

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TRANSGENE and BIOINVENT INTERNATIONAL AB,
Petitioner,

v.

REPLIMUNE LIMITED,
Patent Owner.

PGR2022-00014
Patent 10,947,513 B2

Before CHRISTOPHER G. PAULRAJ, RYAN H. FLAX, and
JAMIE T. WISZ, *Administrative Patent Judges*.

PAULRAJ, *Administrative Patent Judge*.

DECISION
Granting Institution of Post-Grant Review
35 U.S.C. § 324

I. INTRODUCTION

Transgene and BioInvent International AB (collectively, “Petitioner”), filed a Petition requesting post-grant review of claims 1–8 and 10–26 of U.S. Patent No. 10,947,513 B2 (Ex. 1001, “the ’513 patent”). Paper 1 (“Pet.”). Replimune Limited (“Patent Owner”) filed a Preliminary Response to the Petition. Paper 8 (“Prelim. Resp.”). As part of its Preliminary Response, Patent Owner included a Statutory Disclaimer of claims 1–8, 10–12, and 14–26 of the ’513 patent, leaving claim 13 as the sole remaining challenged claim in this proceeding. Prelim. Resp. 1; Ex. 2001. Pursuant to our authorization, Petitioner filed a Preliminary Reply addressing Patent Owner’s arguments for discretionary denial under 35 U.S.C. § 325(d). Paper 12 (“Prelim. Reply”).

In view of Patent Owner’s Statutory Disclaimer, we treat claims 1–8, 10–12, and 14–26 as having never been part of the ’513 patent, such that Petitioner cannot seek post-grant review of those claims. *See Vectra Fitness, Inc. v. TNWK Corp.*, 162 F.3d 1379, 1383 (Fed. Cir. 1998) (“This court has interpreted the term ‘considered as part of the original patent’ in section 253 to mean that the patent is treated as though the disclaimed claims never existed.”) (*citing Guinn v. Kopf*, 96 F.3d 1419, 1422 (Fed. Cir. 1996)); 37 C.F.R. § 42.107(e) (“No *inter partes* review will be instituted based on disclaimed claims.”). Grounds 1, 2, 3, and 5 set forth in the Petition (*see, e.g.*, Pet. 3–4), which are directed to the disclaimed claims, are also hereby deemed moot. And, because no post-grant review will be instituted based on disclaimed claims, we do not consider claims 1–8, 10–12, and 14–26 to be within the scope of this proceeding. *Cf. General Elec. Co. v. United Techs. Corp.*, IPR2017-00491, Paper 9 (PTAB July 6, 2017) (precedential) (denying institution of *inter partes* review in view of a statutory disclaimer

of *all* challenged claims). We base our decision to institute on the only remaining challenged claim (claim 13, which depends from independent claim 1 and intervening claim 11) that has not been disclaimed.

To institute a post-grant review, we must determine whether the information presented in the Petition, “if such information is not rebutted, would demonstrate that it is more likely than not that at least 1 of the claims challenged in the petition is unpatentable.” 35 U.S.C. § 324(a). Upon consideration of the Petition and the Preliminary Response, for the reasons set forth below, we determine that the evidence and arguments presented in the Petition are sufficient to satisfy the “more likely than not” standard regarding the asserted unpatentability of claim 13 in the ’513 patent. Therefore, we authorize a post-grant review to be instituted as to claim 13.

Our determinations at this stage of the proceeding are based on the evidentiary record developed thus far, and do not constitute a final decision as to patentability of claims for which post-grant review is instituted. Our final decision will be based on the full record developed during trial.

A. Real Parties-in-Interest

Petitioner identifies Transgene and BioInvent International AB as the real parties-in-interest (“RPI”). Pet. 1. Patent Owner identifies only itself as the RPI. Paper 6, 1. There is no dispute over RPIs in this proceeding.

B. Related Matters

The parties do not identify any related matters. See Pet. 2; Paper 6, 1.

C. The ’513 Patent (Ex. 1001)

The ’513 patent is titled “Engineered Virus.” Ex. 1001, code (54). The ’513 patent issued from application 16/068,830, filed January 9, 2017, but claims earliest priority to three Great Britain applications filed January 8,

2016. *Id.* at codes (21), (22), (30) (discussed in detail below in Section II.A. as to post-grant eligibility).

The Specification explains that a number of viruses are known for the oncolytic treatment of cancer. *Id.* at 2:9–11. Viruses may treat cancer by directly infecting tumor cells, and by generating an immune response against tumor cells not infected with the virus. *See id.* at 1:22–46. The Specification refers to such viruses as oncolytic viruses, meaning “a virus that infects and replicates in tumor cells, such that the tumor cells are killed.” *Id.* at 9:10–12. Notably, oncolytic viruses should be disabled so that they are no longer pathogenic. *See id.* at 2:11–14.

The Specification explains that herpes simplex virus (HSV) was a known oncolytic virus. *See id.* at 2:9–11. “A number of disabling mutations to HSV, including disruption of the genes encoding ICP34.5, . . . have been identified which do not prevent the virus from replicating in culture or in tumor tissue *in vivo*, but which prevent significant replication in normal tissue.” *Id.* at 2:14–19. The specification further describes HSV oncolytic viruses that deliver a therapeutic gene for treating cancer. *Id.* at 2:25–27. For example, the Specification describes clinical trials that tested an HSV virus encoding a heterologous gene for granulocyte macrophage colony-stimulating factor (“GM-CSF”) in place of the gene for infected cell protein-34.5 (“ICP34.5”). *Id.* at 2:27–31. Finally, the Specification describes combining such oncolytic immunotherapy with immune checkpoint blockers, such as agents targeting anti-cytotoxic T lymphocyte-associated antigen-4 (“CTLA-4”), programmed cell death protein-1 (“PD-1”), or programmed cell death protein ligand-1 (“PD-L1”). *See id.* at 2:49–3:11.

