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571-272-7822

Paper 17
Date: August 22, 2023

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SYNAFFIX B.V.,
Petitioner,

v.

HANGZHOU DAC BIOTECH CO., LTD.,
Patent Owner.

IPR2022-01531
Patent 10,131,682 C1

Before ZHENYU YANG, DEVON ZASTROW NEWMAN, and CYNTHIA M. HARDMAN *Administrative Patent Judges.*

NEWMAN, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314, 37 C.F.R. § 42.4

I. INTRODUCTION

A. Background and Summary

Synaffix B.V., ("Petitioner") filed a Petition (Paper 2, "Pet.") requesting institution of *inter partes* review of claims 1–17, 20–21, 24–26, and 29–34 ("the challenged claims") of U.S. Patent No. 10,131,682 C1 (Exs. 1001, 1002 (reexamination), "the '682 patent"). Hangzhou DAC

Biotech Co., Ltd. ("Patent Owner"), filed a Preliminary Response (Paper 9, "Prelim. Resp."). With authorization (Paper 10), Petitioner filed Petitioner's Preliminary Reply to Patent Owner's Preliminary Response (Paper 11, "Pet. Prelim. Reply") and Petitioner's Brief in Response to Patent Owner's Preliminary Sur-Reply (Paper 15, "Pet. Resp. Brief"), and Patent Owner filed Patent Owner's Pre-Institution Sur-Reply (Paper 14, "PO Sur-reply") and Patent Owner's Pre-Institution Response to Petitioner's Brief (Paper 16, "PO Resp. Brief").

An *inter partes* review may be instituted only if "the information presented in the petition . . . and any [preliminary] response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a) (2018). Upon consideration of the briefing and the evidence of record, we conclude that Petitioner has not established a reasonable likelihood of prevailing on its assertion that the challenged claims are unpatentable based on the grounds advanced here. Accordingly, we deny institution of *inter partes* review of claims 1–17, 20–21, 24–26, and 29–34 of the '682 patent.

B. Real Parties in Interest

Petitioner states that the "real-parties-in-interest are Petitioner, Synaffix B.V., and Lonza Group, AG, which recently acquired Synaffix." Paper 12, 2[1] (Updated Mandatory Notices).

[1] Paper 12 is not paginated. We reference the pages therein as if Paper 12 had been paginated beginning at the first page after the cover sheet.

Patent Owner "certifies that HANGZHOU DAC BIOTECH CO., LTD. is the real party-in-interest" and also states it is the assignee of the '682 patent. Paper 8, 1.[2]

C. Related Matters

Petitioner states that the '682 patent was "re-examined as Reexamination Control Number 90/014,390, yielding, *inter alia*, amended claims 1, 3, 20, and new claims 24-26 and 29-34" and identifies no other related matters. Pet. 1.

Patent Owner lists the following related matters: U.S. Patent No. 10,131,682 issued from U.S. Patent Application No. 14/432,073, filed on March 27, 2015, which is a U.S. National Stage of International Application No. PCT/IB2012/056700, filed on November 24, 2012; and U.S. Application No. 90/014,390, filed on October 16, 2019, which is a reexamination of U.S. Patent No. 10,131,682. Paper 8, 1.

D. The '682 Patent (Ex. 1001)

1. Specification Overview

The '682 patent is titled "Hydrophilic Linkers and Their Uses for Conjugation of Drugs to Cell Binding Molecules" and issued from U.S. Application No. 14/432,073 (the '073 Application), a national stage entry of PCT/IB2012/056700 that was filed on November 24, 2012. Ex. 1001, codes (54), (10), (21), (86), and (22).

The '682 patent regards protein/drug conjugates for targeted delivery of drugs to specific cells. Ex. 1001, Abstract. The Specification discloses that

[2] Paper 8 is not paginated. We reference the pages therein as if Paper 8 had been paginated beginning at the first page after the cover sheet.

> the use of the cell binding molecule – drug conjugates, such as antibody-drug conjugates (ADCs) with cancers has been limited by the availability of specific targeting agents (carriers) and of conjugation methodologies, which can result in undesirable aggregation of the protein at the higher levels of drug loading required for cancer treatment.

Id. at 2:25–29. The Specification states that "[n]ormally the tendency for cytotoxic drug conjugates to aggregate is especially problematic when the conjugation reactions are performed with hydrophilic linkers. *Id.* at 2:33–36. Moreover, "higher drug loading increases the inherent potency of the conjugate," making it desirable to have "as much drug loaded on the carrier" as possible while maintaining binding ability to the protein. *Id.* at 1:37–39.

