

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PASSAGE BIO, INC.,
Petitioner,

v.

THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA
and REGENXBIO, INC.,
Patent Owner.

PGR2021-00073
Patent 10,695,441 B2

Before JOHN G. NEW, SHERIDAN K. SNEDDEN, and ZHENYU YANG,
Administrative Patent Judges.

YANG, *Administrative Patent Judge.*

DECISION
Denying Institution of Post-Grant Review
35 U.S.C. §§ 324(a), 325(d)

I. INTRODUCTION

Passage Bio, Inc. (“Petitioner”) filed a Petition (Paper 2 (“Pet.”)), requesting a post-grant review of claims 1–15 of U.S. Patent No. 10,695,441 B2 (Ex. 1001, “the ’441 patent”). The Trustees of the University of Pennsylvania and the exclusive licensee REGENXBIO, Inc. (collectively “Patent Owner”) filed a Preliminary Response (Paper 7 (“Prelim. Resp.”)). With our authorization, Petitioner filed a Reply (Paper 9), and Patent Owner filed a Sur-reply (Paper 10).

For the reasons provided below, we exercise our discretion under 35 U.S.C. §§ 324(a) and 325(d), and deny institution of a post-grant review.

A. Related Matters

According to Patent Owner, the ’441 patent is part of a family of related applications, some of which are pending. Paper 4, 1–2. The parties state that no other judicial or administrative matters may affect or be affected by a decision in this proceeding. *Id.* at 2; Pet. 3.

B. The ’441 Patent

The ’441 patent relates to “[s]equences of novel adeno-associated virus [AAV] capsids and vectors and host cells containing these sequences.” Ex. 1001, Abstract.

According to the ’441 patent, prior art “suggested that AAV vectors may be the preferred vehicle for gene delivery.” *Id.* at 1:49–50. Before the ’441 patent, “there ha[d] been several different well-characterized AAVs.” *Id.* at 1:50–52. “AAVs of different serotypes exhibit different transfection efficiencies.” *Id.* at 1:53–54.

The '441 patent discloses “a human AAV serotype previously unknown, designated herein as clone 28.4/hu.14, or alternatively, AAV serotype 9.” *Id.* at 2:9–11. According to the '441 patent, “novel serotype AAV9 refers to AAV having a capsid which generates antibodies which cross-react serologically with the capsid having the sequence of hu.14 [SEQ ID NO: 123] and which antibodies do not cross-react serologically with antibodies generated to the capsids of any of AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7 or AAV8.” *Id.* at 13:24–30. “The AAV9 nucleic acid sequences of the invention include the DNA sequences of SEQ ID NO: 3, which consists of 2211 nucleotides.” *Id.* at 13:32–34.

The '441 patent discloses that

The AAV capsid is composed of three proteins, vp1, vp2 and vp3, which are alternative splice variants. . . . The AAV9/HU.14 capsid proteins include vp1 [amino acids (aa) 1 to 736 of SEQ ID NO: 123], vp2 [about aa 138 to 736 of SEQ ID NO: 123], vp3 [about aa 203 to 736 of SEQ ID NO: 123], and functional fragments thereof. Other desirable fragments of the capsid protein include the constant and variable regions, located between hypervariable regions (HVR). Other desirable fragments of the capsid protein include the HVR themselves.

Id. at 14:49–59.

The '441 patent “provides ‘superfamilies’ or ‘clades’ of AAV of phylogenetically related sequences. These AAV clades provide a source of AAV sequences useful for targeting and/or delivering molecules to desired target cells or tissues.” *Id.* at 1:63–67. Specifically, the '441 patent discloses Clade F, which is “identified by the name of a novel AAV serotype identified herein as hu.14/AAV9 [SEQ ID Nos: 3 and 123]. In addition, this

clade contains other novel sequences including, hu.31 [SEQ ID NOs: 1 and 121]; and hu.32 [SEQ ID Nos: 2 and 122].” *Id.* at 10:50–54.

According to the ’441 patent, Clade F includes an AAV having “a capsid with an amino acid identity of at least 85% identity, at least 90% identity, at least 95% identity, or at least 97% identity over the full-length of the vp1, the vp2, or the vp3 of the AAV9 capsid, SEQ ID NO: 3 and 123.” *Id.* at 10:55–59. It also includes “an AAV having a capsid derived from one or more of hu.14/AAV9 [SEQ ID Nos: 3 and 123], hu.31 [SEQ ID NOs: 1 and 121] and hu.32 [SEQ ID Nos: 1 and 122].” *Id.* at 10:60–64.

The ’441 patent states that “[t]he AAV clades of the invention are useful for a variety of purposes, including providing ready collections of related AAV for generating viral vectors, and for generating targeting molecules.” *Id.* at 10:65–11:1.