In view of this background, the ’513 patent discloses “oncolytic viruses expressing GM-CSF and at least one molecule targeting an immune

co-stimulatory pathway.” *Id.* at 4:3–5. The immune co-stimulatory pathway activating molecule may include “a protein capable of blocking signaling through CTLA-4,” for example a CTLA-4 binding antibody. *Id.* at 4:65–67. “The virus is preferably a herpes simplex virus (HSV), such as HSV1” that “does not express functional ICP34.5.” *Id.* at 5:9–11.

The ’513 patent discloses examples of viruses expressing GM-CSF and CTLA-4. *See id.* at 30:43–31:14. Specifically, the Specification describes fusogenic viruses expressing mGM-CSF, gibbon ape leukemia virus (“GALV”), and anti-mouse and anti-human CTLA-4. *See id.* The GM-CSF and CTLA-4 expressing viruses are Virus 27 and Virus 31, illustrated in Figures 5 and 13, reproduced below. *Id.*

Figure 5B

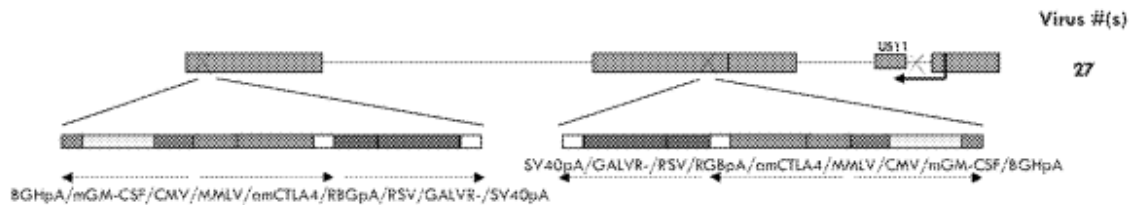
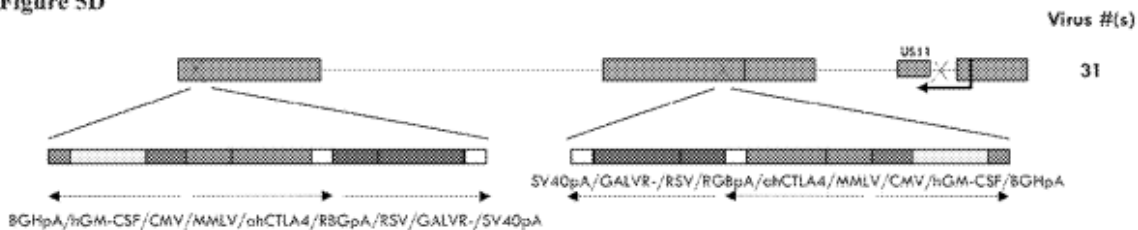


Figure 5D



Figures 5B and 5D “depict structures of HSV1 viruses modified by the deletion of ICP34.5 and ICP47 such that the US11 gene is under control of the ICP457 immediate early promoter and containing heterologous genes in the ICP34.5 locus.” *Id.* at 6:10–15. Figure 5B illustrates Virus 27. *See id.* at Fig. 5B. Figure 5D illustrates Virus 31. *See id.* at Fig. 5D.

Figure 13 of the '513 patent is reproduced below:

Figure 13

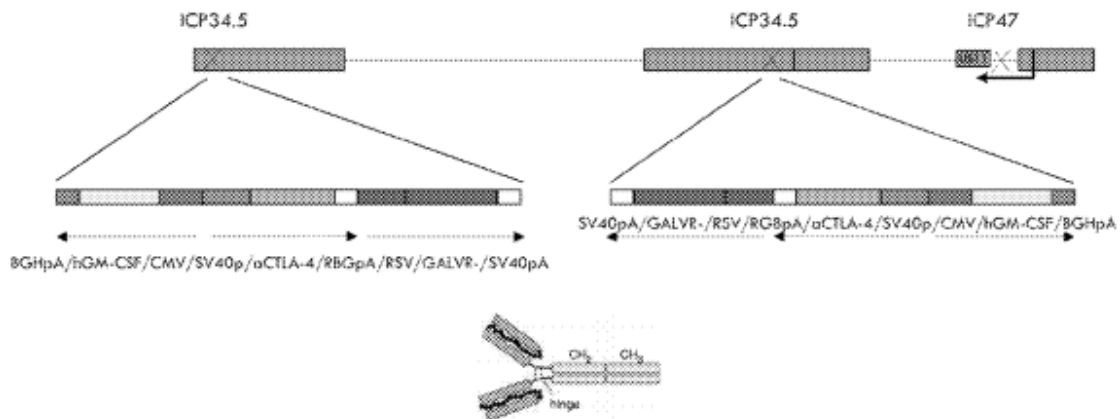


Figure 13 “shows the structure of ICP34.5 and ICP47 deleted viruses expressing [] GM-CSF and codon optimized anti-mouse or anti-human CTLA-4 antibody constructs,” and the resulting structure of the CTLA-4 antibody. *Id.* at 7:9–17.