The '682 patent discloses "hydrophilic linkers containing phosphinate, sulfonyl, and/or sulfoxide groups to link drugs to a cell-binding agent (e.g., an antibody)." Ex. 1001, 2:53–55. The Specification discloses that the hydrophilic linkers containing these specific groups confer the following advantageous hydrophilic properties to the cell binding molecule-drug conjugates: reduced aggregation in water-based media, enabling higher drug-per-cell binding to molecule ratio, permitting higher potency, and increased drug retention in the target cell after the drug is released from the conjugate. *Id.* at 2:60–65.

Using these hydrophilic linkers, the Specification discloses antibody-drug conjugates with the preferred formula "Cb-(-L-Drug)$_n$, wherein Cb is a cell-binding agent, L is a hydrophilic linker, Drug is a drug molecule and n is an integer from 1 to 20." *Id.* at 2:55–60. The drug is a cytotoxic agent and is a "small molecule drug" identified in the Specification as "an organic, inorganic, or organometallic compound that may have a molecular weight of for example 100 to 1800, more suitably from 120 to 1400." *Id.* at 29:46–50.

The cell-binding agent "may be of any kind presently known, or that become[s] known, molecule that binds to, complexes with or reacts with a moiety of a cell population sought to be therapeutically or otherwise biologically modified." *Id.* at 14:39–44. When an antibody is used as a cell-binding agent, this may permit immune-targeted delivery of the drug to a specific cell population, such as "cancer cell antigens, viral antigens, microbial antigens or a protein generated by the immune system that is capable of recognizing, binding to a specific antigen or exhibiting the desired biological activity." *Id.* at 14:54–57. The Specification discloses that, "[in] preferred embodiments, R1, R2, R3, and R4 are linear alkyl having from 1-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, p=1~100." *Id.* at 9:8–10.

Figure 6 discloses embodiment 55 of the Specification, copied below:

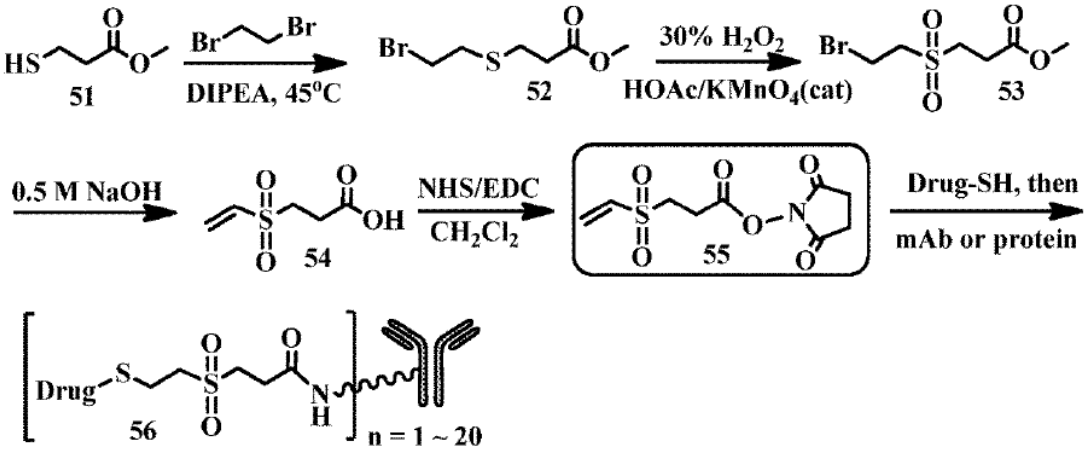


Fig. 6 (Ex. 1001, p. 12). The above figure shows a method of synthesis of embodiment 55 of the invention. *Id.*

Figure 7 discloses embodiment 75 of the Specification, copied below:

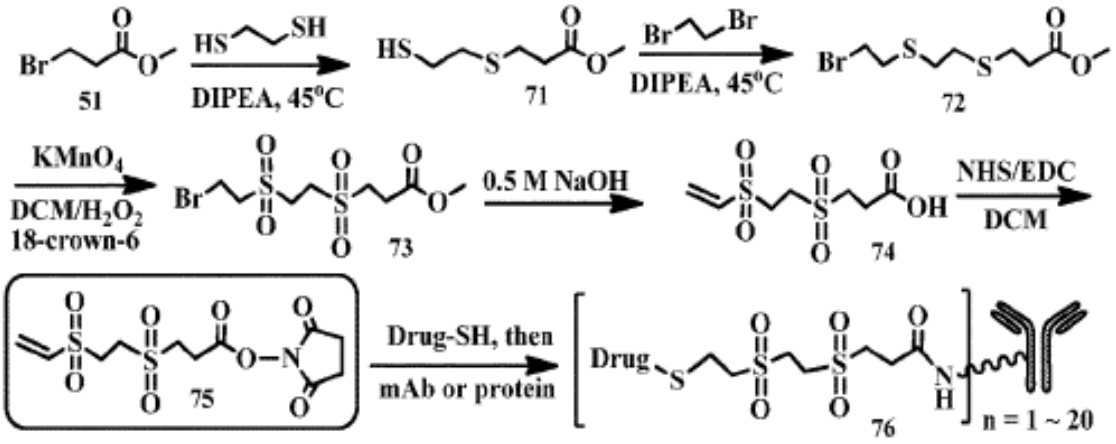


Fig. 7 (Ex. 1001, p. 13). The above figure shows a method of synthesis of embodiment 75 of the invention. *Id.*