C. Illustrative Claims

Claims 1, 4, 7, and 10 are independent and are reproduced below:

1. A cultured host cell containing a recombinant nucleic acid molecule encoding an AAV vp1 capsid protein having a sequence comprising amino acids 1 to 736 of SEQ ID NO: 123 (AAV9) or a sequence at least 95% identical to the full length of amino acids 1 to 736 of SEQ ID NO: 123, wherein the vp1 protein having at least 95% identity has up to 37 amino acid modifications in the amino acids 1 to 736 limited to an amino acid position of SEQ ID NO: 123 selected from amino acids: [list of 499 amino acid positions].
4. A cultured host cell containing a recombinant nucleic acid molecule encoding an AAV vp2 capsid protein having a sequence comprising amino acids 138 to 736 of SEQ ID NO: 123 (AAV9) or a sequence at least 95% identical to the full length of

amino acids 138 to 736 of SEQ ID NO: 123, wherein the vp2 protein having at least 95% identity has up to 29 amino acid modifications in the amino acids 138 to 736 limited to an amino acid position of SEQ ID NO: 123 selected from amino acids: [list of 426 amino acid positions].

7. A cultured host cell containing a recombinant nucleic acid molecule encoding an AAV vp3 capsid protein having a sequence comprising amino acids 203 to 736 of SEQ ID NO: 123 (AAV9) or a sequence at least 95% identical to the full length of amino acids 203 to 736 of SEQ ID NO: 123, wherein the vp3 protein having at least 95% identity has up to 26 amino acid modifications in the amino acids 203 to 736 limited to an amino acid position of SEQ ID NO: 123 selected from amino acids: [list of 366 amino acid positions].

10. A cultured host cell containing a recombinant nucleic acid molecule comprising (a) nucleotides 1 to 2208 of SEQ ID NO: 3 or a sequence at least 98% identical to nucleotides 1 to 2208 of SEQ ID NO: 3 that encodes an AAV capsid protein; (b) nucleotides 412 to 2208 of SEQ ID NO: 3 or a sequence at least 98% identical to nucleotides 412 to 2208 of SEQ ID NO: 3 that encodes an AAV capsid protein; or (c) nucleotides 607 to 2208 of SEQ ID NO: 3 or a sequence at least 98% identical to nucleotides 607 to 2208 of SEQ ID NO: 3 that encodes an AAV capsid protein, wherein the AAV capsid protein has at least 95% identity to the full-length of the amino acids 1 to 736 of SEQ ID NO: 123 (AAV9 capsid protein), and wherein the protein has up to 37 amino acid modifications in the amino acids 1 to 736 limited to an amino acid position of SEQ ID NO: 123 selected from amino acids: [list of 499 amino acid positions], wherein the recombinant nucleic acid molecule further comprises a heterologous non-AAV sequence, and wherein the recombinant nucleic acid molecule is a plasmid.

D. Asserted Grounds of Unpatentability

Ground	Claims Challenged	35 U.S.C. §	Reference/Basis
1	1–15	112(a)	Written Description
2	1–15	112(a)	Enablement

Ground	Claims Challenged	35 U.S.C. §	Reference/Basis
3	1–15	101	Utility
4	1–15	102	'111 patent ^{1,2}

In support of its position, Petitioner relies on the declaration of Dr. Mark Kay (Ex. 1003).

II. ANALYSIS

A. Grounds 1 and 2

Patent Owner asks us to exercise our discretion under 35 U.S.C. § 325(d) and deny this Petition. Prelim. Resp. 51–61. Patent Owner argues “Petitioner’s written description and enablement challenges are not new.” *Id.* at 52. According to Patent Owner,

[t]he prosecution history of this patent family involved numerous rejections concerning the same § 112 issues that are raised in the Petition. These rejections were all directed to claims that were identical, in relevant part, to the issued claims of the '441 patent. Petitioner rehashes the same arguments raised by the Examiner over more than a decade of prosecution. Patent Owner ultimately overcame these rejections. The Petitioner, moreover, fails to articulate any material error by the Patent Office in issuing the claims.

Id. at 52–53. We find Patent Owner’s arguments persuasive.

Under § 325(d), in determining whether to institute a post-grant review, “the Director may take into account whether, and reject the petition

¹ U.S. Patent No. 7,906,111 B2, issued March 15, 2011 (Ex. 1019, “the '111 patent”). The '111 patent is in the same family as the challenged '441 patent. *See infra*, Section II.A.1.

² Petitioner contends that “[w]hile Petitioner discusses the '111 prior art patent, other printed publications – all within the '441 patent’s family – are also prior art because they published more than one-year prior to October 2, 2018.” Pet. 73 n.14.

or request because, the same or substantially the same prior art or arguments previously were presented to the Office.” Our § 325(d) analysis employs a two-prong framework: (1) whether the arguments presented in the petition are the same or substantially the same as those previously presented to the Office; and (2) if so, whether the petitioner has demonstrated a material error by the Office in its prior consideration of those arguments. *Advanced Bionics, LLC v. Med-El Electromedizinische Geräte GmbH*, IPR2019-01469, Paper 6, 8 (PTAB Feb. 13, 2020) (precedential). When analyzing the second prong, “[i]f reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability.” *Id.* at 9. “At bottom, this framework reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown.” *Id.*

1. The Same or Substantially the Same Arguments

The ’441 patent issued from application No. 16/149,218 (“the ’218 application”), filed on October 2, 2018. Ex. 1001, codes (21), (22). Through continuation, the ’218 application claims priority to a series of earlier applications (“priority applications”),³ including application

