Trials@uspto.gov
571-272-7822

Paper 9
Date: April 1, 2020

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

REGENERON PHARMACEUTICALS, INC.,
Petitioner,

v.

KYMAB LTD.,
Patent Owner.

IPR2019-01577
Patent 9,505,827 B2

Before ZHENYU YANG, KRISTI L. R. SAWERT, and MICHAEL A. VALEK, *Administrative Patent Judges.*

YANG, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314

INTRODUCTION

Regeneron Pharmaceuticals, Inc. ("Petitioner") filed a Petition (Paper 2, "Pet."), seeking *inter partes* review of claims 1–5 and 7–10 of U.S. Patent No. 9,505,827 B2 (Ex. 1001, "the '827 patent"). Kymab Ltd. ("Patent Owner") filed a Preliminary Response (Paper 6, "Prelim. Resp."). With our authorization, Petitioner filed a Reply (Paper 7, "Reply") and Patent Owner filed a Sur-Reply (Paper 8, "Sur-Reply").

For the reasons provided below, we exercise our discretion under 35 U.S.C. § 325(d) and deny institution of an *inter partes* review.

Related Matters

Petitioner filed IPR2019-01578, IPR2019-01579, and IPR2019-01580, "challenging other patents owned by Patent Owner and claiming subject matter overlapping with the subject matter of the '827 patent claims." Pet. 71–72.

The '827 Patent

The '827 patent relates to non-human animals and cells that are engineered to produce antibodies and antibody chains. Ex. 1001, 1:21–27. Specifically, it discloses methods "for constructing a chimaeric human heavy and light chain loci in a non-human mammal, for example a mouse." *Id.* at 2:13–15.

Before the '827 patent, the strategy used to generate mice with human immune systems was to "knockout the heavy and light chain loci in ES cells and complement these genetic lesions with transgenes designed to express the human heavy and light chain genes." *Id.* at 1:28–33. According to the '827 patent, although these models could generate fully human antibodies, they had several major limitations. *Id.* at 1:33–49.

For example, because the transgenic loci used for the prior-art models were of human origin, "even in those cases when the transgenes were able to complement the mouse locus so that the mice produced B-cells producing fully human antibodies, individual antibody affinities rarely reached those which could be obtained from intact (non-transgenic) animals." *Id.* at 6:11–17. The '827 patent explains that is because the control elements of the locus are human, and thus, "the signalling components, for instance to activate hyper-mutation and selection of high affinity antibodies are compromised." *Id.* at 6:18–22.

The '827 patent discloses producing functional chimeric antibodies between the human variable and non-human mammal (e.g., mouse) constant region by inserting a human IgH VDJ region into the mouse genome upstream of the constant region. *Id.* at 4:57–63, 5:8–9. The human IgH VDJ region comprises "DNA from a human genome that encodes all the exons encoding human V, D and J portions and suitably also the associated introns," and the mouse constant region comprises "all of the DNA required to encode the full constant region or a sufficient portion of the constant region to allow the formation of an effective chimaeric antibody capable of specifically recognising an antigen." *Id.* at 4:63–67, 5:10–13.

In the invention the '827 patent, host mouse constant regions are maintained and

> it is preferred that at least one [mouse] enhancer or other control sequence . . . is maintained in functional arrangement with the [mouse] constant region, such that the effect of the enhancer or other control sequence, as seen in the host [mouse], is exerted in whole or in part in the transgenic animal.

Id. at 6:23–30. According to the '827 patent, this approach "is designed to allow the full diversity of the human locus to be sampled [and] to allow the

same high expression levels that would be achieved by non-human mammal control sequences such as enhancers." *Id.* at 6:31–34.

