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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENZYME CORPORATION,
Petitioner

v.

GENENTECH, INC. AND CITY OF HOPE
Patent Owners

Case IPR2016-00383
Patent 6,331,415

PATENT OWNERS' PRELIMINARY RESPONSE UNDER 37 C.F.R. § 42.107

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I. INTRODUCTION

In July 2015, Sanofi, through its wholly owned subsidiary, sanofi-aventis U.S. LLC, filed a petition in IPR2015-01624 (the "'1624 IPR"), contending that certain claims of U.S. Patent No. 6,331,415 (the "Cabilly '415 patent") are unpatentable over prior art. Five months later, and more than a month after Patent Owners filed their preliminary response in that proceeding, Sanofi, through another wholly owned subsidiary, Genzyme Corp., filed the present petition ("the '383 Petition") in which it similarly challenges the patentability of the Cabilly '415 patent. This second petition should be rejected for two reasons.

First, the Board should dismiss the '383 Petition using the authority of 35 U.S.C. § 325(d), as it raises not just one, but nearly all of the factors that the Board has identified as warranting dismissal of petitions under that authority. Those factors include: (i) that the same real party-in-interest has challenged the same patent in a prior petition; (ii) that the petitioner knew about and could have asserted the references and grounds asserted in the second petition in the first petition; (iii) that the patentability grounds raised in the second petition are substantially the same as those asserted in the first petition; and (iv) that consolidation is not possible, which unfairly provides the petitioner with a "second bite" at issues raised in the first proceeding via a second petition.

Each of these factors is present here: (i) Sanofi is explicitly identified as the

real party-in-interest in both petitions (filed by the same counsel); (ii) Sanofi knew about the references and grounds cited in the '383 Petition at the time it filed the '1624 Petition—the '1624 Petition relies on the same three references that provide the basis for the '383 Petition ("Salser" (Ex. 1002), "Southern" (Ex. 1004), and "Ochi" (Ex. 1003)); (iii) often using verbatim language, the petitions raise substantially the same patentability grounds; both cite a primary reference ("Bujard" (*Sanofi-Aventis U.S. LLC v. Genentech, Inc.*, IPR2015-01624, Ex. 1002) versus Salser) for its use of the plural term "genes" and inclusion of certain proteins in a laundry list of potential targets; and both rely on similar, if not identical, secondary references, including the same Southern article; and (iv) because of Sanofi's five-month delay in filing the '383 Petition, consolidation is not possible, which means that if trial is instituted, Sanofi unfairly will get two chances to press substantially the same grounds.[1] Any one of these considerations would warrant denial of the '383 Petition; together, they make a compelling argument for the Board to exercise its discretion under section 325(d).

Second, the '383 Petition fails on the merits because it does not establish a reasonable basis for finding any contested claim unpatentable. Salser—the

[1] To conserve Board resources, Patent Owners asked Petitioner to withdraw the duplicative '383 Petition, but Petitioner refused to do so, without any substantive explanation. Ex. 2025, Email from Patent Owners to Petitioner (Feb. 17, 2016).

primary reference for each ground—plainly does not disclose every element of the claimed invention, and is directed to a completely different problem than the one the Cabilly inventors solved. Salser, in Petitioner's own words, is directed to "gene replacement therapy," *i.e.*, attempting to fix a genetic deficiency (*e.g.*, sickle-cell anemia) by introducing cells expressing a particular protein into a host organism that is expressing mutant forms of that same protein. Salser is "specifically focused on treatments for hemoglobin-based genetic deficiencies." Paper 2 at 29. This is a far different enterprise than the Cabilly '415 patent, which uses cultured host cells to produce functional antibodies targeting specific antigens by co-expressing immunoglobulin heavy and light chain DNA in the host cells, and which recovers functional antibodies. The host cells in the Cabilly '415 patent function as the factories that produce these functional antibodies.

Even if the materially different objective and purpose of the Salser process is ignored, it does not provide any guidance or suggestion that is relevant to the Cabilly '415 patented invention. Nowhere in Salser is there any mention of antibodies or immunoglobulins. Nor does Salser anywhere address the issues of culturing host cells to produce and isolate proteins, much less complex multimeric proteins like immunoglobulins.

The particular focus of the Salser method—correction of deficient expression of the beta-globin gene cluster—also provides no suggestion to produce

two or more constituent polypeptides of a multimeric protein in a single host cell. Most notably, that method aims to produce only ***a single polypeptide***—the beta chain of the hemoglobin protein. Although Salser discusses strategies to introduce a beta-globin gene cluster, which includes multiple discrete "genes," that gene cluster in cells only functions to produce one of the components of the hemoglobin protein—a beta chain. The five "multiple genes" in that gene cluster are not all expressed together, nor do any of the expression products from the beta-globin cluster combine with one another to form a multimeric protein.

Salser thus provides no insight into the challenge of producing a multimeric protein by transfecting a host cell to contain and express DNA sequences encoding the constituent polypeptides of that multimeric protein. And, given the focus of Salser on gene replacement therapy, it provides no insight into the challenge of isolating functional immunoglobulins produced in a co-transformed host cell.

In the face of these omissions, the '383 Petition attempts to stitch together unrelated phrases from Salser and, using improper hindsight, attempts to credit Salser with guidance and teachings that simply are not there. It uses these faulty arguments both in an anticipation ground and in obviousness grounds where there is no discernable motivation for a person of ordinary skill to combine the references with a reasonable expectation of success in performing the claimed invention. The Federal Circuit has made clear that unsupported and hindsight-

driven assertions like these cannot serve as the basis to invalidate patent claims.

The Petition thus falls far short of the standard required by 35 U.S.C. § 314, and should be denied.

II. THE '383 PETITION SHOULD BE DENIED UNDER 35 U.S.C. § 325(d)

A. Legal Framework

35 U.S.C. § 325(d) allows the Board to exercise its discretion to deny institution of a petition for *inter partes* review when "another proceeding or matter involving the patent is before the Office" and "the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d). *See*, *e.g.*, *HTC Corp. v. NFC Tech., LLC*, IPR2015-00384, Paper 11 at 9-11 (relying on section 325(d) to deny a second petition where "[the prior art] references applied against [the claims] in the present Petition are substantially the same as those applied in [an] earlier Petition"); *Nora Lighting, Inc. v. Juno Mfg., LLC*, IPR2015-00601, Paper 13 at 9-13 (denying petition asserting prior art that was "duplicative" of art presented during reexamination).

This provision aims to ensure that post-grant proceedings are not used to subject patent owners to "repeated litigation and administrative attacks on the validity of a patent. Doing so would frustrate the purpose of the section as providing quick and cost effective alternatives to litigation." America Invents Act,

H.R. Rep. 112-98, pt. 1 at 48 (2011) (hereinafter "AIA H.R. Rep.").[2] Furthermore, one of the "core functions" of the IPR rules requiring a petitioner to identify the real party-in-interest is to "assure proper application of the statutory estoppel provisions . . . [and] to prevent parties from having a 'second bite at the apple' . . . ." Office Patent Trial Practice Guide, 77 Fed. Reg. 48756 at 48759 (Aug. 14, 2012); *see also* AIA H.R. Rep., pt. 1 at 48 ("In utilizing the post-grant review process, petitioners [and] real parties in interest . . . are precluded from improperly mounting multiple challenges to a patent . . . .").

Accordingly, the Board has interpreted section 325(d) to preclude a "second bite at the apple" where a petitioner knows about the cited references at the time it files an earlier petition and fails to provide an adequate explanation for its failure to assert grounds based on those references at that time. *See*, *e.g.*, *Jiawei Tech. (HK) Ltd. v. Richmond*, IPR2015-00580, Paper 22 at 4 (denying institution where "[t]here is no question . . . that [the references] were available to Petitioner at the time of filing the earlier Petition" because "the prior art presented in the instant

[2] During Congressional hearings on the AIA, Senator Kyl stated the bill "impose[s] limits on serial challenges" to a patent and that section 325(d) "allows the Patent Office to reject any request for a proceeding . . . if the same or substantially the same prior art or arguments previously were presented to the Office with respect to that patent." 157 Cong. Rec. S1042 (daily ed. Mar. 1, 2011) (Stat. of Sen. Kyl).

proceeding . . . also was presented in the earlier proceeding"). For example, the Board invoked section 325(d) to deny a second petition in *Ford Motor Co. v. Paice LLC*, when a reference underlying the grounds "was relied on in explaining the state of the art" in an earlier petition, even though the second petition also cited additional, new prior art. IPR2015-00767, Paper 14 at 6-7; *see also Samsung Elecs. Co. Ltd. v. Rembrandt Wireless Techs., LP*, IPR2015-00555, Paper 20 at 7-9 (denying petition under section 325(d) where petitioner asserted same prior art in earlier petitions); *Unilever v. The Procter & Gamble Co.*, IPR2014-00628, Paper 21 at 11 (denying petition where "Unilever does not argue that the other references applied in the instant Petition . . . were unknown or unavailable at the time of filing the [first] Petition."); *HTC Corp.*, IPR2015-00384, Paper 11 at 10 (denying petition where "Petitioner provides no explanation, however, as to why [reference] was not or could not have been applied in the earlier Petition").

The Board has applied this principle even where a second petition involved a different nominal petitioner but the same real party-in-interest as a previously instituted IPR, as is the case here. *See Medtronic, Inc. v. Robert Bosch Healthcare Sys., Inc.*, IPR2014-00436, Paper 17 at 12 ("We have taken into account that Petitioner here is a real party-in-interest in the ongoing *inter partes* review of the '469 patent. *See Cardiocom*, IPR2013-00451, Paper 26."); *see also Roche Molecular Sys., Inc. v. Illumina, Inc.*, IPR2015-01091, Paper 18 at 12-13 (denying

second petition involving different nominal petitioner, noting "both the Petitioner in this case, Roche, and the Petitioner in IPR2014-01093, Ariosa, are both designated as real parties-in-interest in both proceedings").

The Board has also identified other considerations that weigh against institution of a second IPR of a single patent. For example, in *Toyota Motor Corp. v. Cellport Systems, Inc.*, the Board denied the second of two petitions for IPR of the same patent pursuant to section 325(d). IPR2015-01422, Paper 8 at 18-22. In addition to the similarities between the two petitions, the Board noted, *inter alia*, that (i) the timing of the second petition raised the potential for gamesmanship because the petitioner was able to preview the arguments included in the patent owner's preliminary response to the first petition; (ii) the 4 ½ month delay between the two petitions made consolidation impractical, and separate proceedings would undermine the interests of judicial economy; and (iii) the petitioner had not adequately explained the reasons for the 4 ½ month delay and gave no reason why it could not have included the allegedly new reference in the initial petition.[3] *Id.* Each of these considerations applies here.