³ The post-grant review provisions apply only to a patent that contains a claim with an effective filing date on or after March 16, 2013. *See Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112-29, 125 Stat. 284 (2011), §§ 3(n)(1), 6(f)(2)(A).* According to Petitioner, even though the ’441 patent, on its face, claims priority to applications filed before March 16, 2013, those applications do not satisfy the written description and enablement requirements. Pet. 26. Thus, Petitioner argues the ’441 patent is eligible for post-grant review. *Id.* The written description

No. 15/227,418 (“the ’418 application”), filed August 3, 2016, now patent No. 10,265,417 (“the ’417 patent”), and application No. 10/573,600 (“the ’600 application”), filed September 30, 2004, now the ’111 patent. *Id.*, code (63). It is undisputed that the ’441 patent specification is identical to those of the priority applications. Pet. 26 n.7; Prelim. Resp. 30 n.6.

Patent Owner argues that “[t]he same Examiner handled the prosecution of all the applications in the chain of priority of the ’441 patent for eleven years.” Prelim. Resp. 53. In Appendix A to its Preliminary Response, Patent Owner compares the written description and enablement arguments presented in the Petition and those considered by the examiner during the prosecution of the ’218 application and the priority applications. According to Patent Owner, Appendix A shows that the examiner “grappl[ed] with the very arguments raised in the Petition” before ultimately “determin[ing] that the ’441 patent Priority Applications fulfill the written description and enablement requirements.” *Id.* We agree with Patent Owner.

i. Representative Number of Species

Petitioner points out that each of challenged claims 1 and 10 recites a cultured host cell containing a recombinant nucleic acid molecule encoding an AAV vp1 capsid protein that is “at least 95% identical” to vp1 of AAV9 and has “up to 37 amino acid modifications” at any of 499 different, specified positions. Pet. 12–14. Claims 4 and 7 are similar to claim 1, with

and enablement arguments to support review eligibility and those to support unpatentability are substantially the same. *Id.* at 66. We do not need to resolve the eligibility issue because, as explained below, we exercise our discretion under §§ 324(a) and 325(d) and deny institution.

claim 4 reciting “at least 95% identical” to vp2 of AAV9 with “up to 29 amino acid modifications” at any of 426 positions, and claim 7 reciting “at least 95% identical” to vp3 of AAV9 with “up to 26 amino acid modifications” at any of 366 positions. *Id.* Because of such language, Petitioner argues, the scope of the challenged claims is “unfathomably large.” *Id.* at 28. Yet, according to Petitioner,

[T]he specification describes only one example falling within the scope of the unfathomable breadth of the claims (AAV9) and two closely related examples (hu.31 and hu.32). These examples are neither a representative number of species nor does the specification, through these three examples or otherwise, provide structural features common to the members of the genus to allow a skilled artisan to visualize or recognize the members of the entire claimed genus[.]

Id. Thus, Petitioner contends “the specification does not show possession of the claims’ vast genera.” *Id.* at 27, 67.

Specifically, Petitioner argues that “the specification discloses **only one** capsid, AAV9, falling within the scope of the genus claimed by each independent claim.” Pet. 31. But even if hu.31 and hu.32, which are naturally occurring sequences, and thus, according to Petitioner fail to meet the limitation of “amino acid modifications,” are considered, Petitioner contends “they would still not be ‘representative species’ of the claimed genus. *Id.* at 31–32. During the prosecution of the ’218 application and the priority applications, the examiner expressed the same concerns.

For example, during the prosecution of the ’418 application (which issued as the ’417 patent), the examiner noted that pending claim 17 recited an AAV comprising an AAV9 capsid “wherein the capsid comprises a vp1 protein that is 95% identical to amino acids 1–736 of SEQ ID NO: 123,” and

other pending claims recited a vp2 protein with 95% identity to amino acids 138–736, and a vp3 protein with 95% identity to amino acids 203–736, of SEQ ID NO: 123. Ex. 1011, 1373. The examiner found the claims “thus are drawn to a large genus.” *Id.*

The examiner observed that “the specification discloses two sequence[s] that have full length correlation with SEQ ID NO: 123 with a few mismatches in the first 50 amino acids.” *Id.* The examiner repeatedly rejected the pending claims for lacking written description support because the “two naturally occurring variants” are “neither representative of the entire genus nor reflect[] the variation that exists between the species of the recited genus.” *Id.* at 1377, 2196.

Similarly, during the prosecution of the ’600 application (which issued as the ’111 patent), the examiner made the same statements regarding the “95% identity” limitation. Ex. 2023, 38–40. The examiner recognized that

To satisfy the written description requirement in the case of a chemical or biotechnological genus, more than a statement of the genus is normally required. One must show that one has possession, as described in the application, of sufficient species to show that he or she invented and disclosed the totality of the genus. The “representative number of species” must be representative of the entire genus and, reflect variation between the species of the genus.

Id. at 39.

