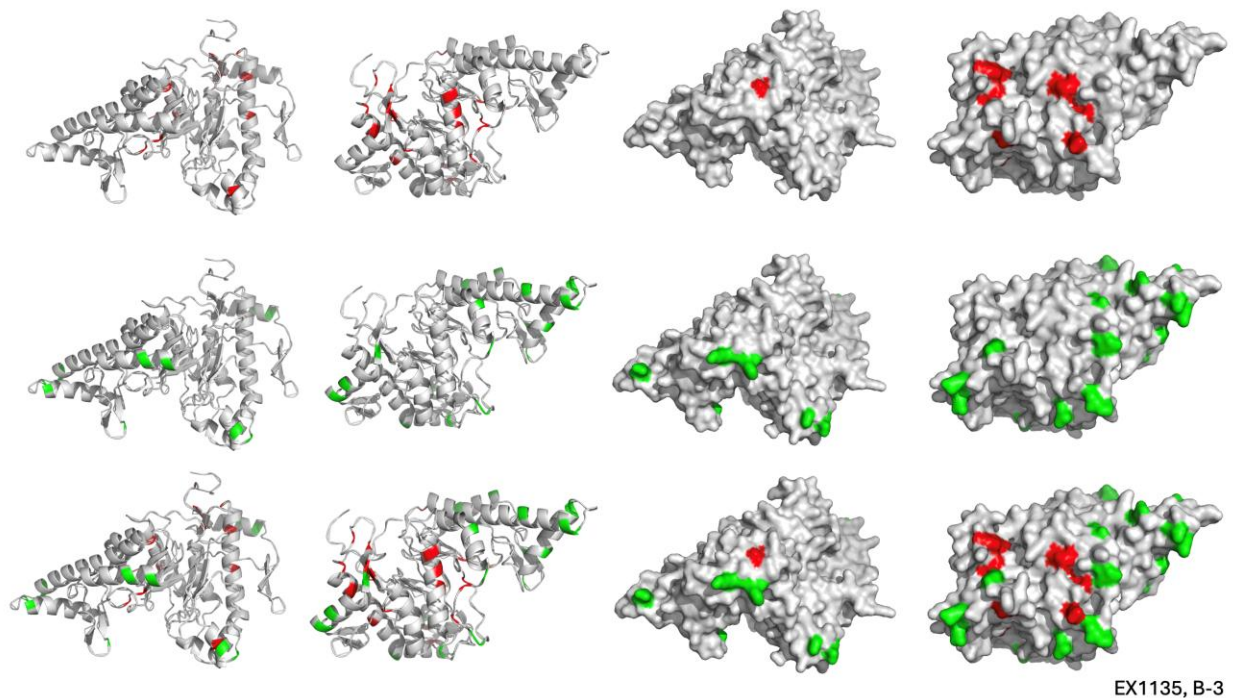
- inadequate numerical, structural context, and physicochemical interrogation of positions prevent reliable ratings of tolerance;
- no use of positive/negative controls in the primary assay, and no evidence of proteins in supernatants or their folded state;
- no activities reported for inactives, precluding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

¹²⁵ Pet., 47-48; EX1133, ¶¶ 75, 248-249; EX1131, 240:19-241:16.

¹²⁶ EX1133, ¶ 249.

¹²⁷ Pet., 49-52; EX1003, ¶¶ 72, 76, 99; EX1133, ¶¶ 291-317, 248-250, 252, 177, 237-238.

Dr. Naismith showed that correcting for these limitations and problems paints very different pictures than Dr. Petsko presented:¹²⁸



The disclosure's unreliable and uninformative data, limitations of homology modeling and experimental capabilities, and the unpredictability of multiple mutations refute Halozyme's assertion that POSAs could predict effects of 5+ mutations on proper folding and activity of PH20s in 2011-2012.¹²⁹

¹²⁸ EX1133, ¶¶ 306-307, 318-325, 244, 240-243, Appendix B (EX1135).

¹²⁹ Pet., 80; EX1003, ¶ 242; EX1004, ¶ 161; EX1133, ¶¶ 259, 263, 282-283; EX1027, 6-11.

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.