[3] The Board further explained that co-pending post-grant proceedings may also give rise to estoppel under 35 U.S.C. § 325(e). IPR2015-01422, Paper 8 at 20-21; *see also infra* Section III.

B. Sanofi Could Have Raised Its Arguments Based on Salser, Southern, and Ochi in Its First Petition But Did Not

Sanofi is a real party-in-interest in both the '1624 IPR and this proceeding. *See* Paper 2 at 58 ("Sanofi, the ultimate parent company of Genzyme, is the real party-in-interest for Petitioner."); *Sanofi-Aventis*, IPR2015-01624, Paper 1 at 59 ("Sanofi (the ultimate parent company of sanofi-aventis U.S. LLC), sanofi-aventis U.S. LLC, and Regeneron Pharmaceuticals, Inc. are the real parties-in-interest for Petitioners.").[4] And Sanofi was aware of the three references (Salser, Ochi, and Southern) that it now relies on when the '1624 Petition was filed. Indeed, all three of the references and their purportedly relevant disclosures are discussed in the '1624 Petition, and all three are exhibits to that Petition. *See Sanofi-Aventis*, IPR2015-01624, Paper 1 at 23 (Salser (Ex. 1038)); 9-10, 21 (Ochi (Ex. 1021)); 2-3, 23, 33-34, 47-50 (Southern (Ex. 1004)). Therefore, Sanofi cannot and "does not contend that the newly cited references were not known or available to it at the time it filed the [first] IPR." *Butamax Advanced Biofuels LLC v. Gevo, Inc.*, IPR2014-00581, Paper 8 at 12 (denying petition under section 325(d) expressly directed to curing deficiencies of first petition). Instead, Sanofi "simply presents arguments now that it could have made in [the first petition] had it merely chosen

[4] The same counsel also filed both petitions. *Compare* IPR2015-01624, Paper 1 at 59, *with* IPR2016-00383, Paper 2 at 59-60.

to do so." *Samsung*, IPR2015-00555, Paper 20 at 8-9. This is precisely the type of serial filing section 325(d) was designed to prevent.

Not only were Salser, Southern, and Ochi cited in the prior Petition,[5] the following chart demonstrates that Sanofi cited them for the same purpose in both Petitions (emphasis added to indicate areas of commonality):

Reference	*Description in '1624 Petition*	*Description in '383 Petition*
Salser	"[Salser] teaches introducing and co-expressing ***multiple independent eukaryotic genes in a single mammalian host cell***. The patent teaches that 'when ***two or more genes*** are to be introduced they may be ***carried on a single chain, a plurality of chains, or combinations thereof***.' Ex. 1038, 3:51-53. 'The DNA employed may provide for a single gene, ***a single***	"The Salser patent discloses transforming ***a single host cell with two DNA sequences*** . . . ." '383 Petition at 36. "The . . . genetic material to be incorporated into the host cell . . . can therefore include '***two or more genes***,' 'a ***single set of genes***' or '***a plurality of unrelated genes***' . . . and they can be '***carried on a single***

[5] Southern is also relied upon by the Board to support Ground 3 of the trial instituted in the '1624 IPR. *Sanofi-Aventis*, IPR2015-01624, Paper 15 at 21-22.

	set of genes, e.g., the beta-globin gene cluster, or ***a plurality of unrelated genes***.'" '1624 Petition at 23.	***chain, a plurality of chains, or combinations thereof***.'" '383 Petition at 37-38.
Ochi	"Ochi (I) . . . reported experiments in which ***light chain DNA*** was ***successfully transformed into and expressed in mammalian host cells***." '1624 Petition at 21.	"Ochi (I) teaches that a foreign ***light chain immunoglobulin DNA*** sequence can be inserted into an expression vector and ***transformed into a mammalian host cell that will successfully express*** the light chain polypeptide." '383 Petition at 48.
Southern	"The Southern prior art publication . . . also teaches ***expressing multiple genes of interest in a mammalian host cell*** by using two vectors to co-transform the cell, with ***each vector containing a different gene of interest***." '1624 Petition at 23.	"Southern taught the feasibility of ***co-expression . . . of two proteins of interest in a single mammalian host cell*** when the ***respective genes are present on separate vectors***." '383 Petition at 53.

Despite Sanofi's awareness of Salser, Ochi, and Southern, Sanofi did not raise any patentability grounds based on Salser or a combination of Salser and these references in the first Petition. Consistent with the policy behind section 325(d), the Board should not give Sanofi a "second bite at the apple" by allowing it to conduct a second, overlapping proceeding based on the '383 Petition after it gains the benefit of seeing Patent Owners' arguments during the '1624 IPR. The '383 Petition should be denied because "what is presented in the instant Petition could have been presented" in the '1624 Petition. *Ford Motor Co.*, IPR2015-00767, Paper 14 at 9.

C. The Grounds Presented in the '383 Petition Are Substantially the Same as Those Presented in the '1624 Petition

The Board also should deny the '383 Petition because the proffered grounds and arguments are substantially the same as those raised in the '1624 Petition. *See*, *e.g.*, *LG Elecs., Inc. v. ATI Techs. ULC*, IPR2015-00327, Paper 13 at 8-12 (declining to institute IPR where substantially the same arguments were presented in first petition); *see also NetApp Inc. v. Crossroads Sys., Inc.*, IPR2015-00776, Paper 12 at 6-8.

In both the '1624 and '383 Petitions, Sanofi cites references involving insertion of DNA into a cell that incidentally use the plural form of the word "genes" (or like terms) and purportedly refer to immunoglobulins. Both Petitions then argue that these disclose the specific elements of the Cabilly '415 patent

claims, including the requirement for co-expression of multiple DNA sequences in a single recombinant host cell to assemble a functional immunoglobulin. Sanofi relies on these putative connections as the heart of its challenge in each petition, for both its anticipation and obviousness grounds. *Compare Sanofi-Aventis*, IPR2015-01624, Paper 1 at 21-32, *with* IPR2016-00383, Paper 2 at 28-30, 33-41.

This distorted reading of the prior art was unpersuasive in the '1624 Petition, and remains unpersuasive now. In the '1624 Petition, the Board rejected similar arguments by Sanofi, concluding that Bujard's generalized use of the term "genes" (and similar terms), coupled with its reference to "immunoglobulins" in a laundry list of potentially relevant proteins, was insufficient to anticipate the challenged Cabilly '415 patent claims. As the Board explained, Bujard "does not describe a specific process or a vector that is 'arranged as in the claim[s]' of the '415 patent[,]" and "Bujard does not teach—either expressly or inherently—that genes encoding for both the heavy and light chains must be incorporated into the same vector or otherwise expressed within a single host cell." *Sanofi-Aventis*, IPR2015-01624, Paper 15 at 15.

The same analysis applies to Salser. Indeed, Petitioner's arguments about what Salser allegedly teaches are even more forced. Salser, for example, does not even mention immunoglobulins in its laundry list of proteins.[6] Moreover, as was

[6] Salser vaguely refers to "production of a wide variety of proteins e.g. hormones,

the case with Bujard, Salser does not describe a vector arranged in the manner specified in the Cabilly '415 patent claims. But most critically, Salser nowhere discusses the challenge of recombinantly producing (even individually) the heavy and light chains of an immunoglobulin, much less the task of producing those two immunoglobulin chains together in one host cell such that a functional antibody is obtained. Salser thus discloses ***even less*** than Bujard, which the Board already found insufficient for anticipation.

Petitioner's obviousness grounds in the '383 Petition likewise present substantially the same arguments as those in the '1624 Petition. Petitioner argues that the combination of Salser and Ochi renders the challenged claims obvious, relying on Salser for its putative multiple gene teaching, and then citing Ochi ***solely*** for "the specific teaching of immunoglobulins . . . ." Paper 2 at 47-48. But Bujard includes immunoglobulins in its list of proteins, so Petitioner's reliance on Salser in combination with Ochi is no better than Bujard standing alone.

Petitioner's final ground in the instant Petition also rehashes arguments

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globulins or the like." Ex. 1002 at 2:35-36. Even if the Board were to accept Sanofi's strained argument that this disclosure of "globulins" is a specific reference to immunoglobulins (it is not, *see infra* Section VI.A.1), Salser is at best duplicative of Bujard, which explicitly recites immunoglobulins in its laundry list of potential proteins of interest.

made in the '1624 Petition. Petitioner now combines Salser with Southern to contend that using two different vectors to co-transform a mammalian host cell would have been obvious to the skilled person in April 1983. Paper 2 at 19-20, 51-54. Petitioner once again strains to connect the passing references to "genes" and "globulins" in Salser to the discussion of multiple vectors in Southern in substantially the same way it sought to connect Bujard with Southern in the '1624 Petition. *Compare* Paper 2 at 51-54, *with Sanofi-Aventis*, IPR2015-01624, Paper 1 at 47-50. Petitioner's third ground in the '383 Petition is thus substantially the same argument as the third ground of the '1624 Petition.

Patent Owners respectfully disagree with the Board's findings regarding what Bujard would have taught the skilled person in April 1983, and will establish that the disclosures in Bujard do not render the challenged claims obvious. But, in considering ***this*** Petition, Petitioner's failure to identify any disclosure in Salser that distinguishes it from Bujard supports denying institution of a second IPR, particularly when Sanofi, through Genzyme, waited five months after the first IPR to raise its duplicative challenges to the Cabilly '415 patent.

D. Sanofi Is Impermissibly Using Patent Owners' Preliminary Response in the '1624 IPR to Inform Its Arguments in This Proceeding

The '383 Petition should be denied for the additional reason that it makes an end run around the prohibition against petitioner replies to patent owner responses

by improperly using Patent Owners' Preliminary Response in the '1624 IPR as a roadmap for offering new, responsive arguments. "[A] petitioner is not permitted to respond to arguments presented by a patent owner in a preliminary response until after a trial has been instituted." *US Endodontics, LLC v. Gold Standard Instruments, LLC*, IPR2015-01476, Paper 13 at 9-10; *see also Samsung Elecs. Co., Ltd. v. Surpass Tech Innovation LLC*, IPR2015-00885, Paper 7 at 3 ("Generally, a petitioner is not authorized to file a reply to a patent owner preliminary response.").