The examiner acknowledged the applicant’s argument that “there are two disclosed sequences SEQ ID NO:121 and 122 that provide examples of sequences that are 95% identical to SEQ ID NO:123.” *Id.* at 38. In response, the examiner stated “[t]his class of naturally occurring variants is neither

representative of the entire genus nor reflects the variation that exists between the species of the recited genus.” *Id.* at 40.

ii. Common Structural Features

Petitioner contends that the challenged claims lack written description support because the specification fails to disclose adequate common structural features. Pet. 36. According to Petitioner, “[w]hile the specification describes twelve hypervariable regions and six ‘other desirable fragments’ within AAV9 (EX1001 at 14:5-15:31), the claims do not specify or preclude modifications in those regions, nor does the specification teach that modification or preservation of those regions is critical or important to the resulting capsid protein.” *Id.* at 37. Petitioner emphasizes the field is “highly unpredictable” and even “small amino acid variations can have large effects on the structure of a capsid and its function.” *Id.* As support, Petitioner points to post-filing date evidence, such as Adachi.⁴ *Id.* at 39. During the prosecution of the ’218 application and the priority applications, the examiner expressed the same concerns.

For example, during the prosecution of the ’418 application, the examiner rejected pending claims reciting proteins with “at least 95% identity” for lack of written description support. Ex. 1011, 1372–73. The examiner found “the disclosure does not demonstrate what sequences must be retained and what sequences are dispensable,” especially given that “there is uncertainty as to what domains, what amino acids and what structures of

⁴ Adachi et al., *Drawing a High-Resolution Functional Map of Adeno-Associated Virus Capsid by Massively Parallel Sequencing*, 5 NAT. COMM. 3075 (2014) (Ex. 1012).

the protein are required to mediate the recited function.” *Id.* at 1373, 1375, 2198–99; *see also id.* at 2196–97 (“[The specification does not provide any guidance as to which amino acids can be changed such that the activity is unchanged.]”).

During the prosecution of the ’218 application, which issued as the challenged ’441 patent, the same examiner similarly rejected the pending claims for lack of written description support. Ex. 1002, 3871. According to the examiner, “the scope of the invention is extremely broad;” yet, “the specification and the art do not describe the nucleotides that can be altered and those which are critical for encoding capsid function for AAVhu14/AAV9.” *Id.* The examiner also repeated the same statements as those made during the prosecution of the ’418 application. *See, e.g., id.* at 3873–74, 5067–69.

Relying on several references, including Wu,⁵ the same reference Petitioner’s expert relies on (*see, e.g.,* Ex. 1003 ¶¶ 134, 141 (citing Ex. 1007)), the examiner emphasized that “minor changes in the capsid, given the lack of characterization of the structure-function relationship have profound effects on the functional properties. In some cases this can be inactivation of the capsid (see Wu) by even minor alterations.” *Id.* at 5078, 5173; *see also id.* at 5073, 5167 (“Wu teaches that single modifications (as compared to 37 as claimed) can begin to define some of the structure-functional relationships of the capsid proteins.”).

⁵ Wu et al., *Mutational Analysis of the Adeno-Associated Virus Type 2 (AAV2) Capsid Gene and Construction of AAV2 Vectors with Altered Tropism*, 74 J. VIROL. 8635–47 (2000) (Ex. 1007).

The examiner also cited to Adachi, the same post-filing date evidence Petitioner relies on, to support the statement that “[a]t time of filing (2004), the capsid proteins of any of the AAVs was not characterized.” *Id.* at 5172. According to the examiner, “the lack of characterization of the capsid protein at the time of filing means one could not know which of the 736 amino acids or 2208 nucleotides could be modified without affecting the ability to form a ‘capsid’ protein.” *Id.*; *see also id.* at 5073, 5167 (“This lack of unifying properties as well as lack of characterization of the proteins exacerbates the unpredictability of identifying the broad genus of amino acids in the face of missing structural requirements.”).

iii. Lists of Positions for Potential Amino Acid Modifications

Petitioner contends that there is no written description support for the listed modification sites. Pet. 43. Petitioner acknowledges that during prosecution of the ’418 application, the applicant argued that “at least one way artificial AAV capsids could be engineered/generated by substituting amino acid residues of the AAV9 capsid with alternative amino acid residues ‘recruited’ from the corresponding position in the other 77 AAV capsids aligned in FIG. 2.” *Id.* (quoting Ex. 1011, 1511, 2888). According to Petitioner, however, Figure 2 provides no such support. *Id.*

Specifically, Petitioner contends although the applicant “suggested during prosecution that Figure 2 teaches ‘non-conserved regions [that] *can be* substituted,’ there is no teaching in Figure 2 or the Priority Applications that such ‘non-conserved regions’ are the 366, 426, or 499 modification positions of the claims.” *Id.* at 45 (quoting Ex. 1011, 1545 (¶ 28), 1859 (¶ 15), 2213, 2888) (emphasis and internal brackets added by Petitioner).

Petitioner also argues that the specification generally provides no support for the claimed lists of amino acid modification positions. *Id.* at 52 (“While the specification recites in attorney boilerplate a permissible sequence nonidentity of no more than 5%, the specification says nothing about where the 5% of changes can be made.”).

Petitioner further contends that its challenge based on “lack of written description support for the claimed ‘lists’ is a new argument not considered by the Examiner in either prosecution record.” *Id.* at 82. We are not persuaded by Petitioner’s argument.

