



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

MERCK SHARP & DOHME LLC,
Petitioner
v.
HALOZYME, INC.,
Patent Owner

Case PGR2025-00003 | U.S. Patent No. 11,952,600
Case PGR2025-00004 | U.S. Patent No. 12,018,298
Case PGR2025-00006 | U.S. Patent No. 12,152,262
Case PGR2025-00009 | U.S. Patent No. 12,123,035

quinn emanuel
quinn emanuel urquhart & sullivan, llp



 **Sterne Kessler**
STERNE KESSLER GOLDSTEIN & FOX

Halozyme Patents



'035 Patent

US012123035B2

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

(16) Patent No.: **US 12,123,035 B2**
(45) Date of Patent: **Oct. 22, 2024**

(54) **PI20 POLYPEPTIDE VARIANTS,
FORMULATIONS AND USES THEREOF**

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

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

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

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

(21) Appl. No.: **18,068,322**

(22) Filed: **Dec. 19, 2017**

(65) **Prior Publication Data**

US 2020/0357739 A1 Nov. 9, 2023

Related U.S. Application Data

(66) Division of application No. 17,327,568, filed on May 21, 2021, which is a continuation of application No. 16,912,590, filed on Jun. 25, 2020, now Pat. No. 11,866,656, which is a continuation of application No. 15,226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, which is a division of application No. 13,694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, said application No. 17,327,568 is a continuation of application No. 16,904,572, filed on Mar. 19, 2020, now Pat. No. 11,041,149, which is a continuation of application No. 15,226,489, filed on Aug. 2, 2016, now Pat. No. 10,865,400, which is a division of application No. 13,694,731, filed on Dec. 28, 2012, now Pat. No. 9,447,401, said application No. 17,327,568 is a continuation of application No. 16,904,572, filed on Mar. 19, 2020, now Pat. No. 11,041,149, which is a continuation of application No. 15,226,489, filed on Aug. 2, 2016, now Pat. 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'600 Patent Claims

Claims 1-4 and 8-21

What is claimed:

1. A modified PH20 polypeptide comprising an amino acid sequence, wherein:

- (a) at least 95% of the residues of the amino acid sequence of the modified PH20 polypeptide are identical to the residues in an amino acid sequence selected from the group consisting of SEQ ID NOs: 3 and 32-66 when the sequence of the modified PH20 polypeptide is aligned at positions corresponding to the sequence selected from the group consisting of SEQ ID NOs: 3 and 32-66 to maximize identical residues, and wherein terminal gaps are treated as non-identical; and
- (b) the amino acid sequence of the modified PH20 polypeptide comprises an amino acid modification at a position corresponding to position 320 with reference to amino acid positions set forth in SEQ ID NO: 3; and
- (c) the modification at position 320 is a replacement selected from among H, K, Rand S.

2. The modified PH20 polypeptide of claim **1**, wherein the amino acid modification is at a position corresponding to position 320 with reference to amino acid positions set forth in SEQ ID NO: 3 is K.

3. The modified PH20 polypeptide of claim **2**, wherein at least 96% of the residues of the amino acid sequence of the modified PH20 polypeptide are identical to the residues in an amino acid sequence set forth in SEQ ID NO:35.

4. The modified PH20 polypeptide of claim **2**, wherein at least 95% of the residues of the amino acid sequence of the modified PH20 polypeptide are identical to the residues in an amino acid sequence set forth in SEQ ID NO:32.

* * *

8. The modified PH20 polypeptide of claim **1** that comprises one or more modifications of the polypeptide selected from among glycosylation, sialylation, albumination, farnesylation, carboxylation, hydroxylation, and phosphorylation.

9. The modified PH20 polypeptide of claim **8** that is glycosylated.

10. The modified PH20 polypeptide of claim **9**, wherein the polypeptide is a glycoprotein that comprises an N-acetylglucosamine moiety linked to each of at least three asparagine (N) residues.

11. A nucleic acid encoding the modified PH20 polypeptide of claim **1**.

12. A recombinant expression vector, comprising the nucleic acid of claim **11**.

13. A host cell, comprising the vector of claim **12**.

14. A pharmaceutical composition, comprising the modified PH20 polypeptide of claim **1**.

15. The pharmaceutical composition of claim **14**, further comprising a therapeutically active agent; wherein the therapeutically active agent is formulated in the same composition or is formulated in a separate composition.

16. A pharmaceutical composition of claim **15**, wherein the therapeutically active agent is a polypeptide, a protein, a nucleic acid, a drug, a small molecule, or an organic molecule.

17. The pharmaceutical composition of claim **16**, wherein the therapeutically active agent is an antibody.

18. The pharmaceutical composition of claim **16**, wherein the therapeutically active agent is a small molecule drug.

19. A method for administering a therapeutically active agent, comprising providing a pharmaceutical composition of claim **15**, and parenterally administering the composition or compositions.

20. The method of claim **19**, wherein said parenterally administering is subcutaneously administering.

21. A method for manufacture of a protein, comprising preparing a plasmid DNA containing a cDNA encoding the protein comprising an amino acid sequence, wherein:

- (a) the protein is a modified PH20 polypeptide;
- (b) at least 95% of the residues of the amino acid sequence of the encoded modified PH20 polypeptide, excluding any signal sequence, are identical to the residues in an amino acid sequence selected from the group consisting of SEQ ID NO: 3 and 32-66 when the sequence of the modified PH20 polypeptide is aligned at positions corresponding to the sequence selected from the group consisting of SEQ ID NO: 3 and 32-66 to maximize identical residues, and wherein terminal gaps are treated as non-identical; and
- (c) the amino acid sequence of the modified PH20 polypeptide comprises an amino acid modification at a position corresponding to position 320 with reference to amino acid positions set forth in SEQ ID NO: 3, and wherein the modification at position 320 is selected from among H, K, Rand S;

wherein the method comprises:
transfecting the plasmid into a host cell;
culturing the cell under conditions for expression of the cDNA as a protein;
harvesting the protein from the culture.

'600 Patent

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

- **Unprecedented comprehensive mutagenesis study.** EX. 2068, ¶¶162-164; EX. 2070, ¶¶233-237

Key Patent Examples

'600 Patent

 US011952600B2	
(12) United States Patent Wei et al.	(10) Patent No.: US 11,952,600 B2 (45) Date of Patent: *Apr. 9, 2024
(54) PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF	(58) Field of Classification Search CPC A61K 9/0019; A61K 38/28; A61K 38/47; A61K 45/06; A61K 47/10; A61K 38/00; (Continued)
(71) Applicant: HALOZYME, INC. , San Diego, CA (US)	(56) References Cited U.S. PATENT DOCUMENTS 3,536,809 A 10/1970 Appleweig 424/28 3,598,123 A 8/1971 Zallaroni 128/268 (Continued)
(72) Inventors: Ge Wei , San Diego, CA (US); II. Michael Shepard , Eugene, OR (US); Qiping Zhao , San Diego, CA (US); Robert James Connor , Oceanside, CA (US)	FOREIGN PATENT DOCUMENTS CN 102065886 A 5/2011 EP 0400472 12/1990 (Continued)
(73) Assignee: Halozyyme, Inc. , San Diego, CA (US)	OTHER PUBLICATIONS Bouga, Helen, et al. "Involvement of hyaluronidases in colorectal cancer." BMC cancer 10 (2010): 1-8. (Year: 2010).*
(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days. This patent is subject to a terminal disclaimer.	(Continued)
(21) Appl. No.: 18/338,189	<i>Primary Examiner</i> — Lora E Barnhart Driscoll <i>Assistant Examiner</i> — Candice Lee Swift
(22) Filed: Jun. 20, 2023	(74) <i>Attorney, Agent, or Firm</i> — Morgan, Lewis & Bockius LLP
(65) Prior Publication Data US 2024/0011008 A1 Jan. 11, 2024	ABSTRACT (57) Modified PH20 hyaluronidase polypeptides, including modified polypeptides that exhibit increased stability and/or increased activity, are provided. Also provided are compositions and formulations and uses thereof.
Related U.S. Application Data (60) Division of application No. 17/327,568, filed on May 21, 2021, which is a continuation of application No. (Continued)	21 Claims, 13 Drawing Sheets Specification includes a Sequence Listing.
(51) Int. Cl. C12N 9/26 (2006.01) A61K 9/00 (2006.01) (Continued)	
(52) U.S. Cl. CPC C12N 9/2474 (2013.01); A61K 9/0019 (2013.01); A61K 38/28 (2013.01); (Continued)	
LNFRAPPVIPNVFFLWAWNAPSEFCIGKFDPEPLMSLFSFIGSPRINATGQGVTFYVDR 60 LGYYPYIDSTTGVTVNGGIPQKISLQDHLDAKKKDITFYMPVDNLGMAVIDWEEWRPTWA 120 RNWPKPDVYKNRSIELVQQNVQLSLTEATEKAKQEFKAGKDFLVETIKLGLLRPNHL 180 WGYYLFPCYNHHYKPGYNGSCINVEIKRNDLWLNNESTALYPSIYLNTPQSPVAAT 240 LYVRNRVREAIRVSKIPDAKSLPFLVFXTRIVFTDQVLKFLSQDELVYTFGETVALGASG 300 IWIWGTLSIMRSMKSCLLDNYMETILNPIIINVTIAAKMCSQVLCQEGVCIRKNWNSS 360 DYLHLNPDNFAIQLEKGGKFTVRGKPTLQLEQFSEKFCYSCYSTLSCKEKADVKTDDV 420 GVCIADGVCIIDAFLEKPPMETEEPQIFYNASPSTLSATMFVSIILFLITSSVASL 474	

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

Patent's Mutagenesis Data

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

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

Patent's Extensive Disclosure Is Unprecedented

Halozyme Expert | Dr. Petsko



234. This level of detailed structure/function mapping was **virtually unheard of** in 2012, and still is, especially in the public domain. **I am not aware of a comprehensive mutagenesis study like this** for any other human protein of comparable size. These data are extraordinarily useful for the POSA seeking to practice the claims.