The Board has repeatedly rejected attempts to respond to a patent owner's preliminary response in an earlier proceeding under the guise of a second, independent petition. For example, in declining to institute multiple serial IPRs filed by the same party, the Board explained that "[t]he timing of the second Petition [filed 4 ½ months after the first Petition] gave Petitioner the opportunity to preview the arguments set forth in the Patent Owner Preliminary Response [to the first Petition]" thereby raising "the potential for gamesmanship." *Toyota Motor Corp.*, IPR2015-01422, Paper 8 at 21. The Board also explained, "[e]specially given the similarity between the earlier application of [the references], ***the opportunity to read Patent Owner's Preliminary Response in [a first IPR], prior to filing the Petition here, is unjust***." *Toyota Motor Corp. v. Cellport Sys., Inc.*, IPR2015-01423, Paper 7 at 8 (emphasis added). Similarly, in *HTC Corp.*, the

Board denied a second petition in part because it "was filed over four months after the filing of the earlier Petition and after Patent Owner had filed a Preliminary Response in the earlier Petition." IPR2015-00384, Paper 11 at 11-12.

The Board has likewise denied institution in the related context where a second petition is filed after issuance of the Board's decision on institution in the first action. For example, in *Unilever, Inc. v. The Procter & Gamble Co.*, the Board denied a petition intended to "obviate[] purported deficiencies" in an earlier petition because "the instant Petition uses our prior Decision on Institution to bolster challenges that were advanced, unsuccessfully, in the [first] Petition." IPR2014-00506, Paper 17 at 8; *see also ZTE Corp. v. ContentGuard Holdings, Inc.*, IPR2013-00454, Paper 12 at 5-6. The underlying rationale in these decisions is that a second petition should not be an opportunity for a petitioner to address perceived defects in its initial arguments.[7]

[7] This is true even when the second petition is directed to claims that were challenged unsuccessfully in a first petition, as is the case with certain of the claims challenged in the '383 Petition. *See BLD Servs., LLC v. LMK Techs., LLC*, IPR2015-00721, Paper 9 at 10-12 (denying a second petition that was "crafted with the benefit of our institution decision in the [first] proceeding" even though it asserted invalidity of some claims for which review was denied in the first action); *see also ZTE Corp.*, IPR2013-00454, Paper 12 (denying petition on claims not

Sanofi's second petition attempts to respond—directly or indirectly—to several arguments that Patent Owners made in their '1624 Preliminary Response. For example, in the '1624 Preliminary Response, Patent Owners argued that the asserted invalidity grounds duplicated arguments that were considered and rejected during the *ex parte* reexamination of the Cabilly '415 patent. *Sanofi-Aventis*, IPR2015-01624, Paper 14 at 27-58. Informed by that argument, Sanofi, in its '383 Petition, asserts that "the present Petition is not simply the '415 patent reexamination redux." Paper 2 at 2. Additionally, Patent Owners' Preliminary Response in the '1624 IPR explained how the references cited in the '1624 Petition failed to disclose the inventions of the Cabilly '415 patent for the same reasons that the Office found the Axel reference insufficient during reexamination. *Sanofi-Aventis*, IPR2015-01624, Paper 14 at 31-39. Sanofi also responds to these arguments in the '383 Petition. *See*, *e.g.*, Paper 2 at 2 ("The Salser patent does not suffer from the infirmities of Axel."). Thus, Sanofi has sought to use the '383 Petition to do that which the IPR rules aim to prevent.

E. Sanofi's Second Bite at the Apple Will Unfairly Prejudice Patent Owners and Waste Board Resources

The delay in filing of the '383 Petition relative to the filing of the '1624 Petition makes consolidation of these proceedings impractical—indeed, Petitioner

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instituted in first proceeding).

has not even requested such consolidation. As a result, if trial were instituted on the '383 Petition, Sanofi, through its wholly owned subsidiaries, would, at every step of the process, have an opportunity to elicit Patent Owners' arguments in the '1624 IPR and then respond to them in this proceeding. This is precisely the type of gamesmanship that the Board has refused to allow. *See*, *e.g.*, *Toyota Motor Corp.*, IPR2015-01422, Paper 8 at 18-22 (denying second petition that "raises the potential for gamesmanship"); *HTC Corp.*, IPR2015-00384, Paper 11 at 12 (denying second petition where "consolidation [with the first IPR] is not practical").

Institution of an *inter partes* review in this proceeding will also waste Board resources and undermine the intent to provide a "just, speedy, and inexpensive resolution of every proceeding." 37 C.F.R. § 42.1(b). Where the timing of subsequent petitions requires concurrent proceedings involving the same parties and the same patent, the Board has generally denied institution in the interests of preserving Board and party resources. In *Toyota Motor Corp.*, a 4 ½ month delay between two petitions rendered consolidation impractical. IPR2015-01422, Paper 8 at 20. Because the delay would have necessitated "two separate trials . . . , requiring the parties, as well as the Board, to expend significant additional resources[,]" the Board denied the petition. *Id.* The Board reached a similar result in *HTC Corp.*, noting "[t]he [second] Petition was filed over four months after the

filing of the earlier Petition and after Patent Owner had filed a Preliminary Response in the earlier Petition. . . . Consequently, consolidation of [this proceeding with the previously-instituted IPR] is not practical." IPR2015-00384, Paper 11 at 11-12 (denying petition).

The same reasoning applies here. The instant Petition was filed on December 30, 2015, over five months after the '1624 Petition. *See Sanofi-Aventis*, IPR2015-01624, Paper 1 (filed July 27, 2015). The Board's decision on institution is not due until June 30, 2016, and (if instituted) discovery would likely extend to the end of January 2017. *See* 77 Fed. Reg. 48756 at 48757 (approximately seven months between decision on institution and conclusion of discovery). A final written decision in the '1624 IPR (instituted February 5, 2016) is likely to issue before this proceeding would reach oral argument, forcing Patent Owners to defend the Cabilly '415 patent claims twice against the same real party-in-interest making substantially the same arguments about the prior art. *See Sanofi-Aventis*, IPR2015-01624, Paper 15. It is precisely this type of circumvention of the IPR rules that Congress sought to prevent through section 325(d). *See* AIA H.R. Rep., pt. 1 at 48; 77 Fed. Reg. 48756.

III. THE PETITION SHOULD BE DENIED BECAUSE, IN VIEW OF THE INSTITUTION OF THE '1624 IPR, SANOFI WILL BE ESTOPPED FROM PURSUING THIS IPR

The Board also should deny institution of the '383 Petition because Sanofi

will be statutorily estopped from pursuing the grounds set forth therein against claims instituted in the '1624 IPR upon issuance of a final written decision from the Board in that proceeding. Pursuant to 35 U.S.C. § 325(e)(1), once a final written decision issues in the '1624 IPR, Sanofi, as a "real party in interest . . . of the petitioner, may not request or maintain a proceeding before the Office with respect to that claim on any ground that the petitioner raised or reasonably could have raised during that post-grant review." *See also* 77 Fed. Reg. 442 at 443 ("The estoppel provision[, section 325(e)(1),] appl[ies] to the real party(ies) in interest of the *inter partes* review . . . and any privy of such a petitioner."). In light of this provision, the Board has denied institution where a second petition seeks review of claims that already are at issue in an earlier-filed action, recognizing that it would be wasteful and inefficient to institute an IPR that a petitioner might ultimately be estopped from pursuing. *See Toyota Motor Corp.*, IPR2015-01422, Paper 8 at 20-21 ("[Under 35 U.S.C. § 325(e)(1),] Petitioner might be unable to 'maintain' the second *inter partes* review upon issuance of a final written decision in IPR2015-00633. . . .Thus, instituting a second *inter partes* review may result in a significant waste of time and resources for the parties and for Board.").

Here, there is no dispute that a final written decision is likely to issue in the '1624 IPR before this proceeding reaches oral argument. *See supra* Section II.E. There also is no dispute that Sanofi is named as a real party-in-interest on the face

of this petition, as well as the '1624 Petition.

Further, as discussed above, Sanofi could have raised each of the arguments asserted here in its first petition. Where "the record demonstrates that [the petitioner] must have known of" the newly asserted prior art, the Board has held that the art necessarily could have been raised in the first petition, thus triggering estoppel. *Ford Motor Co. v. Paice LLC*, IPR2014-00884, Paper 38 at 14-15; *see also Apotex Inc. v. Wyeth LLC*, IPR2015-00873, Paper 8 at 6-7 ("[T]he record demonstrates that Petitioner was aware of the prior art references asserted in Ground 2 when it filed the [first] IPR. . . .Petitioner cites [the prior art reference] for the same teaching in the instant Petition."). There is no question that Sanofi was aware of and could have raised grounds based on the Salser, Ochi, and Southern references at the time of filing the first Petition—it cited each reference in that earlier Petition. *See supra* Section II.B. As a result, Sanofi will be estopped from maintaining the instant IPR upon issuance of a final written decision in the '1624 IPR. To avoid wasting Board resources, the Board should deny this Petition.

IV. FIELD OF THE INVENTION OF THE CABILLY '415 PATENT

A. Prior Art Antibody Production Techniques

The Cabilly '415 patent is directed to use of recombinant DNA techniques to produce immunoglobulins, also referred to as antibodies. As shown in Figure 1 of the Cabilly '415 patent (Ex. 1001), an antibody is a multimeric protein composed

of four polypeptide chains. Naturally occurring antibodies consist of two identical "heavy" chains and two identical "light" chains that form what is schematically depicted as a Y shaped molecule. Ex 1001 at 3:17-27; Ex. 2005, Harris Decl. II at ¶ 17. The heavy and light chains are so-called because they differ in molecular weight. Assembled immunoglobulins are large and complex molecules and require significant post-processing for their assembly. Ex. 2006, McKnight Decl. II at ¶ 10.[8]

Antibody-based drugs have revolutionized the treatment of cancer and other diseases and represent a large and growing segment of the drug market. Ex. 2001, Adler at 1-20. The ability to manufacture these drugs required the development of methods to reliably produce large quantities of pure antibodies. Ex. 2002, Kelley at 443.

Before the work that led to the Cabilly '415 patent, scientists created antibodies to an antigen by immunizing an animal (*e.g.*, a rat, mouse, or rabbit) with the antigen. *See generally*, Ex. 1001 at 1:42-2:19. But this technique

[8] An antibody is a complex tetramer that links four discrete polypeptides together via multiple disulfide bonds and noncovalent interactions. Ex. 2003, McKnight Decl. II at ¶ 10. Antibody light chains have between 210 and 220 residues, and heavy chains have between 455 and 550 residues; an assembled antibody weighs approximately 150 kD. *Id.*

generated a mixture of antibodies, each of which bound to a different unique epitope on the antigen. *Id*. These antibodies are called polyclonal antibodies because they are produced by multiple different cells in the animal in response to the foreign antigen. *Id.* The therapeutic usefulness of polyclonal antibodies is limited because they are not uniform in their specificity (*i.e.*, they bind to a variety of locations on an antigen). *Id*. at 1:61-63.