As explained below, during the prosecution of the ’218 application and the priority applications, the examiner rejected the pending claims for failing to sufficiently describe the positions for potential amino acid modifications. In fact, the “lists” of the positions for modification were added specifically in response to such concern of the examiner. *See infra*, Section II.A.2.

For example, during the prosecution of the ’218 application, the examiner found “the claims amount to random and non-coordinated substitutions at up to 37 positions.” Ex. 1002, 5074, 5168. The examiner noted

Applicants’ main argument for the ability to generate variable AAV capsids is based upon the availability of AAV sequences that can then be aligned with support from the alignment of hu.31 and hu.32. This demonstrate what amino acids differ and that the specification teaches that chimeras can be made by substituting amino acids with alternative amino acids recruited from the corresponding positions.

Id. at 5078. The examiner considered, but found unpersuasive, the applicant's suggestion that "using anyone of the 390 non-conserved positions as choices to substitute heterologous sequences from another capsid." *Id.* at 5078–79, 5173; *see also id.* at 5079 ("Applicants also rely on a comparison of a number of AAV and argue that one SHOULD use the remaining 390 non-conserved positions as those to be modified.").

Similarly, during the prosecution of the '418 application, the examiner "noted that applicants refer to positions 'identified' in figure 2." Ex. 1011, 2210. The examiner stated that "the disclosure of potentially 390 amino acids that are non-conserved amino acids that *can* be modified is not sufficient." *Id.* at 2210. According to the examiner,

Given that the protein can be absent 5% of full length, fragments are claimed. Furthermore, for proteins with 5% variability of sequence, a protein of 736 amino acids can have as many as 37 different *combinations* of amino acids mutated. 37 mutational combinations, randomly made, amounts to characterizing the structure for allowable mutations. The specification teaches only SEQ ID NO: 123 and does not provide those variable amino acids nor any fragments such that a person of skill in the art would recognize those amino acids that are related by 95% to SEQ ID NO: 123 and have capsid formation and function.

Id. at 1374, 2198. The examiner stated "Applicants have suggested that the non-conserved regions can be substituted with AAV9 sequences. Given the lack of characterization of the AAV9 functional domains, a means of reciting just such limitation would provide some of the necessary description." *Id.* at 2213.

iv. Enablement

Petitioner argues that despite the broad scope of the challenged claims, the specification “provide[s] no teaching regarding the generation of functional, useful (operable) capsid proteins having such modifications.” Pet. 54. According to Petitioner, “[f]inding such capsid proteins requires a skilled artisan to prepare each individual protein and test it; thus, it requires skilled artisans to perform undue experimentation.” *Id.* at 54–55. Petitioner analyzes the *Wands* factors and concludes that the challenged claims are not enabled. *Id.* at 55–65. During the prosecution of the ’218 application and the priority applications, the examiner conducted substantially the same *Wands* factors analysis, and rejected pending claims for lack of enablement.

For example, during the prosecution of the ’600 application, the examiner observed that the pending claims were drawn to, among others, “an AAV comprising an AAV9 capsid comprising at least 95% identity to amino acids 203–736 of SEQ ID NO:123.” Ex. 2023, 10. “By recitation of the protein in terms of identity,” the examiner continued, the claims encompass “a potentially large number of proteins . . . that may or may not encode a protein with the capabilities of capsid function.” *Id.* at 10–11 (“[T]he claims are directed to a large genus of proteins that are variants and fragments with no requirement of structure.”).

The examiner stated that “the specification teaches only SEQ ID NO: 123 and does not provide those variable amino acids nor any fragments such that a person of skill in the art would recognize those amino acids that are related by 95% . . . with capsid function.” *Id.* at 12; *see also id.* at 11 (“[T]he specification teaches only that SEQ ID NO: 123 is essential to form

a capsid or else use of a number of sequences in the context of an entire capsid protein.”).

The examiner found that “[t]he amount of direction presented and the number of working examples provided in the specification are very narrow compared to the breadth of claims at issue.” *Id.* at 11. Citing numerous references, the examiner pointed out “even limited amino acid modifications can have dramatic effects on protein structure and function” and “these effects are highly unpredictable.” *Id.* at 12–15. As a result, the examiner concluded:

Given the large size and diversity of the recited sequences, the absence of disclosed or art recognized correlations between structure and function and the large number of potential sequences or homologues, variants, and fragments[,] and in view of the unpredictability of the art of predicting the functional and structural nature of homologues, variants, and fragments of SEQ ID NO:123[,] undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the unpredictability of the art, the poorly developed state of the art with regard to predicting the structural/functional characteristics of a protein from primary sequence alone, the lack of adequate working examples and the lack of guidance provided by applicants, the skilled artisan would have to have conducted undue, unpredictable experimentation to practice the claimed invention.

Id. at 16; *see also id.* at 11 (“The breadth of enabled subject matter is not commensurate in scope with the claims.”). Later, the examiner repeated these statements and maintained the enablement rejection. *Id.* at 30–37.