D. Illustrative Claims

Petitioner challenges claim 13 of the '513 patent, which depends on claim 11, which in turn depends on independent claim 1.¹ We reproduce claims 1, 11, and 13 below:

1. An oncolytic virus comprising: (i) a heterologous GM-CSF-encoding gene; and (ii) a heterologous CTLA-4 inhibitor encoding gene, wherein both heterologous genes are inserted into the genome of the virus.

11. The virus of claim 1, which is a herpes simplex virus (HSV).

¹ Claim 13 is treated as independent by virtue of its dependency from, and its incorporation of the limitations of disclaimed independent claim 1 and intervening dependent claim 11.

13. The virus of claim 11, wherein the GM-CSF-encoding gene and the CTLA-4 inhibitor encoding gene are inserted into the ICP34.5 encoding locus, either by insertion, or partial or complete deletion, in a back to back orientation in relation to each other, each under separate regulatory control.

Ex. 1001, 81:51–54; 83:17–18, 20–25.

E. Prior Art and Asserted Grounds

Petitioner asserts that claim 13 would have been unpatentable on the following grounds:

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
13	103	Silvestre ²
13	103	Du ³ , Choi ⁴ , Zitvogel ⁵

Petitioner relies on the declaration of John C. Bell, Ph.D. (Ex. 1007).

II. ANALYSIS

A. Post-Grant Eligibility

Post-grant reviews are available only for patents “described in section 3(n)(1)” of the Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) (“AIA”). AIA § 6(f)(2)(A); *see Arkema Inc. v. Honeywell Int’l Inc.*, PGR2016-00011, Paper 13 at 15 (PTAB Sept. 2, 2016). These patents issue from applications “that contain[] or contained at any time . . . a claim to a claimed invention that has an effective filing date as defined in section 100(i) of title 35, United States Code, that is on or after” “the

² Silvestre et al., US 10,555,981 B2, issued Feb. 11, 2020 (Ex. 1002).

³ T. Du et al., *Tumor-specific oncolytic adenoviruses expressing granulocyte macrophage colony-stimulating factor or anti-CTLA4 antibody for the treatment of cancers*, 21 CANCER GENE THERAPY 340–348 (2014) (Ex. 1003).

⁴ Zitvogel et al., US 10,765,710 B2, issued Sept. 8, 2020 (Ex. 1004).

⁵ K-J Choi et al., *Concurrent delivery of GM-CSF and B7-1 using an oncolytic adenovirus elicits potent antitumor effect*, 13 GENE THERAPY 1010–1020 (2006) (Ex. 1005).

expiration of the 18-month period beginning on the date of the enactment of” the AIA. AIA § 3(n)(1). Because the AIA was enacted on September 16, 2011, post-grant reviews are available only for patents that issue from applications that at one point contained at least one claim with an effective filing date of March 16, 2013, or later. *See also* 37 C.F.R. § 42.204(a) (requiring that “petitioner . . . certify that the patent for which review is sought is available for post-grant review”).

The ’513 patent issued on March 16, 2021, from U.S. Application No. 16/068,830 (“the ’830 application”), filed on January 9, 2017 as PCT/GB2017/050038. Ex. 1001, codes (21), (22), (45), (86). The ’830 application further claims benefit of priority to three GB patent applications filed on January 8, 2016. *Id.* at code (30). Accordingly, the ’513 patent issued from applications having a filing date of March 16, 2013 or later. Petitioner filed the request for post-grant review on December 15, 2021, which is within nine months of the grant of the ’513 patent. 35 U.S.C. § 321(c). *See* Pet. 3.

Patent Owner does not challenge the eligibility of the ’513 patent for post-grant review. We determine that the ’513 patent is eligible for post-grant review.

B. Level of Ordinary Skill in the Art

Petitioner proposes that a person of ordinary skill in the art (“POSA”) “would have had a Ph.D. in molecular biology, or a related field, with expertise in virology (including expertise growing, isolating, and rescuing viruses), immunology, and cancer biology with at least four years of post-Ph.D. experience in those areas.” Pet. 6 (citing Ex. 1007 ¶¶ 35, 96). Patent Owner does not argue otherwise. *See* Prelim. Resp. 16–17.

At this stage of the proceeding and for purposes of our analysis in this Decision, we adopt Petitioner’s uncontested definition as that definition is consistent with the level of skill in the art reflected by the prior art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required “where the prior art itself reflects an appropriate level and a need for testimony is not shown” (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985))). It is from the perspective of such a person of ordinary skill that we consider the claims and prior art.

C. Claim Construction

We interpret a claim “using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b).” 37 C.F.R. § 42.200(b) (2019). This standard requires that we construe claims “in accordance with the ordinary and customary meaning of such claim[s] as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” *Id.*

Petitioner contends that the Specification defines the term “‘oncolytic virus’ as ‘a virus that infects and replicates in tumor cells, such that the tumor cells are killed.’” Pet. 6 (citing Ex. 1001, 9:10–12). Petitioner argues that the Specification “distinguishes this broader definition from the allegedly narrower subcategory of ‘selectively replication competent’ viruses that ‘replicate[] more effectively in tumor tissue than in non-tumor tissue.’” *Id.* (citing Ex. 1001, 9:12–17).

Patent Owner does not dispute Petitioner’s construction of “oncolytic virus.” *See* Prelim. Resp. 17.