EX. 2070, Petsko Decl., ¶234

Claim Construction



Claims Define The Invention By Structure

'600 Patent

	
US011952600B2	
(12) United States Patent Wei et al.	(10) Patent No.: US 11,952,600 B2 (45) Date of Patent: *Apr. 9, 2024
(54) PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF	(58) Field of Classification Search: CPC: A61K 9/0019; A61K 38/28; A61K 38/47; A61K 45/06; A61K 47/10; A61K 38/00; (Continued)
(71) Applicant: HALOZYME, INC., San Diego, CA (US)	

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

- “at least 95% identical” to SEQ ID NOs
- specific change to H, K, R, or S at position 320

MGVPTFQK...
RHWKPKOVYKNSIELVQQQNVQLSLTEATEKAKQEFERAGKDFLVTETIKLGLLRPNHL 180
WGYYLPFDQCYNHHYKPGYNGSCNVEIKRNDLWLNRESTALYPSIYLNTOQSPVAAT 240
LYVMNRVREAIRVSKIPDAKPLPVFAYTRVFDQKFLSQDELVTFTGETVALGASG 300
IVWGTLSIMRSMKSCLLLDNYMETILNPYIINVTLAARMCQVLCQEGVCIRKNNHSS 360
DYLHLPNFPAIQLEKGGKFTVRGKPTLQLEQFSEKPYCSCYSTLSCKEKADVDKTIW 420
GVCIADGVCIADFLKPPMETEEPQIFYNASPSTLSATMTFVSIILFIISVASL 474

1. A modified PH20 polypeptide comprising an amino acid sequence, wherein:

(a) at least 95% of the residues of the amino acid sequence of the modified PH20 polypeptide are identical to the residues in an amino acid sequence selected from the group consisting of SEQ ID NOs: 3 and 32-66 when the sequence of the modified PH20 polypeptide is aligned at positions corresponding to the sequence selected from the group consisting of SEQ ID NOs: 3 and 32-66 to maximize identical residues, and wherein terminal gaps are treated as non-identical; and

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

(c) the modification at position 320 is a replacement selected from among H, K, R and S.

EX. 1001 at cl. 1

Petitioner's Expert Agrees There Is No Activity Requirement

Merck Expert | Dr. Kelsoe



Q. And I'd like you to review claim 1 of the '600 patent and tell me if claim 1 requires the modified PH20 polypeptides to contain any hyaluronidase activity?

A. It does not. It simply claims 95 percent identity.

* * *

Q. There's no activity requirement in the claim, right?

A. That is the claim, that's correct.

* * *

Q. So You don't read claim 1 to require any hyaluronidase activity, right?

A. To the best of my understanding, no.

EX. 2302 (Kelsoe), 41:6-9; 41:18-21; 48:1-4 (objections omitted)

Petitioner's Construction Rewrites The Claims

Paper No. 1
Filed: November 12, 2024

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyme Inc.,
Patent Owner.

Case No. PGR2025-00003
U.S. Patent No. 11,952,600

PETITION FOR POST GRANT REVIEW

PETITION FOR POST GRANT REVIEW

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

Pet. at 22

Paper No. 16
Filed: March 24, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
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Halozyme Inc.,
Patent Owner.

Case No. PGR2025-00003
U.S. Patent No. 11,952,600

REPLY IN SUPPORT OF PETITION FOR POST GRANT REVIEW

“[T]he claims as a whole require modified PH20s that are ‘properly folded and enzymatically active.’”

Reply at 2

“Modified PH20 Polypeptide” Definition

Definitional →

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

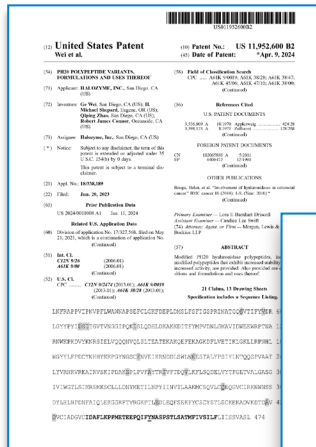
Not Definitional →

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

EX. 1001, 48:38-53

Petitioner's Construction Contradicts Specification

'600 Patent

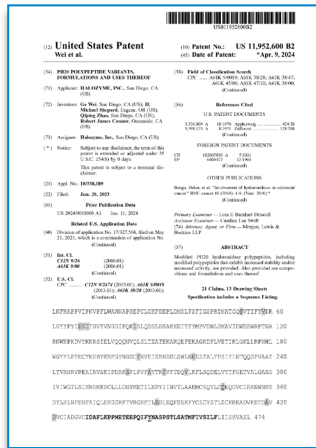


Provided herein are modified PH20 polypeptides that contain one or more amino acid replacements in a PH20 polypeptide and that are inactive, whereby the polypeptides do not exhibit hyaluronidase activity or exhibit low or diminished hyaluronidase activity. The modified PH20 poly-

EX. 1001, 119:13-17, 43:49-44:53, 79:27-29, 75:47-49, 75:56-58, 119:30-120:27, 120:36-43, 195:3-6, 257:23-258:37

Petitioner's Construction Contradicts Specification

'600 Patent



DETAILED DESCRIPTION

Outline

A. DEFINITIONS

B. PH20 HYALURONIDASE

1. Structure

2. Function

3. Soluble PH20 Polypeptides

C. MODIFIED PH20 POLYPEPTIDES

1. Active Mutants

a. Increased Activity

b. Increased Stability

i. Phenophiles

ii. Thermophiles

iii. Absence of Salt

2. Inactive Mutants

3. Additional Modifications and Conjugates

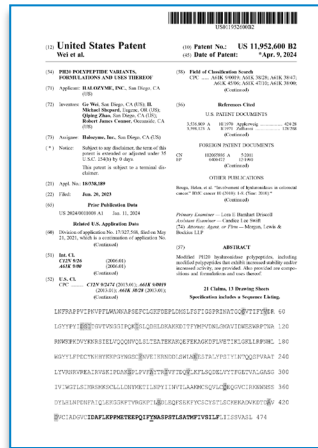
a. Decreased Immunogenicity

b. Conjugation to Polymers

EX. 1001, 43:49-67

Term “PH20” Is Distinct From “Modified PH20 Polypeptide”

'600 Patent

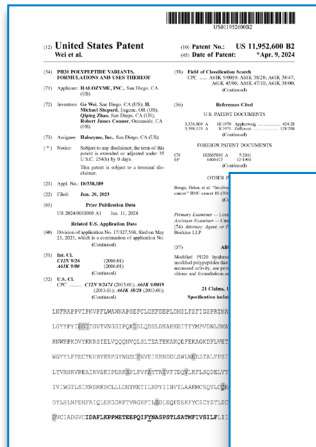


As used herein, PH20 refers to a type of hyaluronidase that occurs in sperm and is neutral-active. PH-20 occurs on the sperm surface, and in the lysosome-derived acrosome, where it is bound to the inner acrosomal membrane. PH20 includes those of any origin including, but not limited to, human, chimpanzee,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

EX. 1001, 45:56-46:6

PH20, Modified PH20 Have Different Properties, Activities

'600 Patent



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

* * *

EX. 1001, 75:44-47

Petitioner's Expert Ignored "Contradictory" Specification

Merck Expert | Dr. Hecht



Q. So, in fact, the patent specification uses the term modified PH20 polypeptides to refer to inactive polypeptides; right?

A. I see that. It seems contradictory. It seems the patent is using contradictory language in that elsewhere it says, "modified so long as active" whereas here it seems to use it in a different way. Seems contradictory.

* * *

Q. Did you consider the fact that the specification uses the term modified PH20 polypeptide to refer to inactive PH20s in your claim construction analysis?

A. I considered the quotes I mentioned to you earlier, where it says, "so long as." I did not consider this because it seemed contradictory. But my interpretation of the claim, referring to active, was also based on several other things, which I can go into.