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

Halozyme and Dr. Petsko contend a POSA would not use directed evolution techniques to produce multiply-modified PH20s.¹³⁰ The disclosure directly contradicts these assertions—the only *specific* procedure it describes for doing so (albeit a research plan) uses directed evolution.¹³¹ Dr. Petsko also confirmed Dr. Hecht's opinion that such methods cannot enable the claimed multiply-modified PH20s, as they generate “billions of sequences that... *are not going to fold* into PH20 proteins” because of mutations at invariant residues, and require screening immense libraries to discover which ones do.¹³²

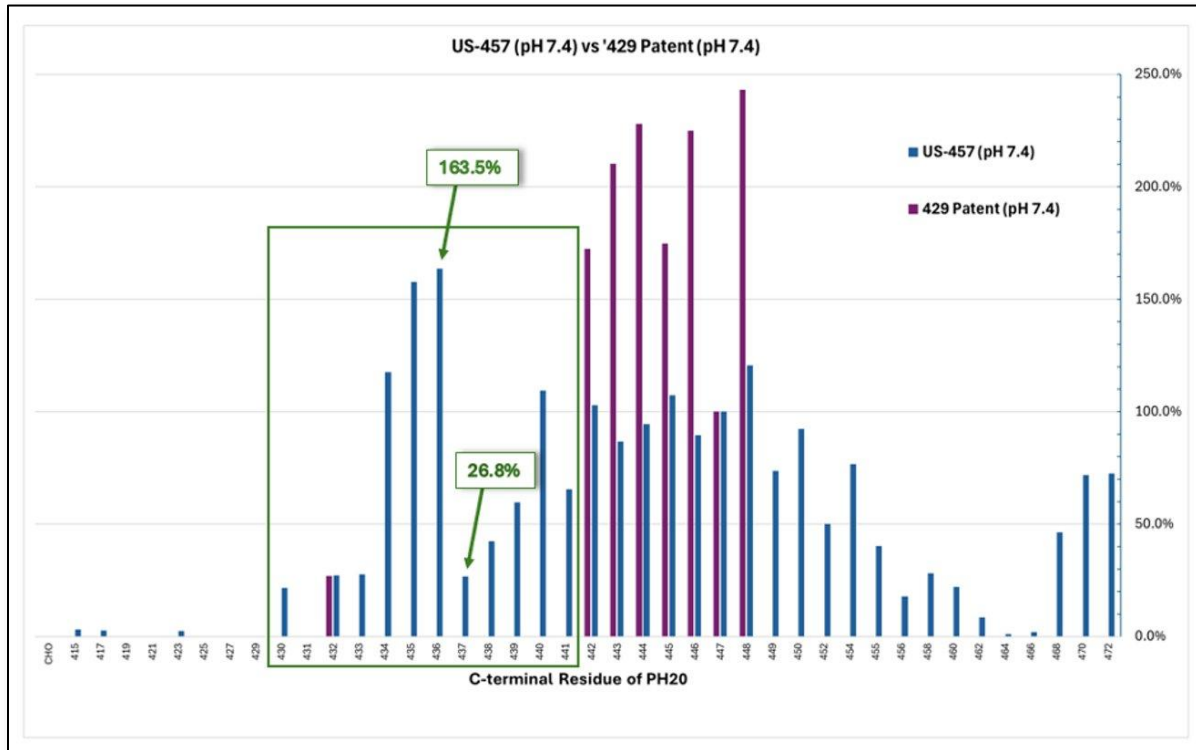
¹³⁰ EX2070, ¶ 349 (a POSA would “not ... generate an enormous library”).

¹³¹ Pet., 52-53; EX1026, 47:11-18, 141:30-33, 150:1-26; EX1003, ¶¶ 50-52, 185-190; EX1133, ¶¶ 206-208.

¹³² EX2070, ¶ 347; EX1133, ¶ 205.

2. C-Terminal Truncations Exhibit Unpredictable Activity

Halozyme cites US-457 to dispute Dr. Hecht's observation that C-terminal truncation mutants that vary by one residue show unpredictable variations in activity.¹³³ But US-457 shows the same phenomenon.¹³⁴



Relying on Dr. Simpson's declaration, Halozyme contends US-457 describes PH20₁₋₄₃₀ and PH20₁₋₄₃₁ (SEQ ID NOs: 86 and 87) as "inactive

¹³³ POR, 51.