Illustrative Claim

Claim 1 is the only independent claim and is reproduced below:

> 1. A transgenic mouse having a germline with a homozygous immunoglobulin heavy chain (IgH) locus comprising unrearranged human IgH variable region gene segments comprising Vs, Ds and Js at an endogenous locus operatively linked to an IgH constant (C) region comprising an endogenous C segment at an IgH locus;
>
> wherein said homozygous IgH locus comprises in 5' to 3' transcriptional orientation said unrearranged human Vs, Ds and Js comprising a 3' JH gene segment, a human/mouse chimeric DNA junction, an enhancer, and said operatively linked C region;
>
> wherein said homozygous chimeric IgH locus comprises a chimeric J/C intron comprising human DNA downstream of and naturally contiguous with said 3' JH gene segment, said human DNA being contiguous with mouse J/C intronic DNA upstream of said enhancer, and wherein said human DNA joins said mouse J/C intronic DNA at said human/mouse chimeric junction within said J/C intron,
>
> wherein DNA between said 3' human JH segment and said human/mouse chimeric DNA junction is less than 2 kb,
>
> said germline comprising all or part of mouse IgH variable region DNA; wherein said homozygous IgH locus of said mouse is capable of undergoing V, D, J joining; wherein said transgenic mouse is capable, upon stimulation with antigen, of producing antibody comprising a chimeric Ig heavy chain comprising a human IgH variable region; and wherein said transgenic mouse is capable of breeding with a second transgenic mouse, said second transgenic mouse having a germline with a homozygous IgH locus comprising unrearranged human IgH variable region gene segments operatively linked to an IgH constant (C) region

> comprising an endogenous C segment of an IgH locus to provide subsequent generation mice, wherein a said subsequent generation mouse comprises:
>
> (a) in its germline an homozygous IgH locus comprising unrearranged human IgH variable region gene segments operatively linked to an IgH constant (C) region comprising an endogenous C segment of an IgH locus, and
>
> (b) in its germline all or part of mouse IgH variable region DNA; and
>
> (c) wherein said IgH locus of said subsequent generation mouse is capable of undergoing V, D, J joining;
>
> (d) wherein said subsequent generation mouse is capable, upon stimulation with antigen, of producing antibody comprising a chimeric Ig heavy chain comprising a human IgH variable region; and
>
> (e) is capable of breeding with a mouse having a germline with a homozygous IgH locus comprising unrearranged human IgH variable region gene segments operatively linked to an IgH constant (C) region comprising an endogenous C segment of an IgH locus to provide further subsequent generation mice.

Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability:

Claims Challenged	35 U.S.C. §	References
1, 3–5, 10	103(a)	Murphy,[1] Morrison[2]
2, 7–9	103(a)	Murphy, Morrison, Adams[3]

In support of its patentability challenge, Petitioner relies on the Declaration of Dr. Anthony L. DeFranco. Ex. 1002.

[1] Murphy et al., WO 02/066630 A1, published Aug. 29, 2002 (Ex. 1005).
[2] Morrison et al., U.S. Patent No. 5,807,715, issued Sept. 15, 1998 (Ex. 1006).
[3] Adams et al., *A genome-wide, end-sequenced 129Sv BAC library resource for targeting vector construction*, 86 GENOMICS 753–58 (2005) (Ex. 1007).

DISCUSSION

Patent Owner asks us to exercise our discretion under 35 U.S.C. § 325(d) and deny this Petition. Prelim. Resp. 4–18. Patent Owner argues that "[t]he '827 patent issued after a lengthy prosecution history where the Examiner thoroughly considered the primary reference (Murphy) presented in the Petition. The Petition presents no new art, evidence, or arguments that go beyond the issues already vetted by the Examiner during prosecution." *Id.* at 1. We agree.

Under § 325(d),

> In determining whether to institute or order a proceeding under . . . chapter 31, the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office.

In evaluating whether to exercise our discretion under § 325(d), we weigh the following non-exclusive factors ("*BD* factors"):

> (a) the similarities and material differences between the asserted art and the prior art involved during examination;
>
> (b) the cumulative nature of the asserted art and the prior art evaluated during examination;
>
> (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
>
> (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;
>
> (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and

> (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of prior art or arguments.

Becton, Dickinson & Co. v. B. Braun Melsungen AG, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential as to § III.C.5, first paragraph).