We do not perceive a need to construe any claim terms of the ’513 patent for purposes of determining whether to institute trial. *See Vivid*

Techs., Inc. v. Am. Sci. & Eng'g, Inc., 200 F.3d 295, 803 (Fed. Cir. 1999) (holding that “only those terms need [to] be construed that are in controversy, and only to the extent necessary to resolve the controversy”); see also *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (applying *Vivid Techs.* in the context of an *inter partes* review).

D. Obviousness over Silvestre

Petitioner asserts that claim 13 would have been obvious over Silvestre. Pet. 54–55 (Ground 4). In our assessment of Petitioner’s obviousness argument for claim 13, we have also considered Petitioner’s anticipation argument (Ground 3) for disclaimed claims 1 and 11. See *id.* at 42–44, 48.

1. *Overview of Silvestre (Ex. 1002)*

Silvestre is a U.S. patent that issued on February 11, 2020 from Application No. 15/325,562, that was filed as PCT/EP2015/066263 on July 16, 2015. Ex. 1002, codes (21), (22), (45), (86). Thus, on its face, Silvestre qualifies as prior art under 35 U.S.C. § 102(a)(2).

Silvestre is directed to an oncolytic virus including a nucleotide sequence that encodes an immune checkpoint modulator. *Id.* at 3:23–26. The oncolytic virus is preferably selected from a group that includes HSV. *Id.* at 3:27–31. The immune checkpoint modulator preferably includes an antagonist molecule that antagonizes the activity of CTLA-4, “with a specific preference for an anti PD-1 antibody and/or an anti CTLA4 antibody.” *Id.* at 3:41–48; see also *id.* at 15:5–12, 45–48.

Silvestre discloses further embodiments of oncolytic viruses. For example, the oncolytic virus may include a herpes virus derived from HSV1. *Id.* at 7:52–60. “The herpes virus may be genetically modified so as to

restrict viral replication in tumors or reduce its cytotoxicity in non-dividing cells.” *Id.* at 7:60–63. For example, the virus may include “defects in the function of genes encoding virulence factors such as the ICP34.5 gene.” *Id.* at 8:1–3.

Silvestre discloses oncolytic viruses including immunostimulatory proteins. *Id.* at 11:55–57. “A vast number of proteins are known in the art for their ability to exert an immunostimulatory effect.” *Id.* at 11:57–59. Silvestre describes a “specific preference for GM-CSF” as an immunostimulatory protein. *Id.* at 12:7–9. Silvestre further describes a known “oncolytic herpes simplex 1 (T-VEC) [] genetically engineered to attenuate the virus virulence, increase selectivity for cancer cells and enhance antitumor immune response (through GM-CSF expression).” *Id.* at 2:32–30.⁶

Silvestre discloses that “[t]he nucleic acid molecule(s) encoding the immune checkpoint modulator(s) and eventually the therapeutic gene(s) can independently be inserted at any location of the viral genome, with a specific preference for a non-essential locus.” *Id.* at 16:4–8.

2. *Analysis of Claim 13*

Petitioner contends that Silvestre discloses all of the features recited in disclaimed claims 1 and 11, from which claim 13 depends. Pet. 42–43, 48. As to claim 1, Petitioner contends that Silvestre discloses an oncolytic virus including heterologous genes inserted into the genome of the virus. *Id.* at 42–43 (citing Ex. 1002, 3:23–26, 31–32, 16:4–8; Ex. 1007 ¶¶ 183–190).

⁶ Citing Neil N. Senzer et al., *Phase II Clinical Trial of a Granulocyte-Macrophage Colony-Stimulating Factor–Encoding, Second-Generation Oncolytic Herpesvirus in Patients With Unresectable Metastatic Melanoma*, 27(34) J. CLIN. ONCOLOGY 5763–71 (2009) (Ex. 1078).

Additionally, Petitioner contends that Silvestre discloses the heterologous genes include at least one therapeutic gene, preferably encoding GM-CSF, and at least one immune checkpoint modulator gene, preferably encoding an anti-CTLA-4 antibody. *Id.* (citing Ex. 1002, 10:8–10, 28–31, 12:7–9, 3:44–48, 15:5–8; Ex. 1007 ¶¶ 183–190). As to claim 11, Petitioner contends that Silvestre describes HSV1 as a particularly preferred virus. *Id.* at 48 (citing Ex. 1002, 7:52–60).

In view of the above, Petitioner shows, and Patent Owner does not dispute (*see* Statutory Disclaimer), that Silvestre teaches the limitations of claims 1 and 11.

As to claim 13, Petitioner contends that Silvestre discloses using T-VEC as an engineered virus. *Id.* at 54 (citing Ex. 1002, 2:33–36). Petitioner contends that “T-VEC was well known to a POSITA to be an oncolytic HSV with a heterologous GM-CSF gene inserted into the ICP34.5 encoding locus via a complete deletion and replacement of the ICP34.5 gene with a GM-CSF encoding gene.” *Id.* (citing Ex. 1007 ¶ 229; Ex. 1078, 5763). Petitioner contends that claim 13’s requirement of inserting the GM-CSF gene and the CTLA-4 inhibitor encoding gene in a back-to-back orientation in relation to each other, each under separate regulatory control, would have been “[t]he simplest and most common method” of inserting the genes. *Id.* at 54–55 (citing Ex. 1007 ¶ 230). Petitioner contends that one of ordinary skill in the art would have been motivated to do so, with a reasonable expectation of success, “because insertion into the ICP34.5 locus had already been successfully demonstrated in the T-VEC oncolytic HSV1 virus.” *Id.* at 55 (citing Ex. 1007 ¶ 230). Petitioner contends that one of ordinary skill in the art would have followed a proven insertion strategy to

avoid a trial-and-error process of identifying a new gene insertion site. *Id.* (citing Ex. 1007 ¶¶ 73–81, 87–88, 230–231).