EX. 2076 (Hecht), 189:1-190:11

Petitioner And Petitioner's Experts Disagree On Scope Of Claims

Merck Expert | Dr. Hecht



Q. All right. Did you interpret the claim to require at least 40 percent hyaluronidase activity?

A. As I said earlier, I'm uncomfortable with fixating on that number. The -- the authors of the patent have chosen that number, so I'll go along with it. But I -- you know, I'm not comfortable with fixating on that number.

Q. So how much activity do you think is required to satisfy the claim?

A. I would say enough activity to be useful in a biomedical application or in any application that uses this enzyme. And since I don't use this enzyme as a practitioner, I'm not sure how much activity is required. They seem to think 40 percent is a cutoff, so that seems reasonable. But I'm very hesitant to say I know exactly what that number should be. I don't have experience in the clinical use of this enzyme, but enough activity to make it useful as a product.

EX. 2076 (Hecht), 213:1-21

Petitioner And Petitioner's Experts Disagree On Scope Of Claims

Merck Expert | Dr. Naismith



Q. Okay. So D320K and SEQ. ID NO:3 with one additional mutation and it is 19% active; does that meet the claims?

A. Robustly measured 19%.

Q. Yes?

A. Yes, that is active.

EX. 2301 (Naismith), 194:9-14

Q. Okay. Now, so you would consider a 7% activity to be an active protein; right?

A. Are we talking about Ph20 here.

Q. Yes.

A. With the mutations.

Q. Yes.

A. In my view if you could accurately measure 7% then it would, it would be within the scope of the claims because I would consider that active.

EX. 2301 (Naismith), 197:10-21 (objections omitted)

Petitioner's Expert Invented New, Unsupported Constructions

Merck Expert | Dr. Naismith



Q. The words in the claims that you are relying on to support your interpretation of the patent fully folded and active, the words specifically is PH20; right?

A. ... Dr. Hecht offers essentially the same opinion. We both read in light of the common disclosure that is claims are directed to active form of the protein that is properly folded.

* * *

Q. Okay. I am trying to get an understanding of what “a meaningful period of time” is, as you use that phrase in paragraph 59. So, like, would 90 minutes in the assay in the patent, is that a sufficiently meaningful period for it to have been considered properly folded?

A. There is, it is obviously a spectrum. To understand it you would take different time points, and two reasonably close together. You would see if there is was a slope between them for example. For the protein to be useful and I would anchor my expectations around what the patent said which was for the inactive mutants they ran they overnight ---- They did overnight incubations for some of the testing they did. So, that would seem a reasonable place to start around sort of, 8-10 hours.

EX. 2301 (Naismith), 167:9-168:10, 138:6-139:4 (objections omitted)

Patent Owner's Construction Is Dispositive of Grounds 1 and 2



PO's Construction: Common Structural Features

The claims define the genus by a common mutation at position 320 and sequence identity to a set number of specific sequences. POPR at 17-21; POR at 31-42

Merck's claim: “Visualizing or recognizing the members of the claimed genus here is impossible” Reply at 10

PO's Construction: Petitioner's Expert Can Recognize Genus

Merck Expert | Dr. Hecht



- Q. Okay. I want to be very clear. Can you tell from an amino acid sequence whether that amino acid sequence is 95 percent identical to, for example, SEQ ID 3 or not?
- A. One can do that, yes.
- Q. So an amino acid sequence of a polypeptide gives you enough information to tell whether that amino acid sequence is 95 percent identical to, for example, SEQ ID 3; correct?
- A. The sequence tells you whether, what percentage is identical, yes.
- Q. And the sequence would also tell you whether there's a mutation at position 320; correct?
- A. That it would.

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

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

Merck Expert | Dr. Naismith



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

A. Sorry, were what in 2012?

Q. The cell culture techniques described in the patent?

A. Were what in 2012, sorry?

Q. Would have been routine in 2012?

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

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

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

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

EX. 2301 (Naismith), 244:22-245:15; *see also* Pet., 13-14, 16

It Would Have Been Routine To Generate Multiply Substituted Modified PH20s

Halozyme Expert | Dr. Simpson



345. As I understand it, there is no dispute that a POSA could make the claimed PH20 *variants*-meaning the set of C-terminal truncated PH20s (SEQ ID NOs: 3 and 32-66) with a D320K, D320R, D320H or D320S substitution. The POSA could readily generate, for example, SEQ ID NO: 3 with the D320R substitution through routine procedures. I do not understand Dr. Hecht to contend otherwise.

347. With respect to the 95% identical sub-variants, a POSA would have readily been able to make and use the full scope of 95% sub-variants using the disclosure of the patent in conjunction with the knowledge in the art and using routine techniques.”

EX. 2068, Simpson Decl., ¶¶345, 347

PO's Construction Is Dispositive Of The 112 Grounds

Trials@uspto.gov
571-272-7822

Paper: 13
Date: March 22, 2023

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

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

35 U.S.C. § 324

Patent Owner Also Prevails Under the Board's Construction



Board's Preliminary Construction Is Addressed Through Remainder Of The Presentation

- The Board preliminarily construed claims to require “some” hyaluronidase activity.
ID at 15-16
- Patent Owner and Patent Owner’s experts addressed the Board’s Construction in POR and sur-reply.
POR at 44; Sur-Reply at 3-4; EX. 2068, ¶1350
- Patent Owner assumed that specification must allow POSAs to reliably distinguish, create, and utilize actives.
POR at 44; Sur-Reply at 3-27
- Under the Board’s construction, patent provides written description and enablement.
POR at 44-81; Sur-Reply at 3-27

Written Description (Ground 1)



Specification Must Reasonably Convey Possession

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

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

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

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

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

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

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

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

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

patent was invalid for failure to provide adequate written
description.

Reversed in part and affirmed in part.

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

Gajarsa, Circuit Judge, filed concurring opinion.

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

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

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

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

Common Structural Features, Structure/Function Correlation

Common Structural Features:

1. **Primary Structure:** $\geq 95\%$ identical amino acid sequence.
2. **Key Mutation:** D320 substitution (H, K, R, or S).
3. **For Actives:**
 - Common active site.
EX. 1001, 70:34-54; EX. 2068, ¶¶303; EX. 2070, ¶¶148-206
 - Same catalytic, binding residues.
EX. 1001, 70:34-41; EX. 2068, ¶¶303; EX. 2070, ¶¶148-206
 - Conserved disulfide bridges, essential glycosylation sites.
EX. 1001, 70:14-33; EX. 2068, ¶¶303; EX. 2070, ¶¶214-217
 - Lack of disclosed inactivating changes.
EX. 2068, ¶¶303, 323; EX. 2070, ¶44
 - Tertiary structure: PH20 α - β barrel fold.
EX. 2068, ¶¶289, 316-323; EX. 2070, ¶¶345, 396, 400-420

Patent's Structure/Function Correlations

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

How POSAs Visualize The Patent Disclosure

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

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

Patent's Informational Content Is Enormous

Halozyme Expert | Dr. Petsko



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

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

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

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

Petitioner Ignores Patent's Structure/Function Correlations

Petitioner's view of the patent data

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

Pet. at 59

What the patent data disclose to a POSA

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

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

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

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

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

[ABBVIE DEUTSCHLAND GMBH & CO., KG](#),
[AbbVie Bioresearch Center, Inc.](#), and AbbVie
Biotechnology, Ltd., Plaintiffs–Appellants,

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

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

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

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

motion for judgment as matter of law. Owner appealed.

Holdings: The Court of Appeals, [Lourie](#), Circuit Judge, held that:

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

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

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

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

Before [LOURIE](#), [O'MALLEY](#), and [CHEN](#), Circuit Judges.

Concurring opinion filed by Circuit Judge [O'MALLEY](#).

Opinion

[LOURIE](#), Circuit Judge.