Factors (a), (b), and (d) relate to whether the art and arguments presented in the petition are the same or substantially the same as those previously presented to the Office. *Advanced Bionics, LLC v. Med-El Electromedizinishe Geräte GmbH*, IPR2019-01469, Paper 6 at 10 (Feb. 13, 2020) (precedential). Factors (c), (e), and (f) "relate to whether the petitioner has demonstrated a material error by the Office" in its prior consideration of that art or arguments. *Id.* Only if the same or substantially the same art or arguments were previously presented to the Office do we then consider whether petitioner has demonstrated error. *Id.*

BD Factors (a), (b), (c), and (d)

Petitioner relies on the combination of prior-art references Murphy, Morrison, and Adams for its patentability challenges. Pet. 22, 57. Petitioner acknowledges that the Examiner considered the teachings of Murphy[4] and Adams, but emphasizes that "Morrison was *not* previously presented to the Office, and therefore, has not been considered individually or in combination with Murphy or Adams." *Id.* at 68. Petitioner argues that we

[4] The Murphy reference asserted in this IPR is in the same family as the Murphy reference discussed during the prosecution. Pet. 28 n.8 (acknowledging that the two Murphy references "share[] relevant subject matter"). Neither party makes any distinction between the two Murphy references. Prelim. Resp. 5 n.1. We do the same.

should not exercise our discretion under § 325(d) because the Petition presents a new art combination. We are not persuaded.

During prosecution, the Examiner repeatedly rejected the pending claims for obviousness over prior-art combinations that, like the grounds in the Petition here, included Murphy as the primary reference. *See* Ex. 2001, 7–15; Ex. 1044, 3–11. The Examiner found that "the mouse disclosed by Murphy appears to be structurally and functionally similar" to those claimed. *See, e.g.*, Ex. 2001, 12. The Examiner described Murphy as teaching a transgenic mouse "having a genome comprising entirely human heavy and light chain variable region loci operably linked to entirely endogenous mouse constant region loci such that the mouse produces a serum containing an antibody comprising a human variable region and a mouse constant region in response to antigenic stimulation." *Id.* at 9–10.

Here, Petitioner argues that Murphy teaches a transgenic mouse having a genome containing a homozygous chimeric IgH locus that is functional to form rearranged human V_H, D_H, and J_H gene segments to express antibodies. Pet. 24–26 (citing Ex. 1005, claim 30). These arguments overlap with the Examiner's findings during prosecution. *Compare* Pet. 24–28, *with* Ex. 2001, 9–12. Thus, we find that, not only did the Examiner consider Murphy's teachings extensively, the Petition presents the same or substantially the same arguments previously considered during prosecution.

Petitioner contends that "Morrison's teachings establish that, for chimeric genes that utilize mouse and human sequences, each of (i) fully mouse, (ii) fully human, and (iii) ***chimeric*** J/C introns can be used." Pet. 14 (citing Ex. 1002 ¶ 64); *see also id.* at 41 ("Morrison establishes that a POSA knew well before July 2009 that using a chimeric J/C intron is one of a

limited number of choices for effective designs, and is a matter of convenience." *Id.* at 41 (citing Ex. 1002 ¶¶ 112–115 (internal quotation marks omitted)).

Morrison was not before the Examiner during prosecution. Patent Owner argues that Morrison is not relevant, or, at most, cumulative of prior art considered during prosecution. Prelim. Resp. 9–16. On the former issue, we disagree with Patent Owner. Instead, we agree with Petitioner that Morrison is analogous at least because it relates to the same general field of endeavor as Murphy and Adams. *See* Reply 2–3. On the latter issue, however, we agree with Patent Owner that Morrison is cumulative of Tanamachi,[5] a reference previously considered by the Examiner. *See* Prelim. Resp. 12–14.

Petitioner relies on Morrison for teaching that a chimeric J/C intron was a known option for joining a variable gene region to a constant gene region to produce functional antibody chains. Pet. 13–16. During prosecution, the Examiner relied on Tanamachi for "disclos[ing] the concept of mouse/human chimeric DNA junction." *See* Ex. 2001, 13 (noting that "the[ ]human/mouse chimeric DNA junction of Tanamachi et al. contains a ~450 bp human DNA downstream and contiguous with the 3′ end of human JH6 and the entire mouse J/C intron").