¹³⁴ EX1133, ¶ 223.

mutants.”¹³⁵ But US-457 and the disclosure *explicitly* label them “*active*,”¹³⁶ which Dr. Simpson ignored when she reclassified them.¹³⁷

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 relies on Dr. Petsko’s positional tolerance table to contend the disclosure identifies multiply-modified active PH20s.¹³⁸ See § III.D.3. It does not. Regardless, the disclosure does not propose to do what Dr. Petsko did—select positions and substitutions based on *a proportion* of active mutants at a position.¹³⁹ Where “tolerance” is used to inform changes, the disclosure instructs POSAs to “generally... not ma[ke]” inactivating substitutions in active PH20s.¹⁴⁰

¹³⁵ POR, 28, 50-51, EX2068, ¶ 188.

¹³⁶ EX2165, ¶ 0362; EX1026, 79:25-31; EX1133, ¶¶ 217-218, 221.

¹³⁷ EX2068, ¶¶ 188, 330; EX1133, ¶¶ 214-221.

¹³⁸ EX2070, ¶¶ 264, 274, 355-365; EX1133, ¶¶ 277-280.

¹³⁹ EX1133, ¶¶ 206-207.

¹⁴⁰ EX1026, 91:30-92:20; EX1133, ¶¶ 208-209, 211.

Dr. Petsko's tolerance table actually induces POSAs to act *contrary* to the disclosure—it led Dr. Simpson to conclude a POSA *would* consider modifying positions 282, 299, 303, and 431, even though the disclosure *expressly instructs otherwise*.¹⁴¹

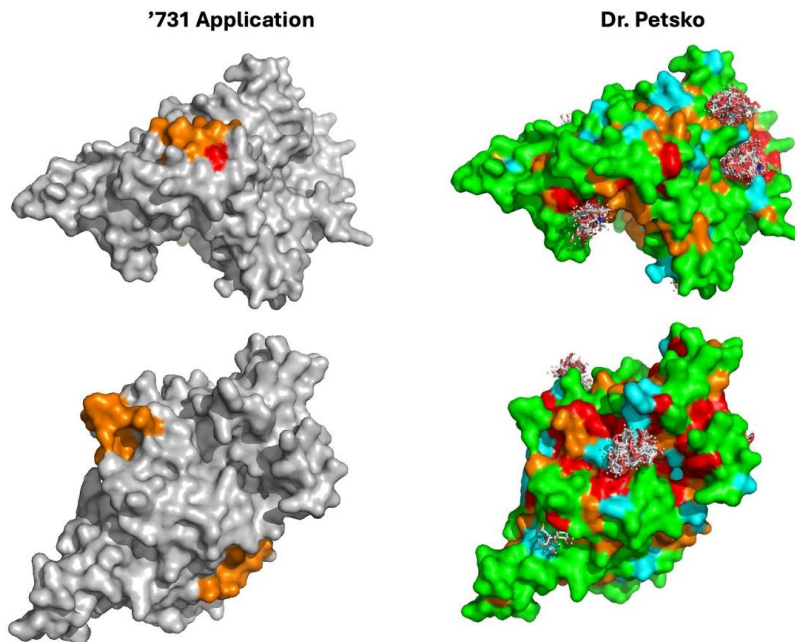
4. Wrong Substrate Binding Sites

Based on an experiment he performed, Dr. Petsko theorizes that additional substrate binding sites exist on PH20.¹⁴² 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).¹⁴³

¹⁴¹ EX1026, 91:30-92:20; EX1130, 191:5-16, 191:17-192:7, 192:8-194:6, 194:7-195:25; EX1133, ¶¶ 210-211.

¹⁴² 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, ¶¶ 225-232.

¹⁴³ EX1026, 81:7-14; EX1133, ¶¶ 225-226, 229-232.



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.¹⁴⁴ The disclosure says nothing about rescue mutations and discovering them would entail the same impossible scale of trial-and-error experimentation required to find active PH20s.¹⁴⁵

IV. Obviousness

Merck explained that Halozyme’s ’429 Patent (with Chao) rendered obvious

¹⁴⁴ POR, 40, 52; EX2070, ¶¶ 374-383.