By the late 1970s and early 1980s, scientists were beginning to realize the value of antibodies specific to the same part of a single antigen, *i.e.*, monoclonal antibodies. Ex. 1001 at 1:63-2:11. As the name suggests, monoclonal antibodies are produced by clones of a single cell, where each cell produces a protein with the same amino acid sequence that will bind to the same epitope. *Id.*

The production of monoclonal antibodies was significantly advanced by the development of hybridoma techniques in 1975 by Georges Kohler and Cesar Milstein. A "hybridoma" results from the fusion of a cancer cell with an antibody producing B-cell, which "immortalizes" the fused cell by including it in the cancer cell. Ex. 2003, Kohler and Milstein. As a result, the hybridoma can be grown in cell culture to produce the antibody naturally produced by the fused B-cell. *Id*.

By April of 1983, the hybridoma technique was in use, but it had a significant drawback: it only produced the antibodies that an immunized animal generated in response to immunization with the antigen. Ex. 1001 at 2:62-66. This

limited the potential of hybridomas in at least three ways: (i) it was not possible to know, *a priori*, the sequence of the generated antibody or what its particular binding properties would be; (ii) hybridomas could become unstable and lose the ability to produce one or both chains of the antibody; and (iii) it was not possible to create new forms of antibodies using hybridomas—they would only produce the type of antibody that the B cell isolated from the immunized host would produce. *Id.* at 2:40-66. A significant need thus existed in 1983 for an alternative way to produce antibodies. *Id*. at 2:40-3:2.

Recombinant DNA techniques produce proteins by introducing into cells predefined DNA sequences not already present in those cells (transfection), and then propagating the cells containing the foreign DNA *in vitro* under conditions that cause the cell to produce the protein coded by the exogenous[9] DNA. However, as of April 1983, protein production using recombinant DNA technology was still in its infancy. By that time, only a few proteins with known therapeutic value had been recombinantly produced, and each success was considered a major scientific breakthrough. *See*, *e.g*., Ex. 2005, Harris Decl. II at ¶¶ 12-13. The only proteins that had been expressed recombinantly in a single host cell by 1983 were

[9] As used herein, an exogenous gene is one that is foreign to a host cell and is introduced using recombinant DNA techniques. An endogenous gene is one that is natively present in the host cell.

small monomeric proteins. Ex. 2004, Harris Decl. at ¶ 16; Ex. 2006, McKnight Decl. II at ¶ 7. Moreover, although scientists had also produced insulin (a multimeric protein) using recombinant DNA techniques by the early 1980s, that was likewise done by producing individual polypeptides in separate host cells. Ex. 2006, McKnight Decl. II at ¶¶ 10-11; Ex. 2005, Harris Decl. II at ¶ 14.

B. The Cabilly '415 Patent

The challenged claims of the Cabilly '415 patent require introducing immunoglobulin heavy and light chain DNA sequences into a single host cell and co-expressing those chains as separate molecules to produce a functional antibody. *See*, *e.g.*, Ex. 1001 at Abstract, Claim 1. The Petition challenges claims 1-4, 9, 11, 12, 14-20, and 33 of the Cabilly '415 patent. Independent claims 1 and 33 define processes, and are reproduced below for convenience of the panel:

> 1. A process for producing an immunoglobulin molecule or an immunologically functional immunoglobulin fragment comprising at least the variable domains of the immunoglobulin heavy and light chains, in a single host cell, comprising the steps of:
>
> (i) transforming said single host cell with a first DNA sequence encoding at least the variable domain of the immunoglobulin heavy chain and a second DNA sequence encoding at least the variable domain of the immunoglobulin light chain, and

(ii) independently expressing said first DNA sequence and said second DNA sequence so that said immunoglobulin heavy and light chains are produced as separate molecules in said transformed single host cell.

33. A process for producing an immunoglobulin molecule or an immunologically functional immunoglobulin fragment comprising at least the variable domains of the immunoglobulin heavy and light chains, in a single host cell, comprising:

independently expressing a first DNA sequence encoding at least the variable domain of the immunoglobulin heavy chain and a second DNA sequence encoding at least the variable domain of the immunoglobulin light chain so that said immunoglobulin heavy and light chains are produced as separate molecules in said single host cell transformed with said first and second DNA sequences.

Independent claim 15 recites a single vector that contains the DNA sequences for both the heavy and light chains at different insertion sites, which is used to transform the single host cell, and independent claim 18 recites a host cell transformed with at least two separate vectors (one that includes heavy chain DNA and one that includes light chain DNA). Ex. 1001 at 29:22-27, 29:31-36.

During reexamination of the Cabilly '415 patent, Dr. Steven L. McKnight,

Distinguished Chair in Basic Biomedical Research and The Sam G. Winstead and F. Andrew Bell Distinguished Chair in Biochemistry at the University of Texas Southwestern Medical Center, described the requirements of the process claims to the Office as follows:

> The '415 patent requires the production of an immunoglobulin molecule[] . . . by expression of DNA sequences encoding both heavy and light immunoglobulin chain polypeptides in a single transformed host cell. This means that all of the following things must happen: (i) host cells must have been successfully transformed with DNA sequences encoding the heavy and light chain polypeptide sequences; (ii) the transformed host cell must independently express both sequences (e.g., each DNA sequence must be accurately transcribed into an mRNA, and each mRNA must be translated into an appropriate amino acid sequence corresponding to each chain); and (iii) the polypeptides must be assembled into an immunoglobulin tetramer . . . either inside or outside of the cell.

Ex. 2006, McKnight Decl. II at ¶ 4.

The Cabilly invention represented a dramatic advance in the field of genetic engineering. As noted above, before April 1983, only a few eukaryotic proteins had been successfully expressed using recombinant DNA techniques, and for each

such protein, only one polypeptide of interest was produced in a given host cell. *See*, *e.g.*, Ex. 1017. The co-expression strategy set forth in the Cabilly '415 patent greatly expanded the potential application of antibodies in scientific research and created a foundation for the development of antibodies. That widespread impact is evidenced, for example, by the pharmaceutical industry's recognition of the Cabilly '415 patent as one of the groundbreaking patents that launched the modern field of antibodies, including through the widespread licensing of the patent. *See*, *e.g.*, Ex. 1045, Walton Rep. at ¶¶ 15, 22-27. Indeed, a representative of a pharmaceutical company developing antibodies testified: "[i]t was well known in the industry that there are certain patents necessary if you are going to be in the antibody field," and the Cabilly '415 patent is among them. *Id.* at 22.

C. Claim Construction

In this proceeding, the terms of the challenged claims are to be given their broadest reasonable interpretation[10] in light of the specification as commonly understood by those of ordinary skill in the art. *See* 37 C.F.R. § 42.100(b). Petitioner states that "the claim terms of the '415 patent are presumed to take on

[10] The Supreme Court is currently reviewing the standard of review for *inter partes* reviews in *Cuozzo Speed Technologies, LLC v. Lee*, No. 15-446 (petition granted Jan. 15, 2016). Patent Owners reserve the right to advance a different claim construction should the Court hold that a different standard of review applies.

the ordinary and customary meaning that they would have had to a POSITA in April 1983." Paper 2 at 16. For purposes of this Preliminary Response, Patent Owners do not dispute Petitioner's position.

D. Person of Ordinary Skill

For the limited purpose of this Preliminary Response, Patent Owners deem it unnecessary to contest the level of ordinary skill in the art identified by Petitioner, Paper 2 at 15, which is consistent with the position Patent Owner identified in the prior reexamination and in litigation. *See*, *e.g.*, Ex. 2007, Fiddes Rep. at ¶ 37 ("Ph.D. in molecular biology or related discipline, such as biochemistry, microbiology or cell biology plus two to three years post-doctoral training and experience (whether in academia or industry) in the application of recombinant DNA technology to protein production").

V. THE ASSERTED PRIOR ART

The Petition advances Salser, Ochi, and Southern to support its anticipation and obviousness grounds. In so doing, the Petition substantially mischaracterizes what each reference discloses and teaches. An accurate description of each reference reveals the flaws of Petitioner's theories of unpatentability.

A. Salser (Ex. 1002)

As Petitioner admits, Salser describes a technique for "gene replacement therapy," Paper 2 at 26, *i.e.*, the idea that a genetic deficiency that prevents the

normal manufacture of a protein in a cell can be corrected by modifying that cell to produce the protein properly. Salser proposes to apply this gene replacement therapy technique to remedy genetically linked illnesses, with a specific focus on "treatments for hemoglobin-based genetic deficiencies." *Id*. at 29. Thus, Salser hypothesizes that "[w]ith bone marrow stem cells, genes could be provided with the correct sequences to correct hemoglobinopathes [*sic*], such as sickle cell disease and thalassemia, [or] defects in the production of plasma coagulation factors, e.g. fibrinogen, pro-thrombin and the various Factors, especially Factors VIII and IX." Ex. 1002 at 6:2-8.

As an example of its proposed therapeutic technique in the context of a hemoglobin-based genetic deficiency, Salser proposes (but does not test) a strategy to introduce into an organism's cells a normal copy of a beta-globin gene (one of the constituent parts of hemoglobin), and speculates that when expressed, the cell will produce a correct form of the beta chain of the hemoglobin protein. *See* Ex. 1002 at 17:23-33.

Importantly, the beta-globin gene does not encode or produce both chains of the hemoglobin protein; the other component of the hemoglobin protein (the alpha-globin chain) is endogenous to the cell. When expressed, the beta-globin gene will only produce one of those chains, the beta chain. Indeed, in focusing on the beta-globin chain, the Salser strategy also depends on the organism correctly expressing

the gene encoding the alpha chain of hemoglobin and cells within the organism that normally make hemoglobin correctly folding, assembling and secreting the multimeric hemoglobin protein.

Critically, Salser never performed this beta-globin expression experiment—it is entirely prophetic. Instead, Salser focused on techniques that could potentially enable such an experiment in the future. In particular, Salser described two experiments—the only actual experiments described in the patent—in which isolated bone marrow cells were transfected to incorporate selective markers (either dihydrofolate reductase ("DHFR") or thymidine kinase ("TK")). Ex. 1002 at 2:10-20. Salser explains that when the modified bone marrow cells containing the markers are reintroduced into living hosts, cells with the selective marker (DHFR or TK) grew more rapidly than cells without the selective marker. Ex. 1002 at 8:60-52.