Petitioner also relies on Morrison for characterizing the exact site of linkage as "a ***matter of convenience*** where there is a convenient restriction site in the introns from the two sources." Pet. 14 (quoting Ex. 1006, 3:60–62, emphasis added by Petitioner). But this does not provide a material, non-

[5] Tanamachi et al., WO 2007/117410 A2, published Oct. 18, 2007 (Ex. 1030).

cumulative disclosure over Tanamachi. To the contrary, Petitioner acknowledges that "Tanamachi describes a mouse including a joined construct including a human/mouse chimeric junction" produced by ligating the mouse fragment into a restriction site 3' of the human VDJ region. *Id.* at 45–46 (citing Ex. 1030, 27:31–28:1). Thus, Petitioner has not shown that Morrison is any more relevant than Tanamachi.

We are also not persuaded by Petitioner's contention that the Final Office Action in related U.S. Patent Application No. 14/040,405 ("the '405 Office Action") "directly refutes" Patent Owner's argument that Morrison is cumulative of Tanamachi. Reply 3–4 (citing Ex. 1069). Petitioner contends that the '405 Office Action, which mailed after the Petition was filed, "reflects a ***material change*** in the Examiner's position regarding the significance of the 'chimeric J/C intron' limitation." *Id.* at 4. According to Petitioner, this change resulted from the Examiner's consideration of Morrison in that examination. *Id.* ("[T]he Examiner, now armed with Morrison, found that it was known in the art that a chimeric J/C intron was 'desirable,' and that the 'site for the chimeric JC intron is not critical to produce a functional antibody'" (quoting Ex. 1069, 12 (brackets omitted))).

We find that the '405 Office Action does not support Petitioner's contentions. There, the Examiner rejected the pending claims as obvious over combinations of references that included Murphy and Tanamachi, as well as other references, but not Morrison. Ex. 1069, 2–3, 7–8. Although the Examiner cited to Morrison, the Examiner did so only as "further support[]" for Tanamachi's teaching that "[t]he concept of a chimeric JC [intron] was known to one of ordinary skill in the art." *Id.* at 12. Thus, the '405 Office

Action, if anything, supports Patent Owner's argument that Morrison is cumulative of Tanamachi.

After considering the parties' respective arguments and evidence, we determine that Morrison's teachings are cumulative to the teachings of Tanamachi, and that Petitioner's arguments about Morrison largely overlap with arguments previously discussed during prosecution.

In sum, we determine that the Petition presents the same or substantially the same art and arguments previously presented to, and considered by, the Examiner.

BD Factor (e)

Petitioner alleges that the Examiner erred in allowing the challenged claims because the applicant presented "an inaccurate and incomplete picture" of the state of the art, including the fertility of the Murphy mice. Pet. 1. According to Petitioner, the Examiner has since reconsidered his position of this issue. Pet. 66. We are not persuaded.

The mouse IgH locus contains an intergenic DNA sequence between the 3' VH and 5' DH gene segments. *Id.* at 9 (citing Ex. 1002 ¶ 52). The Adam6 genes, which are involved in sperm migration, are located within this intervening sequence. *Id.* (citing Ex. 1009 ¶¶ 77, 218, 389). "Male mice that lack the ability to express any functional ADAM6 protein surprisingly exhibit a defect in the ability of the mice to mate and to generate offspring." Ex. 1009 ¶ 207.

Petitioner does not dispute that the methods taught in Murphy result in transgenic mice with disrupted Adam6 genes. *See* Ex. 1002 ¶ 92. Petitioner, however, emphasizes that disrupting the Adam6 genes only impacts fertility in male mice, and thus, a female Murphy mouse would be "capable of

breeding" as claimed. *See* Pet. 9, 20–22, 31. But claim 1 expressly requires that the claimed transgenic mouse be capable of breeding "with a second transgenic mouse" where both mice are "homozygous" for the recited IgH locus. Ex. 1001, 131:55–133:10. Thus, even if the claimed mouse is female, it must still be capable of breeding with a transgenic male that is also homozygous for the recited IgH locus. Petitioner has not shown that Murphy teaches homozygous transgenic mice that are capable of breeding with other homozygous transgenic mice to produce offspring that are also homozygous for the recited IgH locus, as recited in claim 1 here.