How POSAs Would Visualize The Patent Disclosure

Halozyme Expert | Dr. Petsko



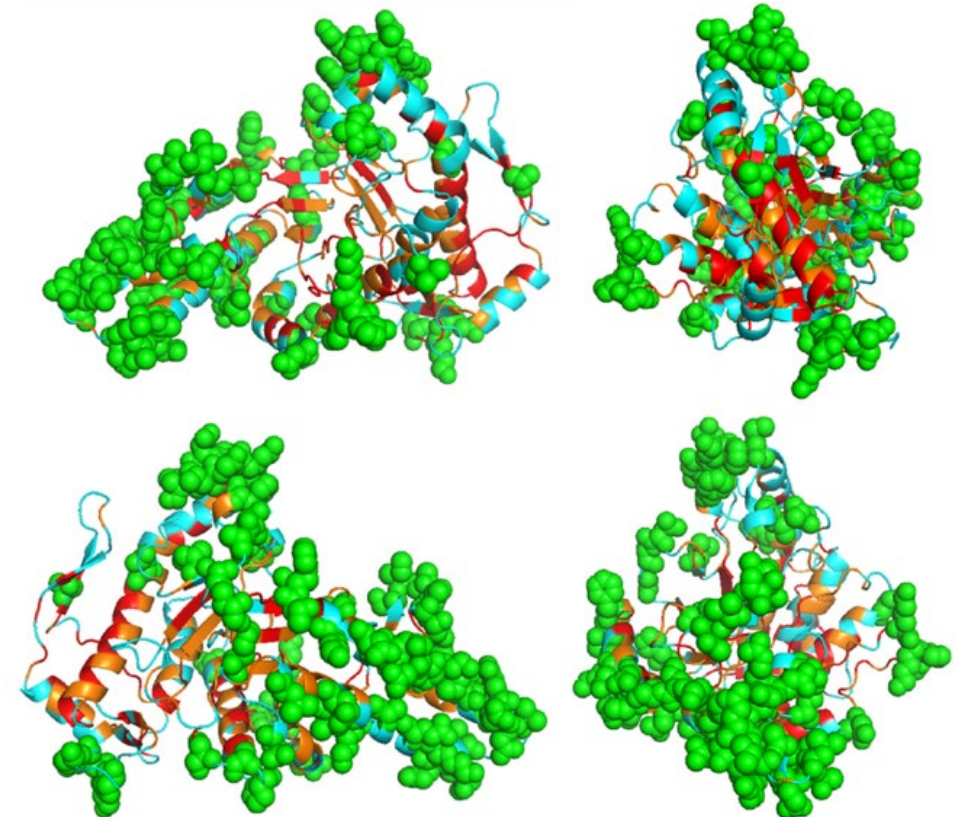
Position-by-position mutagenesis data for all 447 positions in SEQ ID NO 3

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

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

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

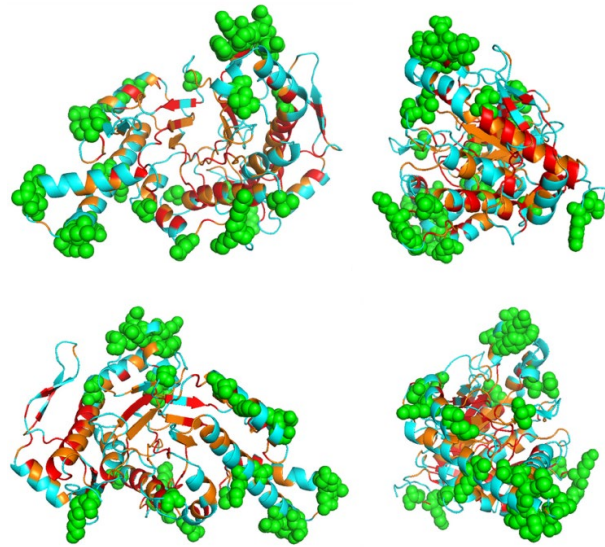
~48% (214/447)
all or most substitutions not tolerated;
includes some essential residues



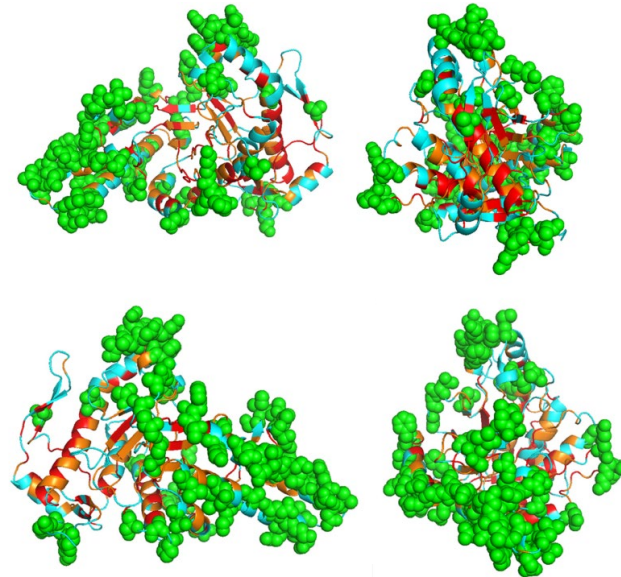
EX. 2070, Petsko Decl., ¶¶264-268, 283-288, 317-321; EX2166

How POSAs Would Visualize The Patent Disclosure

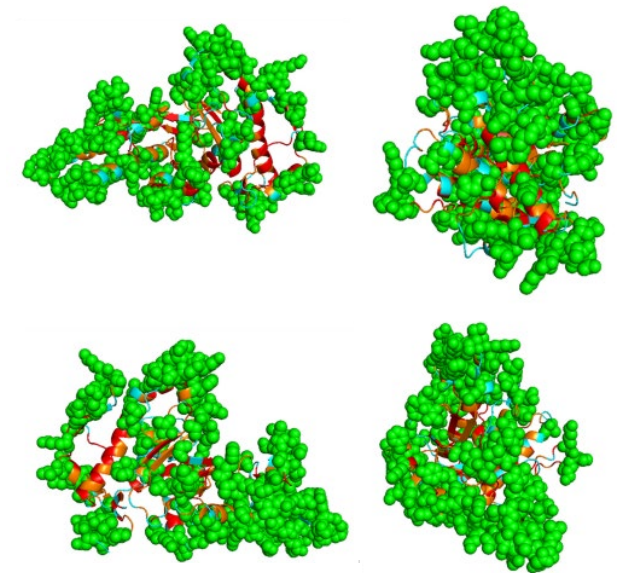
Halozyne Expert | Dr. Petsko



43 positions
(green spheres) that tolerated
all tested substitutions



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



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

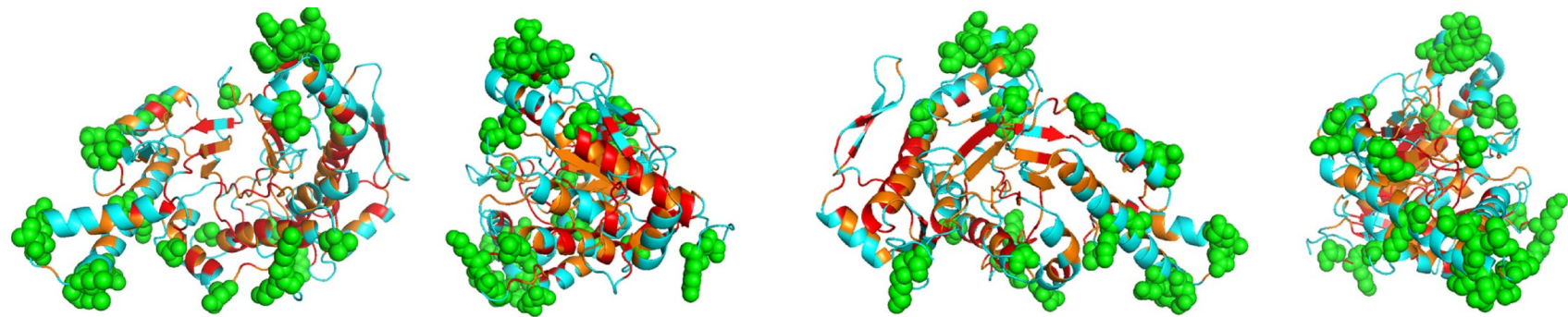
EX. 2070, Petsko Decl. at ¶¶ 317-321, 358-359; EX2166

Patent Disclosure Makes Multiply Mutating PH20 Predictable

Halozyme Expert | Dr. Petsko



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



EX. 2070, Petsko Decl., ¶355

Patent Disclosure Allows Reliable Predictions About Any Species

Halozyme Expert | Dr. Petsko



- Q. So using that dataset, the person could predict which combinations might yield an active form of a mutated PH20 polypeptide let's say with 15 changes to it?
- A. You could, but as I said, you would not tend to do that. A person of skill in the art would tend to only be interested in a much smaller number of mutations, because you can almost certainly get where you want to go that way.
- Q. So a POSA is not interested in trying to practice the entire scope of this genus, they would focus on a portion of it, right?
- A. A POSA would have the capability of both visualizing and practicing the full scope of the claims if they needed to. They could -- that is to say, they could look at any particular type of variant that fit the claim and they could make that variant and they would be able to predict beforehand what that variant might do with a -- in many cases, on a high degree of confidence.
- Q. And they could do that for 1049 -- a number that -- I'm sorry. They can do that for a number of modified PH20 polypeptides that approaches 1049 different sequences?
- A. They can do that for any member of the 1049 sequences that they wish to examine. Okay? A person of skill in the art would do it that way.

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

Patent Disclosure Makes Modifying PH20 Predictable

Halozyme Expert | Dr. Simpson



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

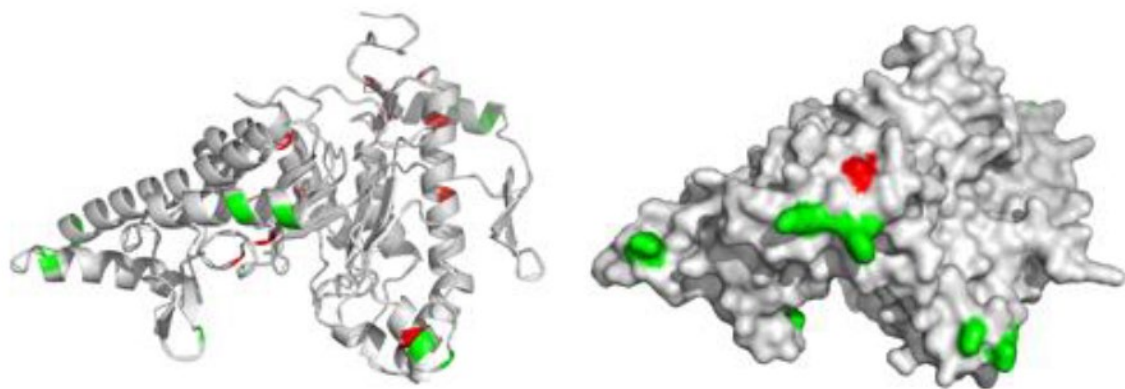
They would be able to visualize the species within the claim.”