In response, Patent Owner first argues that Petitioner improperly relies on “common knowledge” to supply claim limitations that are not taught or suggested by Silvestre. *See* Prelim. Resp. 18–22 (citing *Arendi S.A.R.L. v. Apple Inc.*, 832 F.3d 1355, 1361 (Fed. Cir. 2016) (“[C]ommon sense is typically invoked to provide a known motivation to combine, not to supply a missing claim limitation.”)). Specifically, Patent Owner argues that Petitioner relies improperly on common knowledge to supply the limitation of “back-to-back orientation of a GM-CSF-encoding gene and a CTLA-4 inhibitor-encoding gene each under separate regulatory control.” *Id.* at 20–21 (citing Pet. 54–55). Patent Owner argues that Petitioner does not provide evidentiary support to explain why one of ordinary skill in the art would use a back-to-back orientation under control of separate regulatory requirements. *Id.* at 21. Patent Owner further argues that Petitioner’s expert declaration merely repeats the argument without evidentiary support. *Id.* at 22 (citing Ex. 1007 ¶¶ 230, 319). Patent Owner argues that the limitation cannot be shown by common knowledge because the “claimed technology is difficult and that there is a high level of unpredictability in the relevant art.” *See id.* at 20–21 (citing Pet. 20, 22–23; *see also Arendi*, 832 F.3d at 1361).

Second, Patent Owner argues that Petitioner did not articulate a motivation to combine Silvestre with the alleged common knowledge with a reasonable expectation of success. Prelim. Resp. 23–26. Patent Owner argues that Petitioner’s proffered motivation to select the known ICP34.5 encoding locus to avoid a trial-and-error process “says nothing about inserting two genes in combination into the same locus.” *Id.* at 23 (citing Pet. 55). Patent Owner further argues that Petitioner fails to identify why

one of ordinary skill “would have been motivated to use a back-to-back orientation under control of separate regulatory elements.” *Id.* at 23–24 (citing Pet. 54–55). Finally, Patent Owner argues that Petitioner does not show a reasonable expectation of success for inserting two genes as claimed, given the difficult technology and the high level of unpredictability in the art. *Id.* at 25 (citing Pet. 55, 20, 22–23, 30).

Based on the present record, we find that Petitioner has shown that it is more likely than not that inserting the GM-CSF gene and the CTLA-4 inhibitor encoding gene in a back-to-back orientation in relation to each other would have been known to a person of ordinary skill in the art. Petitioner’s expert Dr. Bell states that “[w]hen inserting two genes into a given locus, the simplest and most common way to do so is to insert them in a back-to-back orientation under control of separate regulatory elements.” Ex. 1007 ¶ 230. While Patent Owner is correct in stating that no sources are cited in paragraph 230, Dr. Bell does cite back to paragraphs 73–81 and 87–88 of his own declaration. *See id.*

In those paragraphs, Dr. Bell explains that the “deletion of endogenous nucleotides requires either pre-existing knowledge of the effect of disrupting the particular gene at the insertion site or requires a difficult and time-consuming trial-and-error process to gain such knowledge.” *Id.* ¶ 73 (citing Ex. 1035). Exhibit 1035 is a review article entitled “Unconventional viral gene expression mechanisms as therapeutic targets.” *See* Ex. 1035. Dr. Bell points to Figure 1 of this article as showing that certain viral genomes include genes that are overlapping and/or that encode polyproteins, which can add to a further level of difficulty in identifying a suitable insertion locus. Ex. 1007 ¶ 74 (citing Ex. 1035, 364, Fig. 1). Dr. Bell further explains that “inactivation of the neurovirulence factor

ICP34.5 in HSV1 has been well-known to direct tumor-specific cell lysis, making HSV1 ICP34.5 knock-outs useful oncolytic virus vectors,” but also notes that “unless such a well-known insertion site is used, determining whether insertion of a heterologous gene at any particular site will be successful requires a difficult and time-consuming trial-and-error process.” *Id.* ¶ 77 (citing Ex. 1039, 292, Ex. 1040, 4–7, Ex. 1041, 575). Accordingly, within paragraphs 73–81 and 87–88, Dr. Bell provides evidentiary support for his conclusions in paragraph 230. *See* Ex. 1007 ¶¶ 73-81, 87-88.

We are not persuaded by Patent Owner’s reliance upon the *Arendi* case to argue that Petitioner improperly relies upon common sense to supply a missing limitation. In *Arendi*, the court noted that “the Board’s presumption that adding a search for phone numbers to [the prior art reference] would be ‘common sense’ was conclusory and unsupported by substantial evidence, the missing limitation is not a ‘peripheral’ one, and there [was] nothing in the record to support the Board’s conclusion that supplying the missing limitation would be obvious to one of skill in the art.” 832 F.3d at 1366–67. But here, as noted above, Dr. Bell cites to several references in support of his rationale that one of ordinary skill in the art seeking to insert both the genes would have started with the known ICP34.5 locus rather than undertaking a rigorous trial-and-error process to find an altogether new insertion locus. We do not find the concern stated in *Arendi* about using common sense “as a wholesale substitute for reasoned analysis and evidentiary support” to be present in this case. *See id.* at 1362. Here, the “common sense” challenged by Patent Owner refers to the “common knowledge” of the ordinarily skilled artisan as of the invention referenced in the Petition and by Dr. Bell, and it is from such a person’s perspective that we must read *Silvestre*. Thus, based on the current record, we determine

that Petitioner has provided sufficient evidence beyond merely a conclusory assertion of “common sense” to show that inserting the genes at issue in a back-to-back orientation would have been known in the art.⁷

Accordingly, for the reasons above, we are persuaded that Petitioner shows that it is more likely than not that it will prevail in establishing unpatentability with regard to claim 13.