In the reasons for allowance provided in the Notice of Allowance, the Examiner stated that

> The term transgenic mouse having germline with a homozygous IgH "capable of breeding" with second homozygous mouse is interpreted . . . as [a] mouse that is fertile and produce[s] subsequent litters without affecting fertility or fecundity in that the average litter size is the same within statistical significance for chimeric loci containing different numbers of human V gene segments.

Ex. 1049, 4–5. Petitioner argues that the Examiner misconstrued claim 1 because "the claims do not require any *degree* of [breeding] capability," and therefore encompass mice whose fertility has been severely compromised by disruption of the mouse Adam6 genes. Pet. 32, *see also id.* at 18–19 ("Within the context of the '827 patent, the phrase 'capable of breeding' means only that the recited transgenic mouse must have *some* ability to breed to produce offspring."). We are not persuaded.

During prosecution, the applicant sought to distinguish claim 1, arguing that "mice made according to the method set forth by Murphy exhibit a severe defect in their ability to breed and to produce subsequent

generation mice," whereas the claimed transgenic mouse "does not exhibit such a defect and is capable of breeding to produce subsequent generation mice." Ex. 1054, 7 (quoting Ex. 1040 ¶ 12). In support, the applicant relied on a Declaration under 37 C.F.R. § 1.132 executed by Glenn A. Friedrich, Ph.D., where Dr. Friedrich "present[ed] evidence demonstrating the fertility of the mice recited in the pending claims." Ex. 1053 ¶¶ 3, 10–12. According to Dr. Friedrich,

> The results . . . demonstrate that (i) both homozygous male and females are fertile and produce litters through three or four generations, (ii) the number of human V gene segments does not affect fertility or fecundity in that the average litter size was the same within statistical significance for chimeric loci containing different numbers of human V gene segments.

Id. ¶ 9. The Examiner credited Dr. Friedrich's Declaration. Indeed, the Examiner's construction of the term "capable of breeding" in the reasons for allowance mirrors the language in Dr. Friedrich's Declaration. *Compare id.*, *with* Ex. 1049, 4. The applicant did not respond to the remarks in the notice of allowance.

In view of this prosecution history, we agree with Patent Owner that the applicant disclaimed "any broader claim scope." Prelim. Resp. 24. The applicant had both set forth and adopted the interpretation the Examiner articulated in the notice of allowance in their efforts to distinguish Murphy and the other cited art. Because the applicant did not attempt to avoid a disclaimer by filing remarks to, or otherwise challenging, the Examiner's characterization in the notice of allowance, claim 1 is limited to the interpretation noted by the Examiner in the notice of allowance. *See Biogen Idec, Inc. v. GlaxoSmithKline LLC*, 713 F.3d 1090, 1096 (Fed. Cir. 2013) ("If an applicant chooses, she can challenge an examiner's characterization

in order to avoid any chance for disclaimer, but the applicant in this case did not directly challenge the examiner's characterization.");[6] *see also TorPharm Inc. v. Ranbaxy Pharm., Inc.*, 336 F.3d 1322, 1330 (Fed. Cir. 2003) (explaining that in ascertaining the scope of an issued patent, "the public is entitled to equate an inventor's acquiescence to the examiner's narrow view of patentable subject matter with abandonment of the rest. Such acquiescence may be found where the patentee . . . lets stand an examiner's restrictive interpretation of a claim" (internal citation omitted)).

Petitioner asserts that the interpretation the Examiner adopted is not supported by the Specification of the '827 patent. Pet. 32–33 n.10. But the Specification specifically describes the infertility problems created by disruption of the Adam6 genes and explains that "the invention improves upon the prior art male transgenic mice that are infertile as a result of genomic manipulation." *See* Ex. 1001, 32:8–19. Thus, we agree with Patent Owner that the Examiner's construction is supported by the intrinsic record. *See* Prelim. Resp. 19–26 (arguing that the construction the Examiner applied

[6] The facts here are distinguishable from cases where the examiner, without any prior discussion of the term in question, adopts a restrictive construction in the notice of allowance and the applicant does not respond. *See Salazar v. Proctor & Gamble Co.*, 414 F.3d 1342, 1345–47 (Fed. Cir. 2005). Here, the applicant affirmatively argued that their claims required mice capable of breeding to a degree that distinguished the prior art. The Examiner then relied on applicant's statements, articulating a claim construction based on the evidence the applicant submitted to distinguish their claims, to which the applicant did not object. In this regard, the facts here more closely align to those in *Biogen*, where the prosecution history evidenced that the applicant had affirmatively adopted the interpretation in question in the arguments it made to secure allowance of the claims. *See Biogen*, 713 F.3d at 1096–97 n.6.

is supported by the claim language, Specification, and prosecution disclaimer).