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

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

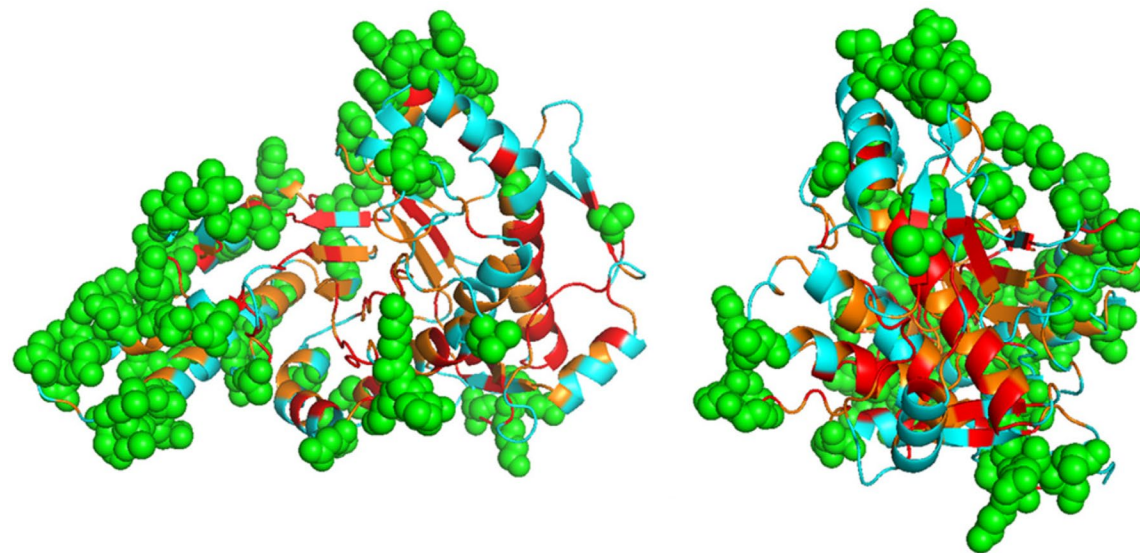
Petitioner's Experts Improperly Disregard Patent Disclosure

Merck Expert | **Dr. Naismith**



EX. 1133, Naismith Decl., ¶ 320

Halozyyme Expert | **Dr. Petsko**



EX. 2070, Petsko Decl., ¶ 321

Considering Structural Context Is “Common And Expected”

Merck Expert | Dr. Park



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

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

POSAs Would Routinely Use Model To Visualize/Practice

Merck Expert | Dr. Park



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

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

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

A. Absolutely.

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

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

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

POSAs Would Routinely Use Model To Visualize/Practice

Merck Expert | Dr. Hecht



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

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

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

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

The Use Of Homology Modeling Was Routine

Halozyne Expert | Dr. Simpson



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

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

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

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

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

[ABBVIE DEUTSCHLAND GMBH & CO., KG](#),
[AbbVie Bioresearch Center, Inc.](#), and AbbVie
Biotechnology, Ltd., Plaintiffs–Appellants,

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

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

any errors with regard to obviousness issue were not

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

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

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

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

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

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

Before [LOURIE](#), [O'MALLEY](#), and [CHEN](#), Circuit Judges.

Concurring opinion filed by Circuit Judge [O'MALLEY](#).

Opinion

[LOURIE](#), Circuit Judge.

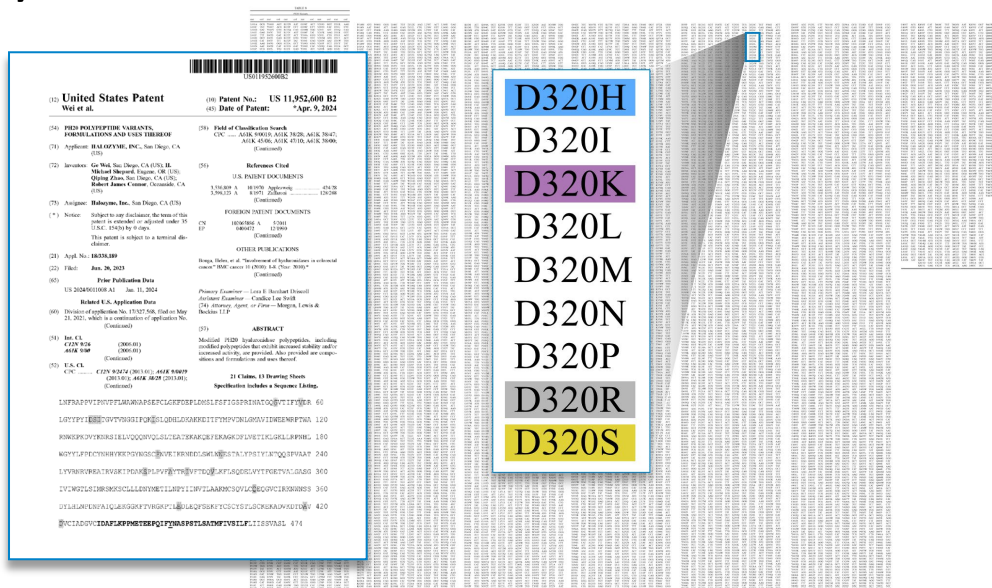
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The Specification Discloses Sufficient Representative Species

'600 Patent

Only **four** D320 variants/sub-variants claimed



Inventors Did NOT Claim

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

EX. 1001, 200:42-231:17

Petitioner Has Not Shown Genus Is Structurally Heterogeneous

AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc., 759 F.3d 1285 (2014) 111 U.S.P.Q.2d 1780	
759 F.3d 1285 United States Court of Appeals, Federal Circuit. ABBVIE DEUTSCHLAND GMBH & CO., KG , AbbVie Bioresearch Center, Inc. , and AbbVie Biotechnology, Ltd., Plaintiffs–Appellants, v. JANSSEN BIOTECH, INC. and Centocor	district court did not abuse its discretion in excluding evidence of interference proceeding; district court did not abuse its discretion in trial over written description requirement by excluding additional testimony summarizing prosecution arguments made to PTO; and any errors with regard to obviousness issue were not prejudicial on issue of written description that was decided in

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

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

that: prior interference ruling by the Board of Patent Appeals and Interferences regarding priority and nonobviousness lacked requisite finality for purposes of collateral estoppel. asserted patent claims for class of fully human antibodies that were defined by their high affinity and neutralizing activity to known human antigen were invalid for lack of adequate written description;	that: J. Oelke, White and Case LLP, of New York, N.Y. Oskar Liivak, Cornell Law School, of Ithaca, N.Y., for amicus curiae Professor Oskar Liivak. Before LOURIE , O'MALLEY , and CHEN , Circuit Judges. Concurring opinion filed by Circuit Judge O'MALLEY . Opinion LOURIE , Circuit Judge.
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Petitioner's Expert Agrees Active PH20s Share Same Fold

Merck Expert | Dr. Naismith



- Q. Is it the case that active modified PH20 proteins share a common structure in terms of the native fold of PH20?
- A. So they would have the same fold, there could be differences as I described and we know exist between the bee venom and the human hyaluronidase, both are active enzymes.

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

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

Merck Expert | Dr. Naismith



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

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

Q. Mmm-hmm.

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

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

Petitioner's Arguments Invite Legal Error

Paper No. 73
Filed: January 28, 2026

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyne Inc.,
Patentee.