Against this backdrop, Salser fundamentally differs from the challenged Cabilly '415 patent claims for at least three reasons.

First, Salser and the Cabilly '415 patent address very different problems. Salser is directed to correcting a genetic deficiency in a host organism that is expressing a mutant gene (what Petitioner refers to as "gene replacement therapy," Paper 2 at 26). Salser contemplates introducing cells that are expressing non-mutant genes into the host to correct such deficiencies. *See* Ex. 1002 at 1:45-2:4

(disclosing that the "host cells are returned to the host" and "[b]y use of this approach, animals were obtaind [*sic*] in which the majority of the type of cells involved contained the added genetic material in a functionally active state"). Salser presumes the cells ***in their native environment*** will produce and assemble the proteins properly, because it speculates that a "normal" form of the protein "should" be produced in the organism. Ex. 1002 at 17:23-33.

By contrast, the Cabilly '415 patent is directed to producing and recovering functional antibodies, and does so using transformed host cells suitable for culturing outside of an organism. *See*, *e.g.*, Ex. 1001 at 8:26-39 (disclosing that "terms 'cell' and 'cell culture' are used interchangeably"); 4:44-46 (disclosing that "means and methods are available for maintaining permanent lines"); 8:40-10:29 (describing suitable host cells to use for production of recombinant antibodies).

Thus, the Cabilly '415 patent and Salser are directed to fundamentally different problems. The Cabilly '415 patent solves the problem of producing recombinant antibodies in cell culture, whereas Salser contemplates (but does not actually show) introducing cells into host organisms to correct a genetic deficiency, *e.g.*, sickle cell anemia. *See* Ex. 1002 at 17:23-27 ("With the hemoglobinopathies, insertion of a normally regulated and structurally normal beta-globin gene should be capable of correcting the defect in beta-thalassemia and sickle cell disease.").

Second, while Petitioner relies heavily on the word "genes" in Salser, the

words "immunoglobulin" and "antibody" do not appear in Salser at all. Salser mentions "globulins" in one instance, referring to a "wide variety of proteins, e.g., hormones, globulins or the like." Ex. 1002 at 2:35-36. Given that Salser is "specifically focused on treatments for hemoglobin-based genetic deficiencies," Paper 2 at 29, one of ordinary skill in the art would have had no reason to focus on immunoglobulins based on this one reference to "globulins."

Third, unlike the Cabilly '415 patent, Salser does not teach, or even contemplate, a single host cell producing a multimeric protein from two different exogenous genes. To begin, Salser does not actually demonstrate that the methods it describes correct any genetic deficiencies. The one passage relied upon by Petitioner, involving using a beta-globin gene to remedy a deficiency in producing hemoglobin, is purely speculative. Paper 2 at 29; Ex. 1002 at 17:23-32 (noting the "insertion of a normally regulated and structurally normal beta-globin gene ***should be*** capable of correcting the defect in beta-thalassemia and sickle cell disease" and the "cells containing the selective marker and structurally normal beta-globin gene ***should proliferate*** under the selective pressure of the drug" (emphasis added)).

Even if one had attempted to test Salser's speculation that an exogenous and structurally normal beta-globin gene could be introduced into a host organism to correct the genetic defect, that experiment would still have involved only the production of a single exogenous gene of interest—the beta-globin chain. Indeed,

the Salser strategy relies on the alpha-globin gene being present in and correctly expressed by the cells of the organism.

By contrast, the Cabilly '415 patent is directed to ***co-transforming*** suitable host cells with ***two different exogenous DNA sequences***, one encoding the heavy chain and one encoding the light chain, culturing the transformed host cells to co-express both exogenous DNA sequences, and then culturing the host cells to recover fully-assembled functional antibodies. Salser does not disclose this.

B. Ochi (Ex. 1003)

Ochi is directed to understanding the regulatory pathways for immunoglobulins—not how to produce them using recombinant techniques. It describes a limited experiment in which a gene encoding an immunoglobulin light chain was introduced into a cell line that had lost the ability to express the light chain, but was still producing the heavy chain. *See* Ex. 2005, Harris Decl. II at ¶¶ 80-81; Ex. 2008, Rice Decl. at ¶ 34. But it does not describe transfecting cells with an exogenous heavy chain gene, or with exogenous heavy and light chain genes. Ex. 2005, Harris II Decl. at ¶¶ 82-84. In this respect, the disclosure of Ochi parallels the one-gene strategy of Salser. Both references describe introducing exogenous DNA coding for a single protein chain into a host, but nothing more. Neither reference teaches introducing DNA encoding different chains of a multimeric protein into a single host cell, co-expressing them, and obtaining a

functional protein.

Ochi was the subject of considerable expert testimony and discussion during a thorough reexamination of the Cabilly '415 patent. As the experts for Patent Owners explained during reexamination, one of ordinary skill in the art reading Ochi in April 1983 would have had no reasonable expectation that she could successfully co-transform a host cell with exogenous heavy and light chain DNA, successfully co-express it, ***and then*** recover functional antibodies, which is what the Cabilly inventors claimed. *See*, *e.g.*, Ex. 2005, Harris II Decl. at ¶¶ 83-84. The Patent Office agreed, and upheld the claims of the Cabilly '415 patent over Ochi and various other pieces of prior art.

C. Southern (Ex. 1004)

Southern discloses a vector used to transform a mammalian host cell with the bacterial selectable marker gene "neo" so that it is resistant to the antibiotic G418 and can be "selected" when G418 is used to eliminate other cells. Ex. 1004 at Abstract. In one experiment, Southern transfects cells with both the new vector (pSV2-neo) and another vector (pSV2-gpt) containing the gpt gene—a known selectable marker that confers resistance to mycophenolic acid (MPA). *Id.* at 336-337. Southern makes no reference to immunoglobulins, nor does it show production of single or multiple genes of interest besides the selectable marker.

VI. THE PETITION SHOULD BE DENIED BECAUSE NO GROUND ESTABLISHES A REASONABLE LIKELIHOOD OF SUCCESS.

A. GROUND 1: The '383 Petition Fails to Demonstrate a Reasonable Likelihood of Showing That Salser Anticipates Claims 1-4, 9, 11, 12, 15-20 and 33.

Among other things, the challenged claims of the Cabilly '415 patent require producing an antibody by co-expressing exogenous DNA sequences encoding all of the polypeptide chains (heavy and light chains) necessary for the formation and assembly of a functional immunoglobulin in a single host cell. Salser fails to anticipate this claim because it does not disclose: (i) immunoglobulins; (ii) transformation of a single host cell with exogenous DNA sequences encoding for all subunits of any multimeric protein, let alone both the heavy and light chains of an immunoglobulin; (iii) any relevant example of protein expression; or (iv) a single vector containing both heavy and light chain DNA.

Given this lack of disclosure, Petitioner attempts to re-write Salser based on "common knowledge" or "simple logic" to supply the many missing elements. Paper 2 at 40. The Board rejected this same approach in its Decision on Institution in the '1624 IPR, where it determined that the Bujard reference failed to anticipate the claims of the Cabilly '415 patent. The same result should apply here.

1. Salser Does Not Disclose the Production of Immunoglobulins.

Salser does not disclose recombinant production of immunoglobulin, which the challenged methods of the Cabilly '415 patent require. Indeed, Salser makes no mention of antibodies at all.

Despite this lack of disclosure, Petitioner claims that Salser actually does disclose antibodies based entirely on a passing reference to "globulins"—contained in a list of a "wide variety" of potential proteins that may be utilized for gene replacement therapy. That is, from an undifferentiated group of "hormones, globulins or the like," Petitioner argues that one of ordinary skill in the art would have zeroed-in on globulins because they were a "defined and limited" genus, and then would have further focused specifically on immunoglobulins within that genus. Paper 2 at 33. That argument fails for several reasons.

First, Petitioner mischaracterizes the "genus" disclosed in Salser. Salser describes a "wide" genus that consists of all hormones, all globulins, and all "like" proteins, not simply a genus of "globulins." Ex. 1002 at 2:34-35. This genus is vast. Even the sub-genus of "globulins" alone includes over ***40 species of proteins***, among them 11 types of alpha globulins, 7 types of beta globulins, multiple different types of immunoglobulins and fragments, and several other sub-species of "globulin" proteins. *See* Ex. 1012 at 256-257. When added to the 40-50 different human hormones known in 1983 (Ex. 2009, Landau at 354), let alone an indeterminate number of "like" proteins, the genus disclosed in Salser is enormous.

Second, Petitioner has not demonstrated that Salser would direct one of ordinary skill in the art to immunoglobulins specifically. The Federal Circuit has repeatedly held that "the disclosure of a genus in the prior art is not necessarily a

disclosure of every species that is a member of that genus." *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006). This is particularly true where, as here, that genus is large. *See Impax Labs., Inc. v. Aventis Pharm. Inc.*, 468 F.3d 1366, 1383 (Fed. Cir. 2006) (no anticipation where prior art disclosed a "large number of compounds . . . and no specific identification" of the claimed species); *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1376 (Fed. Cir. 2006) (affirming finding that claimed species was not anticipated by prior art disclosure of genus because, *inter alia*, "a chemist theoretically had at least fifty different pharmaceutically acceptable salts from which he could have chosen for formulation"); *Ex Parte Lettmann*, Appeal No. 2008-1185, 2008 WL 552716 at *5 (BPAI Feb. 29, 2008) (no anticipation where "one must pick and choose from two long lists of [approximately 55] available pigment compounds" because "this picking and choosing [is] excessive" (internal quotation marks omitted)).

Moreover, to prove anticipation of a species by reference to disclosure of a genus, Petitioner must show that Salser itself demonstrates a "pattern of preferences" that would lead a person of ordinary skill in the art from the genus to the species. *See Sanofi-Synthelabo*, 470 F.3d at 1377 (rejecting argument that species was anticipated by genus where alleged prior art reference did not exhibit a "pattern of preferences" leading to the claimed species); *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1376 (Fed. Cir. 2006) (challenger must show

a "limited number of specific preferences from a specifically defined group"). But Petitioner points to nothing in Salser that would lead a person of ordinary skill from the broad, generic disclosure of "hormones, globulins or the like" to antibodies specifically. Instead, by resorting to extrinsic evidence including testimony from its expert and a medical publication index, Petitioner implicitly admits that Salser does not disclose immunoglobulins or a pattern of preferences for immunoglobulins. Salser thus is insufficient to show anticipation.