E. Obviousness over Du, Choi, and Zitvogel

Petitioner asserts that claim 13 would have been obvious over the combination of Du, Choi, and Zitvogel. Pet. 74 (Ground 6). Petitioner’s obviousness argument as to claim 13 also refers to Petitioner’s obviousness argument for disclaimed claims 1 and 11 in view of Du, Choi, and Zitvogel. *See id.* at 64–68, 74.

1. Overview of Du (Ex. 1003)

Du is a journal article that bears a publication date of 2014. Ex. 1003, 340. Petitioner contends that Du was published and accessible to the public no later than July 18, 2014. Pet. 5 (citing Ex. 1011 ¶¶ 47–55). Thus, on its face, Du qualifies as prior art under 35 U.S.C. § 102(a)(1). *Id.*

⁷ We recognize that Petitioner in its Preliminary Reply also cites to Exhibit 1084, Fig. 1 as “showing back-to-back insertion of two genes at ICP34.5 in HSV1 virus.” Prelim. Reply 5. Patent Owner contends that this is improper as it goes beyond the scope of our authorization to file a Preliminary Reply limited to the § 325(d) issue. Paper 13, 1; Paper 9, 2. We are not persuaded that Petitioner’s reliance on Exhibit 1084 is improper as it further demonstrates material error under the *Advanced Bionics* framework (discussed *infra*). In any event, Patent Owner has been put on notice that Exhibit 1084 may indeed be relied upon to support Petitioner’s contentions regarding the obviousness of the back-to-back insertion limitation of claim 13. The parties are invited to further develop the record with regard to this exhibit at trial.

Du discloses oncolytic adenoviruses expressing either GM-CSF or anti-CTLA4 antibody for the treatment of cancers. Ex. 1003, 340. Du discloses two viruses, SKL001 and SKL002. *Id.* at 341. SKL001 encodes the heavy and light chains of anti-CTLA4 monoclonal antibody (“mAb”). *Id.* SKL002 replaces the coding region of anti-CTLA4 with the cDNA of GM-CSF. *Id.* at 341. Du discloses that administering both viruses in combination, was “significantly more effective” in treating tumors than administering each virus alone. *Id.* at 345–346.

2. *Overview of Choi (Ex. 1005)*

Choi is a journal article that bears a publication date of 2006. Ex. 1005, 1010. Petitioner contends that Choi was published and accessible to the public no later than March 9, 2006. Pet. 5 (citing Ex. 1011 ¶¶ 38–46). Thus, on its face, Choi qualifies as prior art under 35 U.S.C. § 102(a)(1). *Id.*

Choi discloses an oncolytic adenovirus that expresses both GM-CSF and B7-1, an immune-stimulatory membrane molecule. *Id.* at 1010. Choi discloses preparing the adenovirus by placing two independent expression cassettes, each separately expressing murine GM-CSF and murine B7-1, in the E1 and E3 region of a replication-incompetent adenovirus. *Id.* at 1011.

3. *Overview of Zitvogel (Ex. 1004)*

Zitvogel is a U.S. patent that issued on September 8, 2020 from Application No. 15/325,576, that was filed as PCT/EP2015/066353 on July 16, 2015. Ex. 1004, codes (21), (22), (45), (86). Thus, on its face, Zitvogel qualifies as prior art under 35 U.S.C. § 102(a)(2).

Zitvogel discloses cancer therapy including a combination of an oncolytic virus with an immune checkpoint modulator. *Id.* at 3:30–33. The oncolytic virus is preferably selected from the group including vaccinia virus and HSV. *Id.* at 3:33–38. Zitvogel discloses an embodiment in which the

oncolytic virus is an HSV mutant with defects in the ICP34.5 gene, including T-VEC as a representative example. *See id.* at 8:10–35.

Zitvogel discloses that the immune checkpoint modulator may preferably be an anti CTLA-4 antibody. *Id.* at 3:51–53. Zitvogel discloses that the immune checkpoint modulator “may be delivered to the subject in the form of a vector expressing the one or more immune checkpoint modulator.” *Id.* at 22:37–43.

Zitvogel discloses an embodiment where the oncolytic virus expresses at least one therapeutic gene encoding an immunostimulatory protein. *Id.* at 3:48–50. “Preferably, the [immunostimulatory] protein is an interleukin or a colony-30 stimulating factor, with a specific preference for GM-CSF.” *Id.* at 12:28–30. Zitvogel discloses that the therapeutic gene is preferably inserted in a non-essential locus of the viral genome. *Id.* at 13:60–63.

4. *Analysis of Claim 13*

Petitioner contends that the combination of Du, Choi, and Zitvogel teaches all of the features recited in disclaimed claims 1 and 11, from which claim 13 depends. Pet. 58–59, 64–66, 74. As to claim 1, Petitioner contends that Du discloses co-administering two oncolytic viruses, a first virus including a heterologous GM-CSF encoding gene and a second virus including a heterologous CTLA-4 inhibitor encoding gene. Pet. 58–59 (citing Ex. 1003, 340). Petitioner argues that one of ordinary skill in the art would have been motivated to “modify Du’s teachings to create a single virus with both claimed heterologous genes” by Du alone, and in combination with Choi and Zitvogel. *Id.* at 66.