¹⁴⁵ EX1133, ¶¶ 212-213.

single-amino acid substitution *mutants* (plural) of PH20₁₋₄₄₇.¹⁴⁶ Dr. Hecht explained the '429 Patent “encouraged [POSAs] to make modified PH20 proteins having single amino acid substitutions in non-essential regions.”¹⁴⁷

Dr. Park described how POSAs would have identified these singly-substituted active mutants using techniques Halozyme’s experts confirmed would have been used in 2011.¹⁴⁸ Without reviewing the disclosure, Dr. Park used those techniques to identify D320K as *one of ~750 such substitutions* suggested by the '429 Patent before 2011.¹⁴⁹ Dr. Naismith found Dr. Park’s analysis objective, rigorous, and unbiased.¹⁵⁰ Thus, per *KSR*, the '429 Patent motivated POSAs to identify single substitutions that *predictably* retain activity, and to use them to increase spreading.¹⁵¹

Halozyme attacks its own '429 patent, contending it doesn’t identify “non-

¹⁴⁶ Pet., 89-91.

¹⁴⁷ EX1003, ¶¶ 219-221, 225-226, 215-218; EX1005, 16:14-26.

¹⁴⁸ EX1004, ¶¶ 22-24, 32; EX1133, ¶¶ 349-351, 359, 362, Appendix B-8.

¹⁴⁹ EX2176; EX1133, ¶ 346; EX1003, ¶ 245-247.

¹⁵⁰ EX1133, ¶¶ 340-345, 354-361; EX1003, ¶ 229.

¹⁵¹ Pet., 89-93.

essential” regions or “provide any guidance on which sites to modify.”¹⁵² But Halozyme *patented all such singly-substituted PH20s*.¹⁵³

Halozyme also reiterates the *identical* hindsight theory it raised in its preliminary response, despite additional discovery and three depositions.¹⁵⁴ That evidence conclusively 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* 68 “essential” positions),¹⁵⁵ and (ii) which substitutions at each position to assess—the most frequently found residues at these non-essential positions.¹⁵⁶

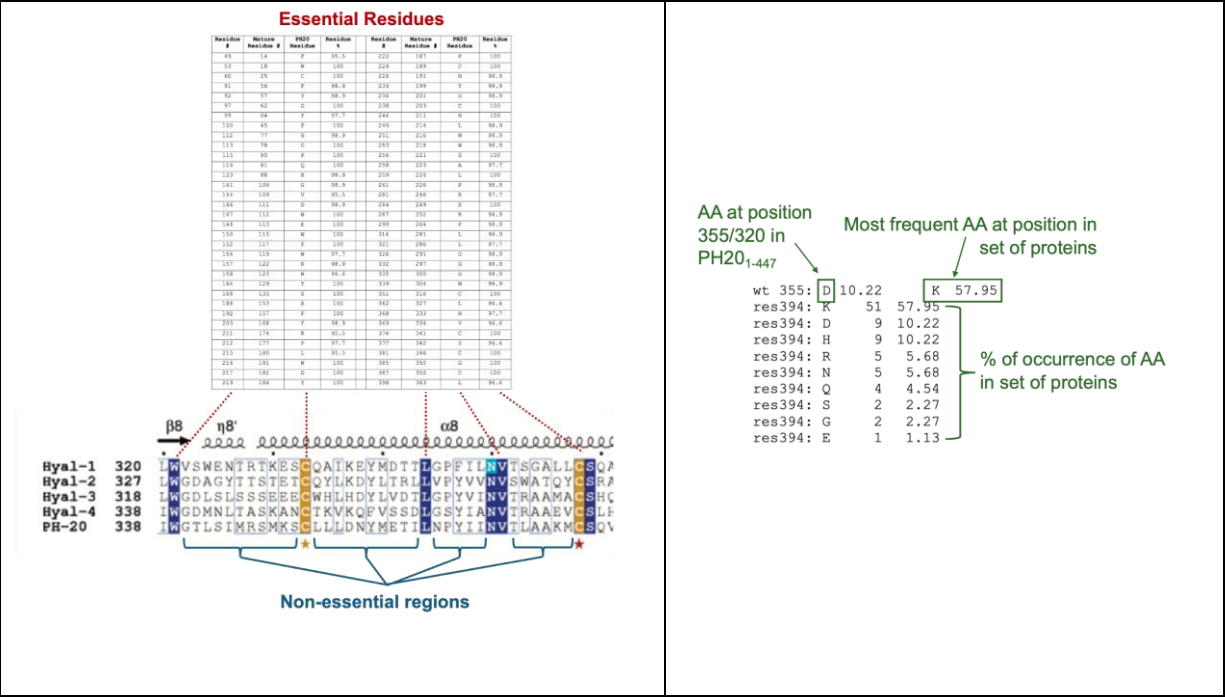
¹⁵² POR, 73-74.