Similarly, during the prosecution of the ’418 application, the examiner rejected the pending claims for lack of enablement “because the

specification, while being enabling for an AAV comprising an AAV9 capsid with a capsid protein comprising the amino acid sequence of 1–736, 138–736 and 203–736 of SEQ ID NO: 123, does not reasonably provide enablement for any other embodiment.” Ex. 1011, 1361–62. After analyzing the *Wands* factors in detail, the examiner concluded:

It would require undue experimentation to determine which of the recited nucleic acids would result in a capsid protein. In view of predictability of the art to which the invention pertains and the lack of guidance in the specification: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Id. at 1362–72.

During the prosecution of the ’218 application, the examiner again rejected the pending claims for lack of enablement. Ex. 1002, 5164 (“[W]here a claim purports to cover all nucleic acids that encode a specific protein and the specification discloses but a single DNA known to do so, the situation is analogous to a single means claim and does not meet the enablement requirement.”). According to the examiner,

The instant claims are drawn to recombinant nucleic acid molecules that encode AAVhu14/AAV9 capsid proteins vp1, vp2 and/or vp3. The claims also recite that the encoding sequences can be 95% related to amino acid sequences of SEQ ID NO:123 or 98 and 99% related to nucleotides sequences of SEQ ID NO:3. However, the specification and the art do not

describe the nucleotides that can be altered and those which are critical for encoding capsid function for AAVhu14/AAV9.

Id. at 5160.

In this instance, as in the prosecution of the '600 and '418 applications, the examiner analyzed the *Wands* factors, finding the pending claims were broad, the specification lacked guidance, and the field was complex, uncharacterized, and unpredictable. *Id.* at 5161–76. The examiner stated:

In light of the art and the specification, a person of skill in the art could not know which of the essentially infinite number of molecules that are related by 90%, 95% or 99% to amino acids of SEQ ID NO: 123. While it is routine to screen for variants comprising multiple substitutions/multiple modifications, the specific amino acid positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success to retain the desired activity are limited and the result of such modifications is unpredictable.

Id. at 5176. Thus, the examiner concluded “[t]he claims lack enablement due to excessively broad scope pertaining to the genus of sequences encompassed.” *Id.* at 5160.

v. *AAV Capsid Protein*

Petitioner asserts that the examiner's § 112 rejections “focused on the lack of a disclosed structure-function relationship tied to biological activity for the capsid proteins,” whereas the arguments in the Petition “are limited to the basic function necessary to be an AAV capsid protein[] (formation of the capsid).” Pet. 81. We are not persuaded by this argument.

As an initial matter, we agree with Patent Owner that “the only functional requirement of the claims is the ability to form a functional

capsid.” Sur-reply 8; *see also* Pet. 21 (proposing that we construe the term “AAV capsid protein” to mean “a protein that can form an AAV capsid”).

More importantly, contrary to Petitioner’s contention, the examiner, during the prosecution of the ’218 application and priority applications, specifically considered the formation of the capsid. *See, e.g.*, Ex. 1002, 5172 (“[T]he lack of characterization of the capsid protein at the time of filing means one could not know which of the 736 amino acids or 2208 nucleotides could be modified without affecting the ability to form a ‘capsid’ protein.”); Ex. 1011, 1374, 2198 (“The specification teaches only SEQ ID NO: 123 and does not provide those variable amino acids nor any fragments such that a person of skill in the art would recognize those amino acids that are related by 95% to SEQ ID NO: 123 and have capsid formation and function.”); Ex. 2023, 11 (“[T]he specification teaches only that SEQ ID NO: 123 is essential to form a capsid.”).

In sum, Petitioner argues that the challenged claims lack written description support and enablement. Having reviewed the prosecution histories, however, we find that Petitioner’s arguments are the same or substantially the same as those previously presented to the Office during the prosecution of the ’218 application and the priority applications.

2. Material Error

Because we find the arguments presented in the Petition are the same or substantially the same as those previously presented to the Office, we must determine whether Petitioner has demonstrated a material error by the Office in its prior consideration of those arguments. *Advanced Bionics*, Paper 6 at 8. We conclude that Petitioner has not.

Petitioner points out that the examiner allowed the challenged claims after the applicant amended the pending claims “to include specific amino acid modification locations and numerical limits” consistent with amendments made in the ’418 application. Pet. 80 (citing Ex. 1002, 5228). Petitioner argues that, “[a]s the Examiner accepted this Amendment without comment, it is not clear that the Examiner sufficiently considered whether this claim language satisfies the written description and enablement requirements.” *Id.* at 81 (internal quotation marks omitted). We are not persuaded.

As discussed above, during the prosecution of the ’418 application, the examiner rejected the pending claims reciting proteins with “at least 95% identity” for lack of written description support. Ex. 1011, 2194. Specifically, the examiner stated “Applicants have suggested that the non-conserved regions can be substituted with AAV9 sequences. Given the lack of characterization of the AAV9 functional domains, a means of reciting just such limitation would provide some of the necessary description.” *Id.* at 2213. In response, the applicant amended the pending claims to include specific amino acid modification locations and numerical limits. *Id.* at 2883–87, 2903–08; *see also id.* at 2888 (“The claims have been amended in a manner consistent with the examiner’s suggestion . . . such that . . . the locations of the amino acid positions which may be modified are now recited in the claim.”). In the next office action, the examiner withdrew the § 112 rejection. *See id.* at 2912–15 (rejecting the pending claims for double patenting only).