None of the authority cited by Petitioner is to the contrary. Paper 2 at 34-35. *In re Baxter Travenol Labs*, *(In re Baxter Travenol Labs,* 952 F.2d 388 (Fed. Cir. 1991)), generally holds that extrinsic evidence may be used to determine the meaning of a prior art reference. To show anticipation of a species by a reference disclosing a genus, however, a Petitioner must still show that the reference narrows the genus in such a way that the person of ordinary skill in the art would be led immediately to envisage the species. *Eli Lilly & Co.*, 471 F.3d at 1376. Likewise, in *Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 872 (Fed. Cir. 2015) and in *Gnosis S.p.A. v. Merck & Cie*, IPR2013-00117, Paper 71 at 11-17, a challenger offered extrinsic evidence merely to confirm the size of a well-defined genus. In neither case was the challenger allowed to cite a "wide" genus and then rely on extrinsic evidence to purportedly demonstrate a pattern of preferences that would have led to a specific species, as Petitioner seeks to do here. Absent evidence in

Salser ***itself*** that would lead a person of ordinary skill to envisage application of Salser's methods to immunoglobulin production in transformed host cells, Petitioner's purported "genus/species" argument fails.

Third, Petitioner's argument concerning the "medical importance" of immunoglobulins as a basis for focusing on antibodies Paper 2 at 35-36,—which also relies exclusively on extrinsic evidence—is unpersuasive. As Petitioner itself acknowledges, other globulin species were "important in their own right." *Id*. In light of that admission, Petitioner has provided no reasonable basis for the Board to determine why a person of ordinary skill supposedly would have been directed to immunoglobulins over any other "important" globulin.

Petitioner also ignores the undisputed fact that Salser "specifically focused on treatments for hemoglobin-based genetic deficiencies," Paper 2 at 29, and that at the time of Salser, blood disorders, *i.e.*, "hemoglobinopathes [*sic*]" themselves were considered an important topic of investigation. Ex. 1002 at 17:14; *see*, *e.g.*, Ex. 2010, Weatherall at 7 ("Apart from their intrinsic medical importance as the commonest group of monogenic disorders in the world population, the thalassemias provide a variety of naturally occurring models for the study of the regulation of hemoglobin synthesis and its developmental genetics. In the relatively short time since the topic was last reviewed (Weatherall and Clegg, Cell 76, 467-479, 1979) there has been spectacular progress in the study of human

hemoglobin."); Ex. 2011, Loukopoulos at 1419 ("Prevention of thalassemia and hemoglobinopathies is the only solution to efficiently reduce the huge medical, social and economic impact of these diseases in countries where they occur in high frequencies.").

If the "importance" of a protein is a key characteristic in identifying it from among a broad genus, as Petitioner contends here, Petitioner fails to explain why the person of ordinary skill would have interpreted the reference to "hormones, globulins or the like" to mean something other than hemoglobin and beta-globin—the specific globins discussed in Salser. Ex. 1002 at 17:23-32, 5:39-6:13, 17:14.

In short, Petitioner has not demonstrated that a person of ordinary skill reading Salser in April 1983 would have pivoted from the clear and exclusive disclosure directed to the important topic of treating hemoglobin-related diseases with "gene replacement therapy" to correct genetic deficiencies—to focus instead on the different problem of using recombinant DNA techniques to produce immunoglobulins, about which Salser says nothing. As a result, there can be no anticipation. *See Metabolite Labs., Inc. v. Lab Corp. of Am. Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004) (no anticipation where prior art reference "discloses no more than a broad genus of potential applications of its discoveries" and "simply invites further experimentation").

2. Salser Does Not Disclose Transformation of a Single Host Cell with Multiple DNA Sequences Encoding Immunoglobulin Heavy and Light Chains.

Petitioner essentially concedes that Salser does not disclose the claimed methods, cells, and vectors, arguing instead that Salser's disclosure of "genes" (plural) "clearly accommodates" the "insertion into the cell of the two (heavy and light chain) DNA sequences . . . required to make an immunoglobulin." Paper 2 at 39. But "accommodating" such functionality is far different from actually teaching it. More is required for anticipation. *Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295 (Fed. Cir. 2002) ("Inherent anticipation requires that the missing descriptive material is necessarily present, not merely probably or possibly present, in the prior art." (internal quotation marks omitted)); *see also Finnigan Corp. v. Int'l Trade Comm'n*, 180 F.3d 1354, 1366 (Fed. Cir. 1999) ("The mere possibility that [the prior art] might be understood by one of skill in the art to disclose [the claimed invention] is insufficient to show that it is inherently disclosed therein.").

The Board's previous rejection of an analogous anticipation theory regarding Bujard is instructive. In declining to institute trial on anticipation grounds in the '1624 IPR, the Board recognized that the "prior art disclosure of elements that merely 'could have been arranged' in the claimed manner is not anticipatory." *Sanofi-Aventis*, IPR2015-01624, Paper 15 at 16. The same logic applies here. Petitioner has only argued that the various disclosures ***could have*** been arranged by

one of ordinary skill in the art in April 1983 to anticipate the challenged claims of the Cabilly '415 patent. That is insufficient.

This error pervades Petitioner's analysis of Salser. Petitioner has cobbled together different passages from disparate parts of the disclosure. Thus, it claims that Salser discloses that "[t]he DNA introduced into the mammalian host cell will also contain 'genetic material'—including 'two or more genes,' 'a single set of genes' or 'a plurality of unrelated genes'—to provide 'genetic functions . . . for a variety of purposes including . . . production of a wide variety of proteins.'" Paper 2 at 28. Petitioner then seeks to link these generic disclosures to Salser's reference to "globulins." *Id.* at 29.

This collection of statements assembled by Petitioner comes from four different sections of Salser (appearing on four different pages). None specifically discusses the transfection of a single host cell with multiple genes of interest with the goal of making a functional multimeric protein. Indeed, each at best describes methods related to gene therapy—correcting a deficiency in a cell by re-introducing a structurally correct gene—and none relates to expressing recombinant DNA in host cells intended to be propagated *in vitro* for the production of recombinant proteins.

The examples disclosed in Salser only teach the use of ***selective markers*** to select for cell populations *in vivo*, with an eye toward ***eventually*** trying to

accomplish other goals in the future, one of which might be the production of other proteins. *See*, *e.g.*, Ex. 1002 at 2:46-5:8 (extended discussion of selective markers), 6:44-17:14 (examples using *only* selective markers), 2:29-36 ("genetic functions can be provided for a variety of purposes"), 17:26-33 (discussing use of selective marker "to allow for selective pressure in the host").[11] Given this limited disclosure, Petitioner reads far too much into Salser. Nothing in Salser suggests that these disparate passages should be combined even to attempt to make an antibody, much less to use the very different host cell procedures specified in the claims of the Cabilly '415 patent.

Petitioner's effort to read into Salser a disclosure of methods to produce in a single host cell multiple eukaryotic proteins of interest, let alone the constituent chains of an immunoglobulin, is therefore fundamentally flawed. *See Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008) (a reference "cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate" if it does not recite "all of the limitations arranged or combined in the

[11] During reexamination, the Patent Office agreed that the Axel reference—which describes introducing a selectable marker and one gene of interest and explicitly discloses antibodies as a protein of interest—was ***not*** sufficient to disclose expression of the heavy and light chains of an immunoglobulin. Ex. 2024, Reexam 11/25/2005 Response at 34; Ex. 2004, Harris Decl. at ¶¶ 20-30.

same way as recited in the claim"); *Ecolochem, Inc. v. S. Cal. Edison Co*., 227 F.3d 1361, 1369 (Fed. Cir. 2000) (separate disclosures in reference did not anticipate claims directed to combination of elements because reference did not discuss or suggest linking the elements); *Finisar Corp. v. DirecTV Group, Inc*., 523 F.3d 1323, 1334 (Fed. Cir. 2008) ("[a]nticipation requires the presence in a single prior art disclosure of all elements of a claimed invention arranged as in the claim" (internal quotation omitted)).

3. The Petition Does Not Cite Any Relevant Example of Protein Expression in Salser.

In the absence of a relevant example related to immunoglobulins, Petitioner attempts to rely on the disclosure in Salser related to the beta-globin chain of hemoglobin. Petitioner asserts that the example of beta-globin, and bare reference to "globulins" in a list of potential proteins of interest, discloses independent expression of heavy and light chains that assemble into a functional immunoglobulin. Paper 2 at 42-43. This argument is flawed for multiple reasons.

First, the mere reference to beta-globin in Salser does not disclose the independent expression of multiple ***and distinct*** genes of interest. Petitioner cites the reference in Salser to a beta-globin "gene cluster" as purportedly teaching "independent expression of separate proteins in a single host cell." *See* Paper 2 at 43, n.16. But this misrepresents the scope of the "beta-globin" disclosure in Salser.

Indeed, Salser provides no actual experiment related to beta-globin. Nor

does Salser discuss any details of the referenced "beta-globin cluster," including its specific content, how it would be expressed, or what specific parts of it would be used by a cell. Salser also does not indicate whether insertion of the entire beta-globin cluster into a cell would result in expression of all components of that cluster, or would yield a functional hemoglobin. Salser's disclosure of beta-globin is therefore very limited and, at most, entirely hypothetical.

Petitioner's assertions about what would happen if the entire beta-globin cluster were inserted into a vector are equally hypothetical. Petitioner suggests that "if the entire [beta-globin] cluster is inserted into a vector and transformed into a mammalian host cell, the five genes will be expressed as five separate polypeptide molecules." Paper 2 at 30. The Petition provides no support for that conclusion. In fact, the articles cited in the Petition (and other contemporaneous publications) show that the beta-globin gene cluster is made up of variants of ***the same gene*** that are expressed at ***different*** times during human development, *i.e.*, all five genes are not expressed together in nature. Ex. 1031 at 853-854; Ex 1032 at 855-856; Ex. 2012, Schechter at 3930-3931; Ex. 2013, Levings at 269. In other words, Petitioner has not shown that its citation to beta-globin discloses independent expression of multiple different proteins at the same time.

Second, the reference to beta-globin is not relevant to the Cabilly '415 patent claims because it is not an example of the transformation of a cell with two

different exogenous genes of interest, expression of two different proteins based on those genes, and assembly of those proteins into a multimeric protein. As Petitioner acknowledges, the reference to beta-globin in Salser is related to "gene replacement therapy designed to provide patients with a 'structurally normal beta-globin gene,'" *i.e.*, treating sickle cell anemia, which is caused by a mutation in hemoglobin beta chain. But hemoglobin proteins consist of two alpha and two beta chains. Ex. 2012, Schechter at 3927. Thus, at most, what the beta-globin reference in Salser suggests is the exogenous introduction of ***one*** of the components of the hemoglobin protein (the beta chain) while other pieces (*i.e.*, the alpha chains) are endogenous to and natively expressed in the host organism to which cells expressing structurally correct beta-globin are theoretically introduced.[12] Salser makes no mention of introducing exogenous alpha and beta chains into a single host organism or host cell.