First, Petitioner argues that “Du provides express motivation” to create a single virus by teaching that co-administering the two viruses provides a synergistic antitumor effect. *Id.* at 59–60 (citing Ex. 1006, 340,

346; Ex. 1007 ¶¶ 247–250). Petitioner contends that one of ordinary skill in the art would have had a reasonable expectation of success in creating a single virus with both heterologous genes inserted, “because it was well known in the art that administering a single oncolytic virus with multiple inserted genes had been done, was preferred, and provided distinct advantages over administering multiple viruses each with different inserted genes, including improved ease of administration.” *Id.* at 61 (citing Ex. 1007 ¶¶ 251–252). Dr. Bell declares that “administering a single virus containing the two heterologous genes would ensure that an infected host cell would receive copies of both heterologous genes and thus should be capable of expressing both proteins,” as opposed to two separate viruses infect different host cells. Ex. 1007 ¶ 251. Further, Dr. Bell declares that “it was well known in the art that more than one heterologous gene can be inserted into the genome of certain oncolytic viruses (such as HSV1) based on the known genomic payload capacity of those viruses.” *Id.* ¶ 252.

Second, Petitioner argues that one of ordinary skill in the art would have modified Du to create a single virus in view of Choi and Zitvogel. *See* Pet. 66–67. Specifically, Petitioner argues one of ordinary skill would have been motivated by Choi’s teaching of inserting genes encoding GM-CSF and B7-1 into a single oncolytic adenovirus, and Zitvogel’s teaching of co-administering an oncolytic virus that possesses heterologous GM-CSF and an anti-CTLA-4 antibody which can be delivered by viral vector. *Id.* (citing Ex. 1007 ¶ 279; Ex. 1005; Ex. 1004, 3:30–55; 16:11–12; 17:4–5; 18:12–13; 30:10–13; 45:14–46:11). Petitioner further argues that Zitvogel teaches the HSV limitation of claim 11. *See id.* at 74 (citing Ex. 1004, 7:49–52). In view of Patent Owner’s disclaimer of claims 1 and 11, Petitioner shows, and Patent Owner does not dispute, that the combination of Du, Choi, and

Zitvogel teaches or otherwise renders obvious the limitations of those claims.

As to claim 13, Petitioner argues that Zitvogel discloses the use of T-VEC as an HSV mutant with defects in the ICP34.5 gene. *Id.* at 74 (citing Ex. 1004, 8:27–34). As discussed above as to Silvestre, Petitioner contends that T-VEC was a known oncolytic HSV with a heterologous GM-CSF gene inserted into the ICP34.5 encoding locus via a complete deletion. *Id.* (citing Ex. 1007 ¶ 319; Ex. 1078, 5763). Petitioner contends that claim 13’s limitation—inserting the GM-CSF gene and the CTLA-4 inhibitor encoding gene in a back to back orientation in relation to each other, each under separate regulatory control—would have been “[t]he simplest and most common way” of inserting the genes. *Id.* Petitioner contends that one of ordinary skill in the art would have been motivated to do so, with a reasonable expectation of success, “because insertion . . . into the ICP34.5 locus had already been successfully demonstrated in the T-VEC oncolytic HSV1 virus.” *Id.* Petitioner contends that one of ordinary skill in the art would have followed a proven insertion strategy to avoid a trial-and-error process of identifying a new gene insertion site. *Id.* (citing Ex. 1007 ¶¶ 319, 73–81, 87–88).

In response, Patent Owner argues once again that Petitioner improperly relies on “common knowledge” to supply claim limitations that are not taught or suggested by the combination of Du, Choi, and Zitvogel. *See* Prelim. Resp. 26–29 (citing *Arendi*, 832 F.3d at 1361). Patent Owner also argues that Petitioner did not articulate a motivation to combine Du, Choi, and Zitvogel with the alleged common knowledge with a reasonable expectation of success. *Id.* at 29–32.

The parties' arguments are similar to the arguments discussed above with regard to the Silvestre-based ground. Accordingly, for similar reasons discussed above, we again find Petitioner's arguments persuasive and Patent Owner's arguments unpersuasive on the present record. Dr. Bell has provided cross-citations to the same portions of his declaration with citations to references showing that a person of ordinary skill in the art would be motivated to insert two genes in combination into the same locus in a back-to-back orientation. Ex. 1007 ¶ 319 (citing ¶¶ 73–81, 97–88 of his own declaration). At this stage, Patent Owner has not provided any expert testimony to contradict Petitioner's expert.

For the reasons above, we are persuaded that Petitioner is more likely than not to prevail with regard to claim 13 based on this ground.

F. Discretionary Denial Under 35 U.S.C. § 325(d)

Patent Owner argues that we should exercise our discretion under 325(d) to deny institution because the same or substantially the same prior art or arguments were previously presented to the Office. Prelim. Resp. 7–16. Petitioner argues that the Board should not deny institution under 35 U.S.C. § 325(d). Pet. 8–9. We address the parties' arguments below.