Case No. PGR2025-00003
U.S. Patent No. 11,952,600

PETITIONER'S REPLY

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

Reply at 16

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

Reply at 9-10

Petitioner’s Arguments Invite Legal Error

Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co., 598 F.3d 1336 (2010) 84 U.S.P.Q.2d 7187	
598 F.3d 1336 United States Court of Appeals, Federal Circuit.	<i>Rehe.:</i> Circuit Judge filed opinion dissenting-in-part and concurring-in-part in which Judge Circuit Judge joined.
ARIAD PHARMACEUTICALS, INC. , Massachusetts Inventors of Technology, The Winthrop Institute for Biomedical Research, and the President and Fellows of Harvard College, Plaintiffs-Appellants, v. ELI LILLY AND COMPANY , Defendants-Appellees.	
No. 2008-1248 1 March 22, 2010	
Synopsis: Background: Owners of patent claiming methods comprising the single step of recombining Nuclear Factor kappa B (NF-κB) activity in eukaryotic cells through subunit action against competitor. After a jury found infringement, and concluded that the asserted claims were not invalid for anticipation, lack of enablement, or lack of written description, the United States District Court for the District of Massachusetts, 350 F.3d 1262, 7-20, 23 Sup.Ct. 2009, found competitor's motion for judgment as a matter of law (JMOL), and a final judgment was entered. 2007 WL 272287. Competitor appealed. The United States Court of Appeals for the Federal Circuit, 350 F.3d 1262, affirmed in part and reversed in part, and remanded for further consideration on remand.	“1337 John M. Winkler, of Silver Spring, MD, argued for plaintiffs-appellants. With him on the brief were James W. DeLong, Stephen S. Yalowitz, and Randy C. Economou, Frost Frank Harris Shriver & Jacobson LLP, of New York, NY, and John F. Duffy, of Washington, DC. Of counsel were Laurie H. Shaw, Daniel A. Gahan, Christopher E. Spivey, Jr., Matthew J. McFadden, and Ronald S. Sub. Key Schedule LLP, of New York, NY. Charles E. Longo, Plaintiff, Henderson, Fashen, Grant & Dunne, L.L.P., of Reston, VA, argued for defendant-appellee. With him on the brief were Robert D. Hargrave, David A. Gorman, Howard D. Levine, Laura J. Monahan, and Jennifer A. Johnson, of Washington, DC, and Jennifer S. Rupp, of Palo Alto, CA. Of counsel on the brief were Paul R. Cantrell, Gilbert T. Noy, and Alexander Wilson, Eli Lilly and Company, of Indianapolis, IN. Of counsel were Laura Schubert, Patricia Henderson, Fashen, Grant & Dunne, L.L.P., of Washington, DC.
Holdings: The Court of Appeals, on remand, Circuit Judge held that: claims requiring that patent specification contain a written description of the invention contained a written description requirement separate from enablement, and patent was invalid for failure to provide adequate written description.	“1338 Mark B. Freeman, Attorney, Appellate Staff, Civil Division, United States Department of Justice, Washington, DC, argued for amici curiae United States. With him on the brief were Ann Ruffel, Acting Assistant Attorney General, and Scott R. McDaniel, Attorney, Of counsel on the brief were James A. Toppin, General Counsel, and Raymond J. Chen, Solicitor, United States Patent and Trademark Office, of Arlington, VA. Roberta J. Munch, of Menlo Park, CA, for amici curiae Roberta J. Munch, Esq., Ph.D. Kenneth J. Bruchfeld, Eugene M. P.L.C., of Washington, DC, for amici curiae Novartis A.S. With him on the brief was John J. Callahan. Christopher M. Holman, University of Missouri-Kansas City School of Law, of Kansas City, MO, for amici curiae Law Professor Christopher M. Holman.
Reversed in part and affirmed in part. Rehears: Circuit Judge, wrote separately, expressing dissenting views. Options: Circuit Judge, filed concurring opinion.	
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“The doctrine never created a heightened requirement to provide a nucleotide-by-nucleotide recitation of the entire genus of claimed genetic material; it has always expressly permitted the disclosure of structural features common to the members of the genus.”

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

Idenix Pharmaceuticals LLC v. Gilead Sciences Inc., 941 F.3d 1149 (2019) 118 U.S.P.Q.3d 1987	
941 F.3d 1149 United States Court of Appeals, Federal Circuit.	<i>Affirmed in part and reversed in part.</i>
IDENIX PHARMACEUTICALS LLC , California <i>(Dkt. No. 18-1494)</i> , Plaintiffs-Appellants, v. GILEAD SCIENCES INC. , Defendants-Appellees.	
2018-1691 1 Decided: October 30, 2019	
Synopsis: Background: Owners brought action against competitor, alleging infringement of patent related to methods and compositions for treating Hepatitis C virus (HCV). The United States District Court for the District of Delaware, Leonard P. Stark, Chief Judge, 2015 WL 1112123, granted judgment as matter of law that patent was invalid for lack of enablement. See district judgment as matter of law for failure to meet written description requirement, after jury verdict in owner's favor. Owner appealed.	Procedural Posture: On Appeal: Motion for Judgment as a Matter of Law (JMOL) (District Court).
Holdings: The Court of Appeals, Judge, Chief Judge, held that: quantity of representative factor in enablement inquiry could support finding only of non-enablement; jury reasonably could have found in enablement analysis that synthesis of individual compound was largely routine; finding of non-enablement was supported on basis that patent did not provide enough guidance as to which 2'-modified nucleotides were effective against HCV, and only working examples provided were exceedingly narrow relative to claim scope; representability of art of using modified nucleotides to treat HCV could support only a finding of non-enablement of patent; insufficient breadth of claim could support finding only of non- enablement; and patent providing 18 positive-to-positive formulae describing “principal embodiments” of compounds that might treat HCV did not satisfy written description requirement.	Attorneys and Law Firms Gregory A. Capompoli, Steve Day, Washington, DC, argued for plaintiffs-appellants. Of counsel were Joseph J. Leland, James E. Linn, James P. Kelly, Chicago, IL; Colton, Griffith, Rosen, Smith & Kane, Cleveland, OH; Jonathan J. Sussman, San Diego, CA; Jeffrey A. Lankford, Santa Monica, California; Michael G. Duffin, Jr., Mobile, Alabama; and John L. L. L. L., DC. James R. Boudreau, Oriskany, Herrington & Scordillo LLP, New York, NY, argued for defendant-appellee. Also represented by Edmund Hirschfeld, Elizabeth Koonen, Menlo Park, CA; Brian P. Kelly, California; San Francisco, CA; Eric S. Sussman, Washington, DC; Frank S. Sussman, Fish & Richardson, PC, Boston, MA; and E. Sussman, N. Calif. State, Jonathan Ellis Sussman, San Diego, CA. Rehe.: Judge, Chief Judge, Rehears and Options , Circuit Judge. Options Dissenting opinion filed by Circuit Judge Rehears Rehe.: Chief Judge.
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“We are mindful of *Ariad’s* caution that written description does not require ‘a nucleotide-by-nucleotide recitation of the entire genus.’ The purpose of that rule is to allow relatively few representative examples or formulas to support a claim on a structurally similar genus.”

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

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

Halozyme Expert | Dr. Petsko



293. This does not mean PH20 is unpredictable or that making and using the claimed modified polypeptides is unpredictable. It means PH20 is generally intolerant to mutations unless those mutations are made in certain places, and the '600 patent teaches where to make mutations to likely retain activity. The '600 patent renders modifying PH20 predictable by identifying these areas that are particularly intolerant to mutation, and those that are tolerant.

EX. 2070, Petsko Decl., ¶ 293

Inactives Data Distinguishes These Facts From *Idenix*

Idenix Pharmaceuticals LLC v. Gilead Sciences Inc., 941 F.3d 1149 (2019)	
941 F.3d 1149 United States Court of Appeals, Federal Circuit. IDENIX PHARMACEUTICALS LLC, Universita Degli Studi Di Cagliari , Plaintiffs-Appellants v. GILEAD SCIENCES INC., Defendant-Appellee	Affirmed in part and reversed in part. Newman , Circuit Judge, filed dissenting opinion. Procedural Posture(s): On Appeal; Motion for Judgment as a Matter of Law (JMOL)/Directed Verdict. *1152 Appeal from the United States District Court for the

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

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

finding of non-enablement was supported on basis that patent did not provide meaningful guidance as to which 2'-methyl-up nucleosides were effective against HCV and only working examples provided were exceedingly narrow relative to claim scope;	Dissenting opinion filed by Circuit Judge Newman .
unpredictability of art of using modified nucleosides to treat HCV could weigh only in favor of non-enablement of patent;	Prost , Chief Judge.
immense breadth of claim could support finding only of non-enablement; and	*1153 Idenix Pharmaceuticals LLC and Universita Degli Studi Di Cagliari (collectively, "Idenix") appeal from the decision of the U.S. District Court for the District of Delaware granting judgment as a matter of law ("JMOL") against Idenix and finding that U.S. Patent No. 7,608,597 is invalid for lack of enablement. <i>Idenix Pharm. LLC v. Gilead Scis., Inc.</i> , 2018 WL 922125, at *25 (D. Del. Feb. 16, 2018) ("JMOL Opinion"). Gilead Sciences Inc., ("Gilead") argues that the patent is also invalid for failure to meet the written description requirement, and that the district court erred by failing to grant JMOL on that ground as well. We affirm as to non-enablement
patent providing 18 position-by-position formulas describing "principal embodiments" of compounds that might treat HCV did not satisfy written description requirement.	
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Similarity to Sequence Is A Common Structural Feature; WD Does Not Require Perfect Correspondence To Structure

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

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

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

“CJ’s argument both assumes too strict a legal standard and reads too much into its cited references. Adequate written description does not require a perfect correspondence between the members of the genus and the asserted common structural feature; for a functionally defined genus like the one at issue here, we have spoken more modestly of a ‘correlation between structure and function.’”