[12] In this way, Salser is similar to Ochi, in that it does not disclose the introduction of an exogenous DNA sequence encoding more than one gene of interest. Salser contemplates introducing only beta-globin DNA into a host animal, and Ochi likewise discloses introducing only light chain DNA into a host cell. Ex. 2005 Harris II Decl. at ¶¶ 82-84; Ex. 2008 Rice Decl. at ¶¶ 33-37. The Office has already held, during re-examination, that the invention of the'415 patent is distinct from such a teaching. Ex. 2019, Notice of Intent to Issue Reexam Cert. at 4-8.

And while the beta-globin gene cluster includes five different genes, each of which encodes a beta-globin variant, these variants do not associate with one another. *See*, *e.g.*, Ex. 2014, Weatherall at 352; Ex. 2015, Baldwin at 103. Rather, regardless of which of the five genes in the beta-globin cluster is expressed, the only protein with which it associates is the one or more of the alpha-globins expressed at the same time during development. *Id*. Normal expression of the beta-globin cluster does not result in co-expression of individual proteins that associate with each other to form a functional, multimeric protein.

Finally, Petitioner's argument with respect to the beta-globin gene cluster is even further removed from the co-expression methods described in the Cabilly '415 patent because the heavy and light chain genes for immunoglobulins are on two separate chromosomes, whereas the beta-globin cluster is all located on a single chromosome, chromosome 11. Paper 2 at 29-30; Ex. 2021, McKnight I Decl. at ¶ 20 (heavy and light chain genes on different chromosomes); Ex. 2017, Malcolm at 135; Ex. 2016, Higgs at 1082. Thus, even if all five genes on the beta-globin cluster were expressed at the same time (which they would not be), this would tell one of ordinary skill in the art little about co-expression of genes that are not naturally located on a single chromosome.

At most, Salser speculates about the possibility of modifying a defective cell by inserting a ***single*** exogenous beta-globin gene cluster, which might express a

single beta-globin chain that associates with an endogenously produced alpha-globin chain to form functional hemoglobin. But the Cabilly '415 patent requires more. Petitioner has not shown why or how a person of ordinary skill would arrive at the claimed methods of co-expressing exogenous heavy and light chain DNA in a single host cell to produce a functional antibody based on Salser's limited teaching and speculation relating to a different problem.

4. Salser Does Not Disclose a Vector Including Both Heavy and Light Chain Sequences as Required by Claim 15.

The Petition fails to identify any disclosure in Salser of a vector containing immunoglobulin heavy ***and*** light chain sequences, as required by claim 15 of the Cabilly '415 patent. The only disclosure in Salser that Petitioner cites in this regard is a reference to the potential options for inserting DNA sequences, which states that "when two or more genes are to be introduced they may be carried on a single chain, a plurality of chains, or combinations thereof." Ex. 1002 at 3:50-53.

Petitioner does not even attempt to explain why, based on Salser, a person of ordinary skill would have chosen to use a "single chain" to insert multiple DNA sequences as opposed to "a plurality of chains" or "combinations thereof," or why he or she would have linked the use of a single chain to the expression of immunoglobulin sequences (which are not discussed in the reference). Absent this linking of the elements, Petitioner's argument that Salser anticipates fails. *Ecolochem,* 227 F.3d at 1369; *Finisar*, 523 F.3d at 1323; *Net MoneyIN*, 545 F.3d at

1371.[13]

5. The Board Has Already Rejected Substantially Similar Anticipation Grounds Based on Bujard.

In the '1624 IPR, the Board found no anticipation based on Bujard because that reference failed to disclose many of the elements of the Cabilly '415 patent. As the Board explained: "Bujard does not teach—either expressly or inherently—that genes encoding for both the heavy and light chains must be incorporated into the same vector or otherwise expressed within a single host cell." *Sanofi-Aventis*, IPR2015-01624, Paper 15 at 15. The same elements that were missing from Bujard are missing from Salser.

Here, Petitioner fails to identify any teaching in Salser that genes encoding both the heavy and light chains must be incorporated into the same vector or

[13] Claim 15 of the Cabilly '415 patent also requires that DNA encoding the heavy and light chains be included in a vector at "different insertion sites." Ex. 1001 at 29:22-27. Again, Petitioner does not cite any disclosure in Salser for this limitation. Rather, it argues that a person of skill in the art "would know that the heavy and light chain DNA sequences ***must necessarily*** be arranged non-contiguously in the vector at different insertion sites." Paper 2 at 45 (emphasis added). Petitioner cites nothing but Dr. Baron's opinion in support of this assertion, but she does not explain why this is necessarily true. Ex. 1058 at 76.

otherwise expressed within a single host cell. Rather, Petitioner argues that Salser's disclosure combined with "common sense" and "simple logic" potentially "accommodates" the claimed invention. Paper 2 at 39. These are all buzz words that tacitly concede that Salser does not actually disclose the claimed invention. As the Board noted in the '1624 IPR, "Petitioners' anticipation arguments require us to draw inferences that are not required by Bujard's generalized teachings." *Sanofi-Aventis*, IPR2015-01624, Paper 15 at 15. The Board therefore properly rejected the argument that Bujard anticipates the claims in the '1624 IPR. Petitioner asks the Board to draw similar inferences in the context of Salser. The Board should reach the same result and decline that request.

B. GROUND 2: The Petition Fails to Demonstrate a Reasonable Likelihood of Showing Claims 1-4, 9, 11, 12, 14-20, and 33 Are Obvious Over Salser in View of Ochi.

In Ground 2, Petitioner argues that "should the Board find that the Salser patent's teaching of the genus of 'globulins' is not a sufficient disclosure for purposes of anticipation . . . the specific teaching of immunoglobulins may be found in Ochi (I)." Paper 2 at 47-48. Thus, the ***only*** element of the Cabilly '415 patent claims that Petitioner contends may not be present in Salser is an immunoglobulin; in Ground 2, Petitioner maintains that all other elements are expressly or inherently disclosed in Salser.

But instead of providing an articulated rationale for why the skilled person

would have combined the teachings of these two unrelated references, Petitioner relies on hindsight in an attempt to somehow arrive at the claimed invention. Petitioner's obviousness grounds based on Salser and Ochi fail for three reasons.

First, Petitioner's argument is internally inconsistent. Petitioner's obviousness theory presumes that Salser does not disclose application of its processes to immunoglobulins. To fill that supposed gap, Petitioner contends the skilled artisan would have been motivated to combine Salser with Ochi because Salser is "directed to the use of rDNA techniques to make heterologous proteins, and in particular, the same type of heterologous protein [as Ochi] (globulins/immunoglobulins, or a chain or chains thereof)." Paper 2 at 49. Petitioner cannot have it both ways—suggesting Ochi as an obviousness combination with Salser on the assumption that Salser fails to disclose immunoglobulins, but then arguing that there is motivation to combine the two because they both relate to immunoglobulins.

Likewise, Petitioner's argument that Salser would motivate a person of skill in the art to "investigate" the art for teachings related to immunoglobulins and then combine them with Salser's techniques also rings hollow. Given the assumption Petitioner has made in this ground—that Salser does ***not*** disclose immunoglobulins—Petitioner fails to address why a person of ordinary skill would have been motivated to look beyond its disclosure, with its focus on gene

replacement therapy for blood disorders. The Board has rejected similar attempts to rely on a "laundry list" of potential targets and derive from that a motivation to pursue a particular member of that list. *See Amgen Inc. v. AbbVie Inc.*, IPR2015-01514, Paper 9 ("We are unpersuaded that the inclusion of [an antibody] in a laundry-list of untested potential targets in [a reference] would have provided sufficient direction to one of ordinary skill in the art to select [the antibody for formulation].").

Second, even if the Board accepts Petitioner's strained argument that Salser teaches co-expressing multiple recombinant genes in a single host cell (which it does not), a person of skill in the art would not have been motivated to combine that teaching with Ochi with any reasonable expectation of successfully expressing exogenous heavy and light chain DNA to yield a functional antibody. As discussed above, Ochi describes an experiment whereby a cell that had lost the ability to express light chain, but was still expressing a heavy chain, was transformed with an exogenous immunoglobulin light chain. Paper 2 at 48. Ochi does not teach or suggest co-transforming any host cell with both exogenous heavy and light chain DNA. Nor does it provide any reason to think that such an experiment would result in co-expression of both genes and assembly of a functional antibody, even if it were performed. The Patent Office thoroughly considered the Ochi reference in combination with Axel (which, unlike Salser, is directed to production and

recovery of desired proteins using transformed host cells, and expressly mentions antibodies) and other prior art and expressly rejected the arguments that Petitioner now seeks to rehash. Ex. 2019, Notice of Intent to Issue Reexam Cert. at 4-8.

As Patent Owners' experts explained during the Cabilly '415 patent reexamination, in April 1983, a person of ordinary skill in the art would not have interpreted the results reported in Ochi as broadly suggesting a likelihood of success in expressing a foreign heavy chain and foreign light chain together: "The authors of the Ochi paper . . . did not suggest that their transfection and expression results would be broadly extendable to any type of cell line or situation. Instead, they chose to employ very limited experimental conditions to test a basic hypothesis - whether one could restore gene expression in a cell line that, due to a random mutation, lost its ability to express the same gene." Ex. 2005, Harris II Declaration at ¶¶ 83-84; *see also* Ex. 2020, Reexam 10/30/2006 Response 62-64; Ex. 2008, Rice II Decl. at ¶ 37; Ex. 2018, Botchan Decl. at ¶¶ 95-100; Ex. 2021, McKnight I Decl. at ¶¶ 109-112; Ex. 2022, Reexam 05/21/2007 Response at 73-74; Ex. 2023, Reexam Appeal Brief at 76-78. In fact, the results reported in Ochi would have led the skilled person to doubt the likelihood of success. As explained during the reexamination of the Cabilly '415 patent, Ochi reports that 10 of the 14 transformed cell lines failed to regain antibody production. Ex. 1003 at Table 1. Notably, Petitioner's declarant, Dr. Baron, makes no effort to address any of these

observations by the reexamination experts.