It is worth noting that the examiner did not just accept the amendments as they were; instead, because the amended claims were “awkwardly written,” she objected to them and recommended further amendments to “simplif[y]” and “more accurately reflect the intent of the claim.” *Id.* at 2912–14. In view of the reasoned § 112 rejections in the previous office action, the withdrawal of those rejections later, and the attention to detail in the phrasing of the claim language throughout prosecution, Petitioner does not persuade us that the examiner’s consideration of the amendment was insufficient.

During the prosecution of the ’418 application, the applicant submitted three declarations. *See* Ex. 1011, 1854–69 (“Kozarsky Declaration”); 1738–1743 (“Wilson Declaration”); 1535–48 (“Second Kozarsky Declaration”). The applicant resubmitted these declarations during the prosecution of the ’218 application. Ex. 1002, 4692–707, 4718–31, 4946–51. It is undisputed that these declarations supported the applicant’s arguments to overcome the § 112 rejections.

Indeed, in her Declaration, Dr. Kozarsky explained how an ordinarily skilled artisan would have read the specification at the relevant time. Ex. 1011, 1856–68 (¶¶ 8–36). She concluded that, based on the disclosures of the specification, the artisan “would have found specific and operative instructions for the design, construction and preparation of rAAVs having capsids that are at least 95% identical to the amino acid sequences recited in the claims.” *Id.* at 1856 (¶ 7).

In her Second Declaration, after discussing each *Wands* factor (*id.* at 1536–47 (¶¶ 5–33)), Dr. Kozarsky concluded:

[T]here was considerable information and instruction in the [specification] for making and using recombinant AAV comprising an AAV9 capsid protein that is at least 95% identical to the amino acid sequences of vp1, vp2, and/or vp3 of AAV9. There was also a high level of skill in the art at the time the application was filed, and all of the methods needed to practice the invention were well known. Thus, it is clear that [the specification] as filed in 2003, was sufficiently enabling to make and use recombinant AAV comprising an AAV9 capsid protein that is at least 95% identical to the amino acid sequences of vp1, vp2, and/or vp3 of AAV9.

Id. at 1536–47 (¶¶ 4–34).

Similarly, Dr. Wilson, a co-inventor of the '441 patent, provided a declaration “as to what was known to those of skill in the art as of the effective date of the claimed invention, to assist in understanding how the skilled artisan would read and utilize the information in the specification.” *Id.* at 1739 (¶ 2). After describing the background of the art, Dr. Wilson concluded “[g]iven the information provided in the specification, one of ordinary skill in the art can readily make and use an adeno-associated virus having an AAV capsid as recited in the claims without undue experimentation.” *Id.* at 1739–42 (¶¶ 3–5).

Petitioner contends that “Patent Owner cannot remedy the absence of any teaching in the '441 patent for the claimed lists of modification sites through a prosecution declaration.” Pet. 48; *see also id.* at 49 (“Patent Owner’s reliance on its expert declaration during prosecution to gain claim allowance . . . cannot be grounds for written description support.”); Reply 8 (arguing that the examiner relied on the declarations to “fill gaps that the patent did not teach” and characterizing Patent Owner’s argument as a “novel legal theory”).

Petitioner argues “written description is based on ‘an objective inquiry into the four corners of the specification.’” Pet. 48 (quoting *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc)). This statement is not wrong; it is, however, incomplete. In *Ariad*, the Federal Circuit instructed that the test for written description support “requires an objective inquiry into the four corners of the specification *from the perspective of a person of ordinary skill in the art.*” 598 F.3d at 1351 (emphasis added). The expert declarations submitted during the prosecution of the ’218 and the ’418 applications provide this perspective.

In *Alton*, an examiner rejected the claims for failure to comply with the written description requirement. *In re Alton*, 76 F.3d 1168, 1172–73 (Fed. Cir. 1996). The applicant submitted a declaration from a person of ordinary skill in the art stating that an ordinarily skilled artisan would have understood the specification as adequately describing the claimed invention. *Id.*; *see also id.* at 1176 (“The . . . declaration addresses why the claimed subject matter, although not identical to the analog described in the specification, was in [the applicant]’s possession.”). The examiner gave little or no weight to that declaration. *Id.* at 1174. The Federal Circuit found that to be error and directed the Office to evaluate the declaration as bearing on the factual issue. *Id.* at 1174–75. Thus, under *Alton*, the examiner did not err in considering the declarations submitted during the prosecution of the ’218 and the ’418 applications.

Petitioner asserts that there were “many errors in the Kozarsky declarations.” Reply 9. For example, relying on the opinion of Dr. Kay, Petitioner contends “certain amino acid modifications within the claim

scope, such as proline substitutions, would result in nonfunctional capsids.” *Id.* (citing Ex. 1003 ¶¶ 114–119, 157–159). But, as Dr. Kozarsky pointed out, both natural variants hu.31 and hu.32 contain proline substitutions. Ex. 1011, 1860 ¶ 17. And “publications from Dr. Wilson’s laboratory . . . show that hu.32, with all its proline substitutions, still formed functional capsids.” Sur-reply 8 n.5 (citing Exs. 2015, 2016). Thus, Petitioner does not persuade us that the Kozarsky Declarations contain so many errors that the examiner erred in according them weight during the prosecution of the ’218 and the ’418 applications.