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

under function-way-result framework:

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

[Taranto](#), Circuit Judge.

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

Misfolding/Aggregation From Mutation Is Rare

Halozyme Expert | Dr. Petsko



“That would not be the case for PH20.”

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

“... usually not the case for most mutation.” and “... it is rare.”

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

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

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

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

Merck Expert | Dr. Park



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

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

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

Halozyne Expert | Dr. Petsko



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

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

Epistasis Relates To Degree Of Activity, Not Existence Of Activity

Merck Expert | Dr. Naismith



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

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

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

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

Q. Okay, and ----

A. Because there is no epistatic effect.

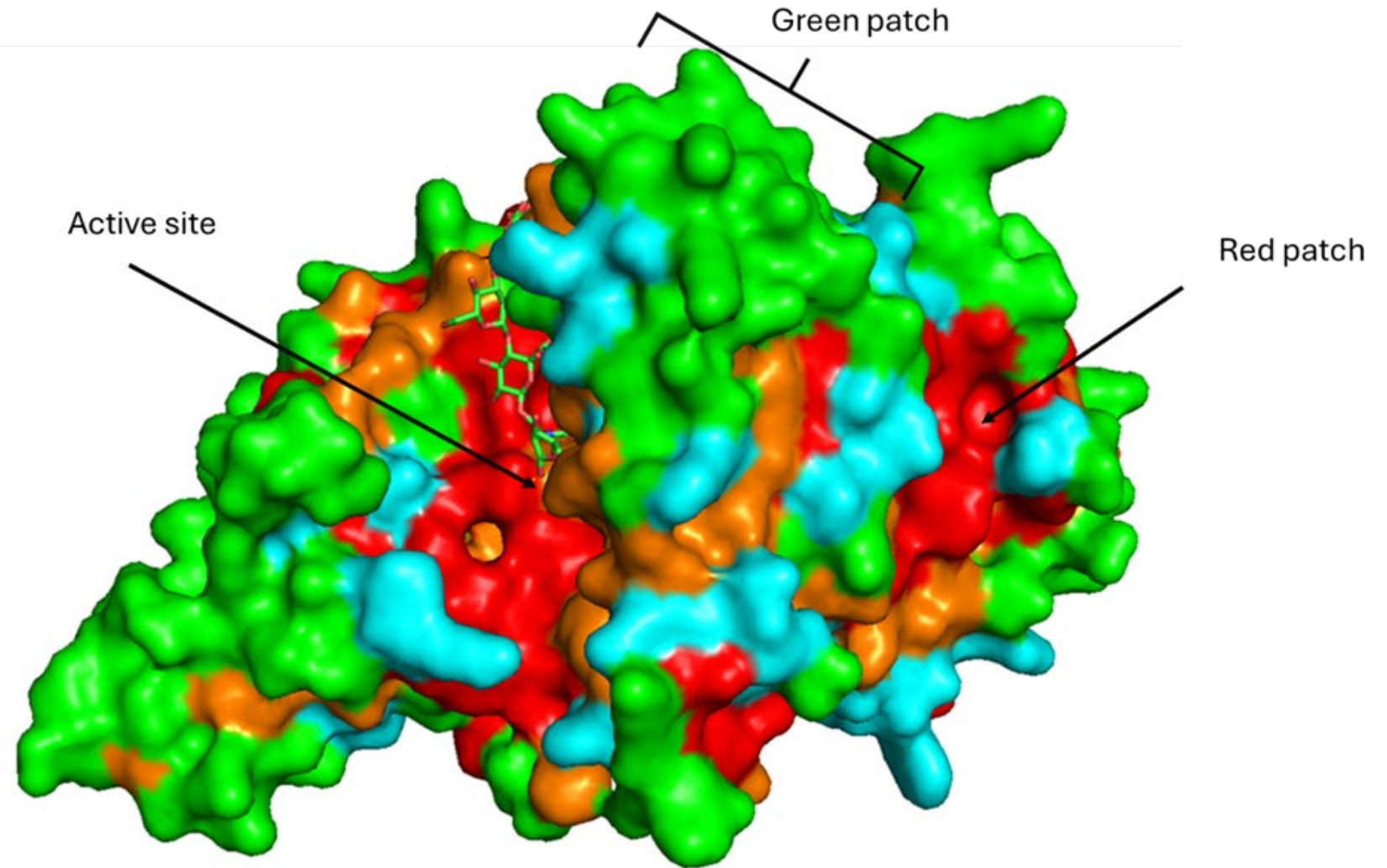
Q. I am trying to understand the additive part?

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

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

Number Of Inactivating Changes Does Not Show Epistasis

Inactivating changes
reflect defined structural
roles, not unpredictability.



EX. 2070, Petsko Decl., ¶ 339

Enablement (Ground 2)



The *Wands* Factors Weigh In Favor Of Enablement

***In re Wands* factors**

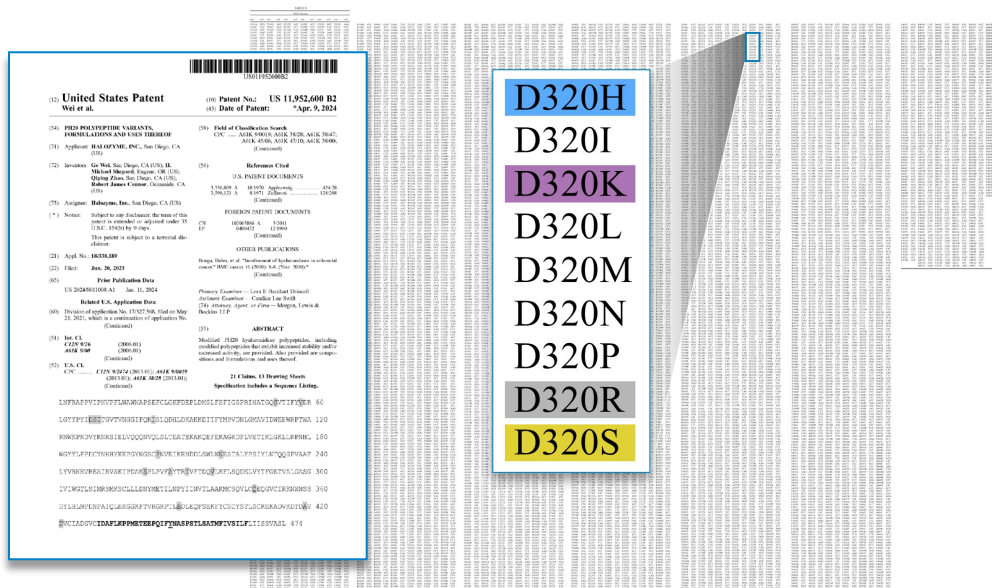
(858 F.2d 731, Fed. Cir. 1988)

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

The Claimed Monopoly Is Extremely Narrow

'600 Patent

Only **four** D320 variants claimed



Subvariants must share $\geq 95\%$ sequence identity

Inventors Did NOT Claim

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

EX. 1001, 200:42-231:17

POSAs Were Skilled And State Of Art Was Developed

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

A POSA would know:

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

EX. 1001, 70:14-54; EX. 2068, ¶303; EX. 2070, ¶¶148-217, 263-342

The Guidance In The Disclosure Is Unprecedented

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

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

The Guidance In The Disclosure Is Unprecedented

Halozyme Expert | Dr. Simpson



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

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

EX. 2068, Simpson Decl., ¶¶ 163-164

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

Application of Angstadt, 537 F.2d 498 (1976)
190 U.S.P.Q. 214

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

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

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

Petitioner's Expert Admits Inactives Guide Practice Of Invention

Merck Expert | Dr. Park



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

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

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

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

Amgen Inc. v. Sanofi, 872 F.3d 1367 (2017)
124 U.S.P.Q.2d 1354

[4] competitors were not entitled to judgment as matter of law

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

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

excluded simply because it post-dated the claims' priority date;

[3] finding of adequate written description could not be permitted merely from finding of ability to make and use;

U.S.C.A. § 112.

6 Cases that cite this headnote

[4] Patents → Genus and species

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Patent Disclosure Makes Modifying PH20 Predictable

Halozyme Expert | Dr. Petsko



- Q. So your opinion is that a POSA could use the data from testing single mutants in the patent to select 15 or 20 substitutions in the PH20 sequence, and you would be able to predict whether that mutated 15 or 20 residue-mutated PH20 will exhibit the activity that you are hoping to get?
- A. My opinion is that you could do so. My opinion is also that you would almost never do so. You would probably rarely, if ever, make that many substitutions. You wouldn't need to.