Given Ochi's limited disclosure of inserting an exogenous light chain to study regulatory pathways, Petitioner has articulated no reason why a person of skill in the art would reasonably expect that exogenous heavy and light chain genes could be introduced into a host cell to produce a functional antibody. The best Petitioner can say is that "a POSITA would have had no reason to believe" that immunoglobulins "would not be amenable to production by rDNA means." Paper 2 at 49-50. This turns the burden on its head—Petitioner must show that there ***was*** a reasonable expectation of success, not that there is purportedly no reason there would ***not*** be. Petitioner offers no basis for why the person of ordinary skill in the art reasonably ***would*** have expected the combination of Salser and Ochi to result in the assembly of a functional antibody. Petitioner admits that the fact that "transformed mammalian cells that do not normally make antibodies are nevertheless able to assemble the heavy and light chains in vivo and secrete them as an assembled tetrameric immunoglobulin" "was ***not*** recognized by a POSITA in April 1983." Paper 2 at 43 (emphasis added). Petitioner's own statement regarding the state of the art undercuts its assertion that a skilled person would have been motivated to express the different chains of an antibody in a single host cell. It also lays bare the fact that Petitioner has not shown that a person of ordinary skill would have had a reasonable expectation that a single-cell approach

would result in the expression of functional antibodies.

Third, while Patent Owners respectfully disagree that the grounds instituted in the '1624 IPR render the instituted claims obvious, it is notable that Salser is not only missing the same disclosures that the Board found wanting in the anticipation ground of the '1624 Petition, it lacks other disclosures that the Board relied on in instituting the '1624 IPR on obviousness grounds based on Bujard.

For example, the Board found that Bujard discloses: (1) "the plasmid vector may have the strong promoter and terminator separated by 'more than one gene, that is, a plurality of genes, including multimers and operons'[,]" *Sanofi-Aventis*, IPR2015-01624, Paper 15 at 10; and (2) "the desirability of inserting 'translational stop codons . . . in one or more reading frames of the vector, which would allow for the multiple structural genes to be translated into separate polypeptides." *Id.* at 19.

Again, Patent Owners respectfully disagree with the Board's findings regarding what Bujard would have taught the skilled person in April 1983, but in considering ***this*** Petition, the absence of comparable disclosures in Salser is fatal. Notably, in the '1624 IPR, the Board chose not to institute on the grounds based on Cohen & Boyer because it, like Salser, does not contain these additional disclosures. *See Sanofi-Aventis*, IPR2015-01624, Paper 15 at 23-24 (declining to institute ground based on Cohen & Boyer because Cohen & Boyer "appears to teach less than Bujard" as it does not disclose "stop codons" or "'multimer' genes

in the vector"). The result should be the same here.

Thus, Petitioner has not met its burden of showing a reasonable likelihood that any of the challenged claims is obvious over Salser in view of Ochi.

C. GROUND 3: Petitioner Has Failed to Demonstrate a Reasonable Likelihood of Showing Claims 2, 18, and 20 Are Obvious Over Salser in View of Southern.

Petitioner has not met its burden of showing a reasonable likelihood that any challenged claim is obvious over Salser in view of Southern. The ***only*** disclosure Petitioner cites Southern is the purported use of two vectors. Paper 2 at 51-54. Petitioner makes no additional argument about obviousness with respect to Salser, and relies on its earlier argument that the elements of the Cabilly '415 patent are explicitly or inherently disclosed in Salser. *Id.* For all the reasons set forth in Section VI.A *supra*, Salser does not explicitly or inherently disclose the elements of the Cabilly '415 patent claims, including, in particular, immunoglobulins.

Southern, which also does not disclose immunoglobulins, does nothing to remedy these deficiencies. Thus, the proposed combination of Salser plus Southern discloses less than the combination of Bujard plus Southern that is the subject of the decision on institution in the '1624 IPR.

Moreover, Petitioner has not adequately explained why the skilled person would have combined the teachings of Salser with those in Southern with a reasonable likelihood of success. Petitioner instead argues that Southern provides

an alternative means for implementing a method that Salser successfully performed. According to Petitioner, "[t]he Salser patent taught that heavy and light chain genes can be ***successfully*** co-expressed when they are present in a single transformed mammalian host cell, whether or not they are contained on the same vector or on separate vectors." Paper 2 at 53 (emphasis added); *see also id.* (arguing that person of skill in the art would have been motivated to "combine Salser with Southern and to modify Salser accordingly by putting the heavy and light chain DNA sequences into separate vectors"). But Salser teaches no such thing. It does not mention immunoglobulins, nor does it suggest that individual immunoglobulin chains can be successfully co-expressed in a single host cell and functional immunoglobulin can be recovered.

There is thus no scientific or logical basis for Petitioner's contention that a "POSITA ***would therefore*** have been confident that the specific application of the Southern approach using heavy and light chains on separate vectors would result in successful co-expression." *Id*. (emphasis added). And, as Petitioner has recognized, the ability of host cells that do not natively make antibodies to assemble heavy and light chains *in vivo* and secrete them as an assembled tetrameric immunoglobulin was not known at the time. *See* Paper 2 at 14-15 n.6. Far from having, in Petitioner's words, "no reason to doubt" success, Paper 2 at 53, the evidence that Petitioner has chosen to ignore establishes the opposite.

Thus, Petitioner has not met its burden of showing a reasonable likelihood that any of the challenged claims is obvious over Salser in view of Southern.

VII. CONCLUSION

The Board should deny Sanofi's Petition, filed through its wholly owned subsidiary Genzyme, pursuant to 35 U.S.C. § 325(d) because Sanofi is a real party-in-interest in the '1624 Petition and indisputably knew about the Salser, Ochi, and Southern references at the time of that petition, refrained from making any argument based on those known references until after receiving the preliminary response in that proceeding, and filed a serial petition making substantially the same arguments as presented in the '1624 Petition. Alternatively, the Board should deny institution because Petitioner fails to demonstrate a reasonable likelihood that it would prevail with respect to any of its proffered grounds.

Respectfully submitted,

Date: April 7, 2016

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CERTIFICATE OF SERVICE

I hereby certify that, on April 7, 2016, I caused a true and correct copy of the foregoing materials:

- Patent Owner Preliminary Response 37 C.F.R § 42.107
- Exhibits 2001-2025
- List of Exhibits for Patent Owner Preliminary Response 37 C.F.R § 42.107

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Patent Owners' Exhibit Number	**Exhibit Name**
2001	Adler et. al., *Therapeutic antibodies against cancer*, Hematol. Oncol. Clin. North Am. 26(3): 447–481 (June 2012) ("Adler")
2002	Kelley, B., *Industrialization of mAb production technology: The bioprocessing industry at a crossroads*, MAbs. 1(5): 443–452 (Sept.-Oct. 2009) ("Kelley")
2003	Kohler, G. and Milstein, C., *Continuous Cultures of Fused Cells Secreting Antibody of Predefined Specificity*, Nature 256:495-497 (Aug. 7, 1975) ("Kohler and Milstein")
2004	Declaration of Dr. Timothy Roy Harris Under 37 C.F.R. § 1.132 in Reexaminations 90/007,542 and 90/007,859 (Nov. 23, 2005) ("Harris Decl.")
2005	Second Declaration of Dr. Timothy Roy Harris Under 37 C.F.R. § 1.132 in Reexaminations 90/007,542 and 90/007,859 (Oct. 26, 2006) ("Harris II Decl.")
2006	Second Declaration of Steven Lanier McKnight Under 37 C.F.R. § 1.132 in Reexaminations 90/007,542 and 90/007,859 (June 3, 2008) ("McKnight Decl. II")
2007	Expert Report of John Fiddes, Ph.D., Bristol-Myers Squibb Company v. Genentech, Inc., No. 2:13-cv-05400-MRP-JEM (C.D. Cal.) (Nov. 10, 2014) ("Fiddes Rep.")
2008	Declaration of Dr. Douglas A. Rice Under 37 C.F.R. § 1.132 in Reexaminations 90/007,542 and 90/007,859 (Oct. 26, 2006) ("Rice Decl.")
2009	Landau, B.R., *Essential Human Anatomy and Physiology* (1980) p. 3542-382 ("Landau")
2010	Weatherall et al., *Thalassemia Revisited*, Cell 29:7-9 (1982) ("Weatherall I)
2011	Loukopoulos, A. K., *Prevention of Thalassemia*, Schweiz. Med. Wschr. 113:1419-1427 (1983) ("Loukopoulos")
2012	Schechter A. N., *Hemoglobin Research and the Origins of Molecular Medicine*, Blood, 112(10) 3927- 3938 (Nov. 15, 2008) ("Schechter")
2013	Levings et al., *The Human β-globin locus control region*, The FEBS Journal 269(6) 1589-1599 (2002) ("Levings")

2014	Weatherall, D.J., *Mapping haemoglobin genes*, British Med. J. 2(6186) 352-354 (Aug. 11, 1979) ("Weatherall II")
2015	Baldwin, J.M., *The structure of human carbonmonoxy haemoglobin at 2.7 Å resolution*, J. of Mol. Bio. 136(2) 103-128 (1980) ("Baldwin")
2016	Higgs et al., *A Review of the Molecular Genetics of the Human α-Globin Gene Cluster*, Blood 73(5) 1081-1104 (1989)
2017	Malcolm et. al., *Chromosomal localization of a single copy gene by in situ hybridization - human p globin genes on the short arm of chromosome 11*, Ann. Hum. Genet., 45, 135-141 (1981) ("Malcolm")
2018	Declaration of Michael Botchan Under 37 C.F.R. § 1.132 in Reexaminations 90/007,542 and 90/007,859 (May 20, 2007) ("Botchan Decl.")
2019	File History of Reexaminations 90/007,542 and 90/007,859: Notice of Intent to Issue Ex Parte Reexamination Certificate – 2/23/2009 ("Notice of Intent to Issue Reexam Cert.")
2020	File History of Reexaminations 90/007,542 and 90/007,859: Response Under 37 C.F.R. § 1.550(b) – 10/30/2006 ("Reexam 10/30/2006 Response")
2021	First Declaration of Steven Lanier McKnight Under 37 C.F.R. § 1.132 in Reexaminations 90/007,542 and 90/007,859 (May 18, 2007) ("McKnight Decl. I")
2022	File History of Reexaminations 90/007,542 and 90/007,859: Response Under 37 C.F.R. § 1.550(b) – 05/21/2007 ("Reexam 05/21/2007 Response")
2023	File History of Reexaminations 90/007,542 and 90/007,859: Appeal Brief – 12/9/2008 ("Reexam Appeal Brief")
2024	File History of Reexaminations 90/007,542 and 90/007,859: Response Under 37 C.F.R. § 1.550(b) – 11/25/2005 ("Reexam 11/25/2005 Response")
2025	Email from Patent Owners to Petitioner (Feb. 17, 2016)