Citing the Examiner's statements made during prosecution of subsequent patent applications, Petitioner argues that the Examiner has since reconsidered his position on the issue of "capable of breeding." Pet. 66 (citing Ex. 1022, 13; Ex. 1023, 6). Patent Owner disagrees, contending that "the statements cited by Petitioner, along with the surrounding portions of the file histories, actually confirm the Examiner's consistent treatment of the art across the various cases in the entire family." Prelim. Resp. 6–9. We find Patent Owner's argument more persuasive.

Petitioner relies on an Office Action rejecting claims of U.S. Patent Application No. 14/516,461 ("the '461 application") as obvious over Murphy and other references. Pet. 66 (citing Ex. 1022, 13). Specifically, Petitioner quotes the Examiner for stating that "***the mouse disclosed by Murphy is capable of breeding***." *Id.* (citing Ex. 1022, 13 (emphasis added by Petitioner)). But, as Petitioner acknowledges, the Examiner ultimately withdrew that rejection and allowed those claims. *Id.* (citing Ex. 1058, 6). Indeed, that application has issued as U.S. Patent No. 10,064,398 B2, which Petitioner challenges in IPR2019-01580.

Petitioner also relies on Office Actions in U.S. Patent Application No. 15/383,101 ("the '101 application") as evidence that the Examiner has reconsidered his views on the patentability of certain claim limitations. *Id.* at 66–68 (citing Ex. 1023, 6; Ex. 1061, 14, 19). But, regarding the limitation "capable of breeding," as Patent Owner points out, the Examiner rejected the claims of the '101 application "because they did not require the step of obtaining or using the transgenic mouse." Prelim. Resp. 8; Ex. 1061, 19.

Indeed, the Examiner stated that "[s]hould applicant amend the instant claim to recite the step of immunizing the mouse previously allowed with an antigen prior to steps of expressing the humanized antibody from a first cells, [the] instant obviousness rejection may be overcome." Ex. 1061, 20. Thus, we agree with Patent Owner that the Examiner's statements, if anything, "establish that he understood the '101 application claims to be directed to a different invention than the previously allowed claims." Prelim. Resp. 8. Those statements do not translate into the Examiner reconsidering his position on the claim limitation "capable of breeding."

Finally, we are not persuaded by Petitioner's argument that the '405 Office Action "contradicts Patent Owner's claim that the Examiner has adopted Patent Owner's overly-narrow construction of 'capable of breeding.'" Reply 5. There, the Examiner stated that breeding "may be cumbersome but the mouse whose genome comprises a human IgH variable gene segment disclosed by Murphy is capable of breeding as required by the claims." Ex. 1069, 15.

As a preliminary matter, the prosecution of the '405 Application is ongoing. Thus, the Examiner's statement there has limited value in this proceeding. After all, as Patent Owner points out, the Examiner initially made a similar statement in examining the '461 application, but later withdrew the rejection and allowed the claims. Sur-Reply 5 (citing IPR2019-01580, Ex. 2003, 4).

More importantly, the Examiner interpreted "capable of breeding" in the challenged claim 1 after Dr. Friedrich presented evidence showing the claimed mice exhibited the same fertility as unmodified mice. Ex. 1049, 4 (citing Ex. 1053 ¶¶ 9–11). Petitioner has not shown that the same evidence

has been presented during prosecution of the '405 application. In fact, the '405 Office Action suggests that the rejection "may be overcome" if such evidence were presented. *See* Ex. 1069, 15.