¹⁵³ EX1005, claim 1.

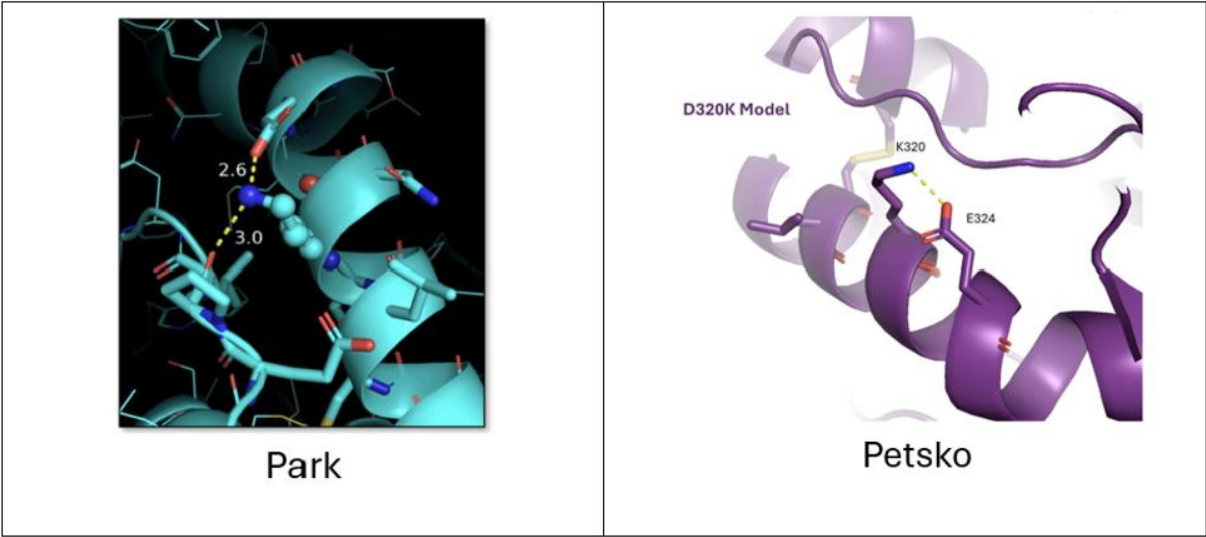
¹⁵⁴ POPR, 73-74; POR, 68.

¹⁵⁵ EX1004, ¶¶ 26-32.

¹⁵⁶ EX1004, ¶¶ 26-32, 41-43; Appendix D-1; EX1003, ¶¶ 225-229; EX1133, ¶ 344.



Dr. Park’s objective and unbiased assessment found D320K tolerated.¹⁵⁷ He and Dr. Petsko identified the same D320K:E324 interaction.¹⁵⁸



¹⁵⁷ Pet., 88-91, 102-110.

¹⁵⁸ EX1004, ¶¶ 116-123; EX2070, ¶ 403; EX1133, ¶¶ 351-353.

Dr. Park confirmed he “did not focus on any particular position” and reviewed “a lot of different types of substitutions.”¹⁵⁹ He also assessed substitutions, position-by-position, at least twice, using the most frequently occurring amino acids from his MSA analysis.¹⁶⁰ EX2176 corroborates Dr. Park’s testimony—it contains his observations and a tolerability rating for each substitution assessed at hundreds of positions.¹⁶¹

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	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			

Moreover, Dr. Park recorded his observations about D320K—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

¹⁵⁹ EX1004, ¶¶ 102-103.

¹⁶⁰ EX2078, 170:22-171:17.

¹⁶¹ EX1004, ¶¶ 85-87; EX1133, ¶¶ 342-348.