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

Patent Disclosure Makes Modifying PH20 Predictable

Halozyme Expert | Dr. Simpson



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

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

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

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

Petitioner's Enablement Theory Starts Where No POSA Would

Halozyne Expert | Dr. Simpson



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

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

POSAs Would Not Screen Large Combinatorial Libraries

Halozyme Expert | Dr. Petsko

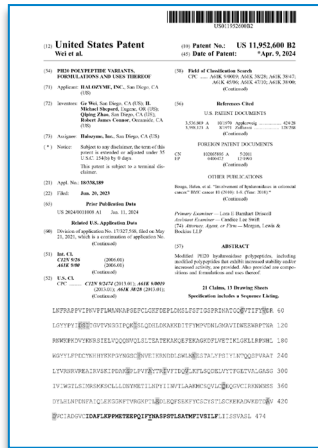


- Q. Are you saying that, after reading the '600 patent, a POSA would not have tried to make PH20 polypeptides by generating combinatorial libraries of mutants having random combinations of substitutions and screening them for activity.
- A. I am saying that under most of the circumstances I can envision, the POSA would not start that way at all. They would start with a much more focused program making use of the data in the patent.
- Q. Did you find anything in the common disclosure suggesting that they should do the path -- should take the path of making combinatorial libraries and screening them to produce PH20 proteins with multiple mutations?
- A. Didn't suggest that to me. Again, I think as long as you are dealing with a -- with a situation like this where you have a wealth of information at every position in the sequence, you would first start to do it by -- if you -- I'm not -- I don't want to use the word "design" in its broadest sense. But if you understand what I mean by that. You would try to -- you would predict -- you would be able to write down sequences where you could predict what you were likely to see and you would test those first.

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

Petitioner Misrepresents Patent Disclosure Re: Screening

'600 Patent



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

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

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

Petitioner Commits Legal Error By Relying On Cumulative Time/Effort

Amgen Inc. v. Sanofi, 598 U.S. 594 (2023)
143 S.Ct. 1243, 215 L.Ed.2d 537, 23 Cal. Daily Op. Serv. 4369...

143 S.Ct. 1243
Supreme Court of the United States.

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

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

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

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

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

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

Petitioner Commits Legal Error By Relying On Cumulative Time/Effort

Paper No. 1

Filed: November 12, 2024

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyme Inc.,
Patent Owner.

Case No. PGR2025-00003
U.S. Patent No. 11,952,600

PETITION FOR POST GRANT REVIEW

“[T]he claim language defines enormous genera: between 10^{49} and 10^{65} distinct polypeptides. To illustrate the real-world absurdity of those claims, consider what practicing their full scope requires. Excluding single-replacement PH20₁₋₄₄₇ mutants, and only focusing on mutants with multiple substitutions in PH20₁₋₄₄₇, a skilled artisan would need to make-and-test $\sim 10^{63}$ mutants having between 2 and 22 substitutions. Producing only one molecule of each—each has to be made and tested to see if it is active or inactive—would require consuming an aggregate mass ($\sim 5.5 \times 10^{27}$ kg,) that exceeds the mass of the Earth ($\sim 6 \times 10^{24}$ kg).⁶⁵ Testing every polypeptide within the claims’ scope in search of ‘active mutants’ is impossible—literally.”

Pet. at 27

Petitioner Commits Legal Error By Relying On Cumulative Time/Effort

In re Wands, 858 F.2d 731 (1988)
57 USLW 2284, 8 U.S.P.Q.2d 1400

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

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

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

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

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

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

Petitioner Commits Legal Error By Ignoring POSA Skill, Guidance

Paper No. 1

Filed: November 12, 2024

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyne Inc.,
Patent Owner.

Case No. PGR2025-00003
U.S. Patent No. 11,952,600

PETITION FOR POST GRANT REVIEW

“They capture a mutant with 5 substituted hydrophobic residues clustered in a small region, as well as one with 22 substitutions mixing polar, charged, aliphatic residues in another, and in any manner.”

Pet. at 33

“[C]laim 4’s parameters would capture that mutant as well as one that also deletes 14 residues from the C terminus.”

Pet. at 33

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

Johns Hopkins University v. CellPro, Inc., 152 F.3d 1342 (1998)
47 U.S.P.Q.2d 1705

152 F.3d 1342

Attorneys and Law Firms

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

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

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

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

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Contraceptive Utility Is Scientifically Credible

- An invention that is at least partially successful in achieving a useful result has credible utility. *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995).
- Petitioner applied a 100% effectiveness standard.
Reply at 39-40
- Petitioner's expert agrees that common contraceptives achieve less than 100% effectiveness.
EX. 2302 (Kelsoe), 131:10-132:19

Contraceptive Utility Is Scientifically Credible

Merck Expert | Dr. Kelsoe



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

A. Contraceptives?

Q. Yes.

A. Yes.

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

A. That's my --

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

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

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

Obviousness (Ground 3)



The Art Did Not Identify The Positions In Question

'429 Patent

Chao

Stern

US007767429B2

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

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

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

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

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

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

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

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

(65) **Prior Publication Data**
US 2004/0268425 A1 Dec. 30, 2004

Related U.S. Application Data
(60) Provisional application No. 60/452,360, filed on Mar. 5, 2003.

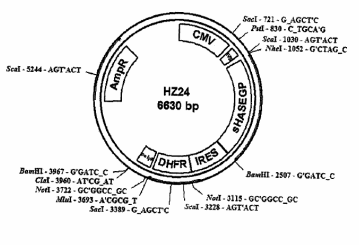
(51) **Int. Cl.**
C12N 9/26 (2006.01)
A61K 38/47 (2006.01)
C12P 21/02 (2006.01)
C07K 14/435 (2006.01)

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

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

(56) **References Cited**
U.S. PATENT DOCUMENTS
3,536,809 A 10/1970 Appierweig 424/435

52 Claims, 1 Drawing Sheet



Petitioner Merck, Ex. 1005, p. 1

EX. 1005

Biochemistry 2007, 46, 6911–6920 6911

Structure of Human Hyaluronidase-1, a Hyaluronan Hydrolyzing Enzyme Involved in Tumor Growth and Angiogenesis^{1,4}

Kinlin L. Chao, Lavanya Muthukumar, and Osant Herzberg*

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

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

ABSTRACT: Mammalian hyaluronidases hydrolyze hyaluronan, a polysaccharide of diverse physiological roles found in all tissues and body fluids. In addition to its function in normal cellular hyaluronan turnover, human hyaluronidase-1 is implicated in cancer proliferation, angiogenesis, and inflammatory diseases; its expression is up-regulated in advanced stages of bladder cancer, whereas the expression of the alternative splice-variants is down-regulated. The crystal structure reveals a molecule composed of two closely associated domains: a catalytic domain that adopts a distorted (β/α)₅ barrel resembling that of bee venom hyaluronidase, and a novel, EGF-like domain, characteristic of involvement in protein–protein interactions and regulatory processes. The structure shows that the fold of this unique EGF-like domain is intact in four alternative splice-variants, whereas the catalytic domain is likely to be unfolded. Thus, these variants may function by competing with the full-length enzyme for the putative protein partner and regulating enzymatic activity in healthy cells.

See <https://pubs.acs.org/doi/10.1021/bi700382g>

invasion, angiogenesis, and inflammatory responses (2–5). The cellular role of HA and the HA-mediated signal transduction pathways depends on its size (recently reviewed by Stern et al. (4)). Large HA polymers function in organizing the extracellular matrix and serve as lubricant and shock absorber. In shock, septicemia, post surgery, blood loss, and burns, the level of circulating high molecular mass HA increases. These HA polymers are antiangiogenic, immunosuppressive, and anti-inflammatory. In contrast, HA fragments of intermediate sizes are involved in the body's alarm system. They stimulate angiogenesis and inflammatory reactions and facilitate cancer progression and invasion (4). Such HA fragments activate several cytoplasmic and extracellular signal transduction pathways associated with Raf-1 kinase, MAP kinase, and ERK. Short HA oligosaccharides

¹ Grant sponsors: National Institutes of Health Grant P01-OM057890. The Advanced Photon Source is supported by the U.S. Department of Energy, Basic Energy Sciences, Office of Science, under Contract W-31-109-Eng-38.

² The coordinates have been deposited in the Protein Data Bank (entry code 3PE1).

³ Corresponding author. Mailing address: Center for Advanced Research in Biotechnology, University of Maryland Biotechnology Institute, 9600 Gudelekys Drive, Rockville, MD 20850. Tel: 240-314-6245. Fax: 240-314-6255. E-mail: osant@carbinst.gov.

⁴ Abbreviations: hHyal, human hyaluronidase; bHyal, bee venom hyaluronidase; HA, hyaluronan; EGF, epidermal growth factor.

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

Petitioner Merck, Ex. 1006, p. 6911

EX. 1006

9/23/25, 9:53 PM Mammalian Hyaluronidases ISSN 1349-9416 / CODEN GLYCAJ

Glycoforum

ISSN 1349-9416 / CODEN GLYCAJ

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June 30, 2000

Mammalian Hyaluronidases (2000 Vol.4, A6)

Hyaluronidase Sequences

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



Robert Stern

<https://www.glycoforum.gr.jp/article/04A6.html>

1/20

Halozyme EX2088
Merck v. Halozyme
PGR2025-00003

EX. 2088

Petitioner's Obviousness Analysis Is Premised On Hindsight

Merck Expert | Dr. Park



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

EX. 1004, ¶103

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

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

Conclusion