The parties disagree on whether the term “amino acid modifications” includes naturally occurring sequences: Petitioner asserts no; Patent Owner argues yes. Pet. 31; Prelim. Resp. 16–19. Petitioner contends that Patent Owner’s proposed construction, which is relevant to the § 112 analysis, was not in front of the examiner. Reply 9–10. We disagree. In her Declaration, Dr. Kozarsky explained that “[t]he specification explicitly describes the invention as encompassing rAAVs engineered with capsids having the amino acid sequence of *naturally occurring* capsids or artificial (e.g., genetically engineered) capsids having at least 95% identity to the aligned amino acid sequence of AAV9 capsid proteins.” Ex. 1011, 1857 (¶ 10) (emphasis added). Thus, the examiner was aware of Patent Owner’s proposed construction of the disputed term when allowing the challenged claims.

In sum, we find Petitioner has not demonstrated a material error by the Office in its prior consideration of the same or substantially the same arguments Petitioner presents now.

B. Grounds 3 and 4

Petitioner argues that the challenged claims are anticipated by intervening art, including the '111 patent. Pet. 72–79. The '111 patent and other patents and published applications within the '441 patent's family (*see supra* n.2) qualify as prior art only if the challenged claims are not entitled to the priority of the priority applications due to lack of sufficient written description support and/or enablement. *See id.* at 72–73. Because the priority applications and the challenged '441 patent share the same specification, the anticipation ground boils down to the same written description support and enablement arguments in Grounds 1 and 2. Because, as explained above, we exercise our discretion under § 325(d) and decline to institute review based on the challenges in Grounds 1 and 2, we similarly decline to institute review of the anticipation ground.

Petitioner further asserts that the challenged claims lack utility. Pet. 68–72. Institution of post-grant review is discretionary. *See* 35 U.S.C. § 324(a); *see also SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1356 (2018) (“[Section] 314(a) invests the Director with discretion on the question whether to institute review” (emphasis omitted)); *Harmonic Inc. v. Avid Tech, Inc.*, 815 F.3d 1356, 1367 (Fed. Cir. 2016) (explaining that under § 314(a), “the PTO is permitted, but never compelled, to institute an IPR proceeding”).⁶

⁶ Even though *SAS* and *Harmonic* address *inter partes* reviews, we see no reason to interpret the statute governing post-grant reviews differently.

In exercising that discretion, we are guided by the statutory requirement, in promulgating regulations for post-grant review, to consider the effect of any regulations on “the efficient administration of the Office [and] the ability of the Office to timely complete proceedings,” 35 U.S.C. § 326(b), as well as the requirement to construe our rules to “secure the just, speedy, and inexpensive resolution of every proceeding,” 37 C.F.R. § 42.1(b). Under the Office Guidance, “if the PTAB institutes a trial, the PTAB will institute on all challenges raised in the petition.” Guidance on the Impact of *SAS* on AIA Trial Proceedings (April 26, 2018).⁷

Here, we determine that 35 U.S.C. § 325(d) is sufficiently implicated that instituting review on all grounds would undermine the statutory purpose of 35 U.S.C. § 325(d). Accordingly, we deny the entire Petition. *SAS* Q&A’s, Part D, Effect of *SAS* on Future Challenges that Could Be Denied for Statutory Reasons, answer to Question D1 (June 5, 2018).⁸

III. CONCLUSION

On the record presented, the circumstances of this case warrant exercise of our discretion to deny institution based on §§ 324(a) and 325(d). The Petition presents § 112 arguments that are same or substantially the same as those the examiner considered during prosecution. Petitioner has not demonstrated that the Examiner materially erred in that consideration. Thus,

⁷ Available at <https://www.uspto.gov/patents/ptab/trials/guidance-impact-sas-aia-trial>.

⁸ Available at https://www.uspto.gov/sites/default/files/documents/sas_qas_20180605.pdf.

we exercise our discretion under § 325(d) and deny review of Petitioner's challenges based on written description support, enablement, and anticipation by intervening art. And because § 325(d) is sufficiently implicated, we deny review of Petitioner's challenge under the utility ground.⁹

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is denied and no post-grant review is instituted.

⁹ Because we deny the Petition under §§ 324(a) and 325(d), we do not reach Patent Owner's additional arguments as to why we should deny institution.

PGR2021-00073
Patent 10,695,441 B2

FOR PETITIONER:

David Telleson
Robert Counihan
Hayan Yoon
FENWICK & WEST LLP
dtelleson@fenwick.com
rcounihan@fenwick.com
hyoon@fenwick.com

FOR PATENT OWNER:

S. Christian Platt
Elizabeth Cary Miller, Ph.D.
Matthew W. Johnson
JONES DAY
cplatt@jonesday.com
cmiller@jonesday.com
mwjohnson@jonesday.com