1. Legal Framework

Pursuant to 35 U.S.C. § 325(d), in determining whether to institute an post-grant review, “the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office.” The Board evaluates two issues in addressing 35 U.S.C. § 325(d):

- (1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2)
- if either condition of [the] first part of the framework is satisfied,

whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) (precedential) (“*Advanced Bionics*”). With respect to the first issue, previously “presented” art includes, among other things, “art provided to the Office by an applicant, such as on an Information Disclosure Statement (IDS), in the prosecution history of the challenged patent.” *Id.* at 7–8. With respect to the second issue, institution generally will be denied if a “petitioner fails to make a showing of material error,” and “[i]f reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability.” *Id.* at 8–9. “[T]his framework reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown.” *Id.* at 9

The Board also considers the following non-exclusive factors when exercising discretion under § 325(d):

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

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

2. *Was the Same or Substantially the Same Art or Arguments Presented to the Office?*

It is undisputed that Silvestre and Du were listed on an IDS and marked as considered by the Examiner during prosecution. *See* Pet. 8–9; Prelim. Resp. 9–12 (citing Ex. 1019). Accordingly, Silvestre and Du are deemed to have been previously presented to the Office. *See Advanced Bionics*, Paper 6, at 7–8.

Patent Owner acknowledges that Choi and Zitvogel were not presented to the Office. *See* Prelim. Resp. 12–13. However, Patent Owner argues that Choi and Zitvogel are cumulative to Silvestre. *Id.* at 8. For example, Patent Owner contends that Zitvogel teaches the use of T-VEC, similar to Silvestre. *See id.* at 12–13. Patent Owner further argues that Choi is cumulative to Silvestre because Petitioner cites Choi for obviousness of claims 1 and 11 and Silvestre for anticipating claims 1 and 11. *Id.* at 13.

Petitioner responds that Patent Owner does not compare Choi and Zitvogel to the prior art evaluated during examination, as required by *Becton, Dickinson*. Prelim. Reply 2–3 (citing Prelim. Resp. 8; IPR2017-01586, Paper 8, 17). Petitioner argues that Choi’s teaching of a single oncolytic adenovirus expressing GM-CSF and B7-1 is not cumulative of Silvestre. *Id.* at 3 (citing Pet. 64–66). Petitioner further argues that Patent Owner does not identify any disclosure cited during prosecution that is cumulative to Zitvogel’s T-VEC disclosure. *Id.* (citing Pet. 74–75).

The record shows that Silvestre and Du were previously presented to the Office. *See* Pet. 8-9; Prelim. Resp. 9–12 (citing Ex. 1019). Thus, we

determine that part one of the *Advanced Bionics* framework with regard to Silvestre and Du is satisfied. It is undisputed that Choi and Zitvogel were not presented to the Office. However, we need not address whether those references are cumulative to other art before the office because the first part of the *Advanced Bionics* framework is already satisfied based on Silvestre and Du.

3. *Did the Office Err in a Manner Material to the Patentability of Challenged Claims?*

In view of our determination that at least some of the prior art relied upon in the Petition is the same or substantially the same as what was previously presented to the Office, we turn to the second part of the *Advanced Bionics* framework, which requires an assessment of whether Petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

In allowing the claims of the '513 patent, the Examiner listed the following reasons for allowance “[No] prior art teaches or suggests an oncolytic virus that is constructed to comprise[] two heterologous sequences, wherein one of sequences encodes and expresses GM-CSF and other encodes [] and expresses [CTLA-4] inhibitor biological molecule of an antibody to CTLA-4.” Ex. 1017, 3. Petitioner contends, however, that the Examiner did not appreciate “the teachings of either Silvestre or Du as neither formed the basis for any rejections.” Pet. 9. Petitioner further argues that “none of the cited art was the basis of any rejection . . . which was error material to patentability.” Prelim. Reply, 3. Petitioner argues that both Silvestre and Du teach oncolytic viruses with two different therapeutic heterologous encoding genes inserted in the virus(es)’ genome, unlike the prior art distinguished during prosecution. *Id.* at 4.

Patent Owner argues that Petitioner does not allege material error by the Examiner. *See* Prelim. Resp. at 13–16. Patent Owner further argues that Petitioner does not allege that Silvestre, Du, Choi, and/or Zitvogel disclose or suggest the limitations of claim 13. *See id.* at 14–15.

Here, Petitioner relies on either Silvestre alone or on Du in combination with Choi and Zitvogel as teaching oncolytic viruses with two different therapeutic heterologous encoding genes inserted in the virus(es)’ genome. *See* Prelim. Reply, 4. For the reasons discussed above, we find that Petitioner has shown that it is more likely than not that at least one claim of the ’513 patent is unpatentable over Silvestre or over Du, Choi, and Zitvogel. In doing so, and in highlighting the Examiner having not directly addressed the presently asserted prior art although being aware thereof, Petitioner demonstrates that the Examiner erred in a manner material to the patentability of the challenged claims.

III. CONCLUSION

Based on our analysis within the *Advanced Bionics* framework, we decline to exercise our discretion to deny institution under § 325(d). For the foregoing reasons, Petitioner has demonstrated it is more likely than not that claim 13 of the ’513 patent is unpatentable. Thus, we authorize a post-grant review to be instituted as to claim 13.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. §324(a), a post-grant review is instituted as to claim 13 of the ’513 patent based on the applicable grounds set forth in the Petition; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 324(c)–(d) and 37 C.F.R. § 42.4, post-grant review of the ’513 patent shall commence on

PGR2022-00014
Patent 10,947,513 B2

the entry date of this Order, and notice is hereby given of the institution of a trial.

PGR2022-00014
Patent 10,947,513 B2

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