In sum, Petitioner has not demonstrated that the Examiner erred in finding the Murphy mouse does not meet the "capable of breeding" limitation recited in the challenged claims.[7]

BD Factor (f)

Petitioner contends that because the Petition presents new evidence concerning the relevant state of the art that was not previously considered by the Examiner, we should not deny the Petitioner under § 325(d). *See* Pet. 69–70. Specifically, Petitioner argues that the Petition presents new evidence contradicting several declarations submitted by Patent Owner during prosecution and relied on by the Examiner in allowing the challenged claims. *Id.* at 69. For example, Petitioner points to a Declaration under 37 C.F.R. § 1.132 executed by Allan Bradley, Ph.D., "contend[ing] that the field was moving away from using 129/129Sv strain mice" at the time of invention. *Id.* (citing Ex. 1039). Petitioner argues that Dr. DeFranco's Declaration, in contrast, demonstrates that at the time of invention, "the recited 129/129Sv mouse strain sequences were well-known in the art, and 129/129Sv mouse strain ES cells were the most commonly used strain of ES cells." *Id.* (citing Ex. 1002 ¶¶ 154–160). We are not persuaded.

First, we note that independent claim 1 does not recite a "129 mouse strain." Instead, this limitation only appears in dependent claim 2 and claims

[7] Because this issue is dispositive, we do not need to address Petitioner's argument that the Examiner also erred in finding that prior art does not teach a chimeric J/C intron as claimed.

7–9, each of which depends from claim 2. Second, in his Declaration, Dr. Bradley stated that "historically, the vast majority of mouse knockouts had been generated using ES cells derived from the 129 mouse strain." Ex. 1039 ¶ 9. Third, even if the applicant or Dr. Bradley stated otherwise, the Examiner did not view using DNA from the 129 mouse strain as conveying patentability. Ex. 1049, 4. Rather, the Examiner explained in the reason for allowance that

> In the instant case, prior art fails to teach or suggest a mouse having germline with a homozygous chimeric IgH locus comprises in 5' to 3' transcriptional orientation: (i) unrearranged human immunoglobulin heavy chain (lgH) variable region (VH) DNA comprising Vs, Ds and Js comprising a human 3 'JH gene segment, (ii) a human/mouse chimeric junction, an enhancer and operatively linked C region, wherein said homozygous chimeric IgH locus comprises a chimeric J/C intron comprising human DNA downstream of and naturally contiguous with said 3 'JH gene segment, said human DNA being contiguous with mouse J/C intronic DNA upstream of said enhancer, and wherein said human DNA joins said mouse J/C intronic DNA at said human/mouse chimeric junction within said J/C intron, and said transgenic mouse is capable of breeding with a second transgenic mouse, said second transgenic mouse having a germline with a homozygous IgH locus to produce subsequent progeny.

Id. Petitioner has not shown the Examiner misapprehended the prevalence of 129/129Sv mouse strain sequences, or relied on such misapprehension in allowing the challenged claims.

Petitioner also asserts that Dr. DeFranco's Declaration is new evidence that was not previously before the Office and warrants "serious consideration." Pet. 70. But the fact that an expert declaration was not before the Examiner during prosecution does not itself demonstrate that the Examiner erred. As explained above, the prosecution history reveals that the

Examiner considered substantially the same arguments and art advanced in the Petition and Dr. DeFranco's Declaration. To the extent Petitioner argues that its evidence demonstrates that the Examiner erred, we have addressed it above and disagree.

Weighing the Factors

Weighing each of these factors, we conclude that, on the record presented, the circumstances of this case warrant exercise of our discretion to deny institution based on § 325(d). The Petition relies on the same and substantially the same references, and presents arguments that are substantially the same as those the Examiner considered and the applicant overcame during prosecution. Petitioner has not demonstrated that the Examiner materially erred in considering such. Thus, we exercise our discretion and deny institution of a trial under 35 U.S.C. § 325(d).

ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is denied, and no *inter partes* review is instituted.

FOR PETITIONER:

Stephanie L. Schonewald
Brenda Herschbach Jarrell
Janet M. Tse
CHOATE, HALL & STEWART LLP
sschonewald@choate.com
bjarrell@choate.com
jtse@choate.com

FOR PATENT OWNER:

Matthew I. Kreeger
Parisa Jorjani
Jian Xiao
MORRISON & FOERSTER LLP
mkreeger@mofo.com
pjorjani@mofo.com
jxiao@mofo.com