¹⁶² EX2078, 320:10-20; EX2176, 39.

assessed and prompted him to assess more substitutions.¹⁶³

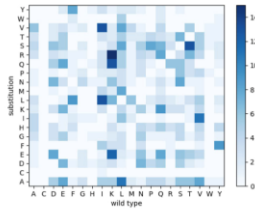
1	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y
2	Hyd1 Residue	Hyd1 Residue	PH20 Residue	PH20 Residue	Alternative Residue	Residue %	Rating (1-5)		Comments	Bright	IRASA	Hydrophobicity	Factors Secondary Structure	Interactions											
3	22	F	39	A	R	15.9	-																		
4	22	39	A	-	T	15.9	-																		
5	22	39	A	-	A	11.36	-																		
6	22	39	A	-	Q	3.4	-																		
7	22	39	A	-	S	3.4	-																		
8	22	39	A	-	E	2.27	-																		
9	22	39	A	-	G	1.13	-																		
10	23	R	40	S	A	14.08	-			3	0.44														
11	23	40	S	-	R	15.9	-																		
12	23	40	S	-	Q	2.27	-																		
13	23	40	S	-	G	2.27	-																		
14	23	40	S	-	T	1.13	-																		
15	23	40	S	-	N	1.13	-																		
16	24	G	41	G	P	14.08	-			5	0.49														
17	24	41	G	-	L	11.36	-																		
18	24	41	G	-	A	4.54	-																		
19	24	41	G	-	G	3.4	-																		
20	24	41	G	-	D	3.4	-																		
21	24	41	G	-	R	2.27	-																		
22	24	41	G	-	S	2.27	-																		
23	24	41	G	-	H	2.27	-																		
24	24	41	G	-	N	1.13	-																		
25	25	F	42	F	P	14.08	-				0.28														
26	25	42	F	-	T	2.27	-																		
27	25	42	F	-	L	1.13	-																		
28	26	L	43	V	-	3.5	-				6	0.23													
29	26	43	V	-	I	27.27	2	gain increased hydrophobic contacts			6	-													
30	26	43	V	-	L	3.5	2	neutral			6	-													
31	26	43	V	-	M	3.4	-																		
32	26	43	V	-	T	2.27	-																		
33	26	43	V	-	Q	2.27	-																		
34	26	43	V	-	N	1.13	-																		

substitution

W
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A C D E F G H I J K L M N O P Q R S T U V W X Y

wild type



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	N	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	V	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

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

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

¹⁶⁴ EX1133, ¶¶ 340-343.

V. Conclusion

The challenged claims are unpatentable.

Dated: May 1, 2026

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EXHIBIT LIST

No.	Exhibit Description
1001	U.S. Patent No. 12,104,185
1002	File History of U.S. Patent No. 12,104,185
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 '185 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 [NEW]	2024 Chemistry Nobel Prize Background
1028	[Reserved]

No.	Exhibit Description
1029	Gmachl et al., “The human sperm protein PH-20 has hyaluronidase activity,” FEBS Letters, 3:545-548 (1993)
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 & Moul, “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)

No.	Exhibit Description
1044	Mihel, “PSAIA – Protein Structure and Interaction Analyzer,” BMC Structural Biology, 8:21 (2008)
1045	Redline Comparison of the '731 and '185 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]

No.	Exhibit Description
1064	Collection of BLAST Webpages from the Internet Archive, navigable from: 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
1074-1075	[Reserved]
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	[Reserved]

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
1116-1124	[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,” <i>Proteins: Structure, Function, and Bioinformatics</i> 93:1067-1073 (2025)
1127-1129	[Reserved]
1130 [NEW]	Melanie Ann Simpson, Ph.D. Deposition Transcript
1131 [NEW]	Gregory Petsko, Ph.D. Deposition Transcript
1132	[Reserved]

No.	Exhibit Description
1133 [NEW]	Declaration of James Naismith, Ph.D.
1134	[Reserved]
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)
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)

No.	Exhibit Description
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)
1154 [NEW]	Second Table Associating Citations from the '185 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

No.	Exhibit Description
1161-1163	[Reserved]
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
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)
1170-1223	[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)

No.	Exhibit Description
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)
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
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
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
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
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 5,592 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 1, 2026

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on this 1st 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

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