Figure 8 discloses embodiment 99 of the Specification, copied below:

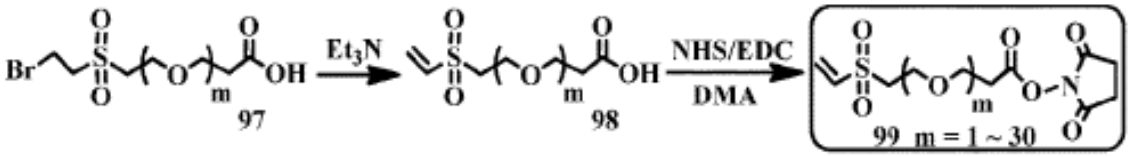


Fig. 8 (Ex. 1001, p. 12). The above figure shows a method of synthesis of embodiment 99 of the invention. *Id.*

Figure 9 discloses embodiment 119 of the Specification, copied below:

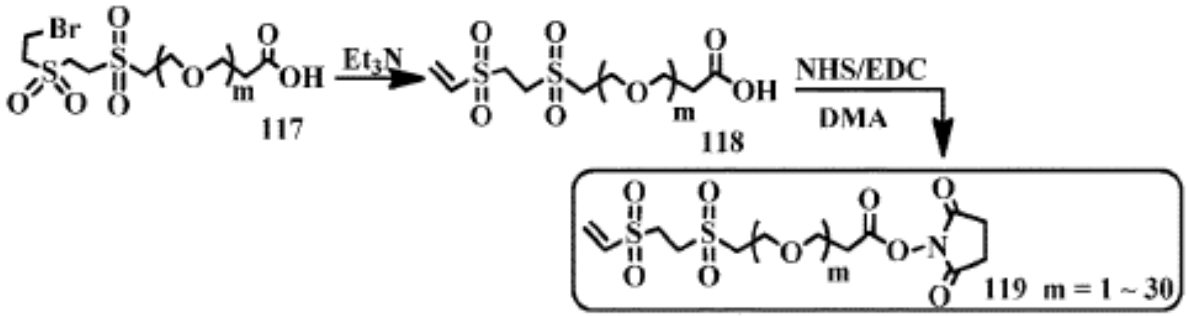


Fig. 9 (Ex. 1001, p. 15). The above figure shows a method of synthesis of embodiment 119 of the invention. *Id.*

Figure 10 discloses embodiment 138 of the Specification, copied below:

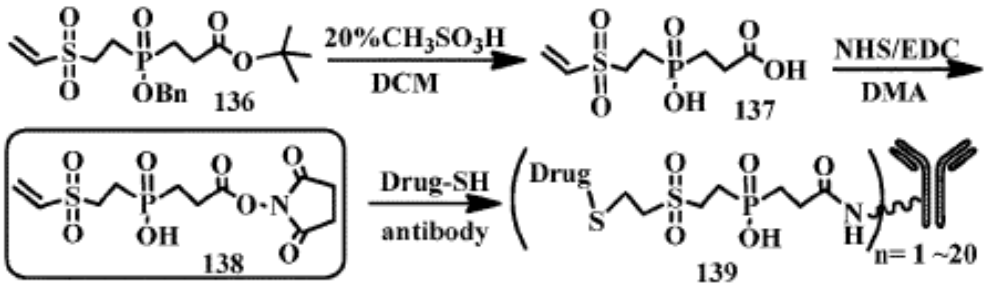
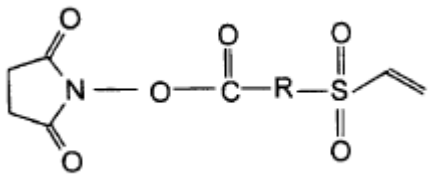


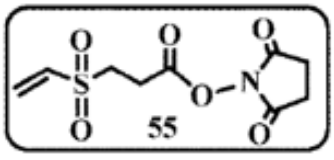
Fig. 10 (Ex. 1001, p. 15). The above figure shows a method of synthesis of embodiment 138 of the invention. *Id.*

2. Relevant Prosecution History

During examination, the Examiner issued a rejection of claim 1 based on a disclosure in Lees[3] of N-hydroxysuccinimide vinylsulfone, copied below.



Ex. 1018, 42–43. The graphic above shows the structure of N-hydroxysuccinimide ("NHS") vinylsulfone. The Examiner found that Lees discloses NHS vinylsulfone as a heterobifunctional linker used to attach a derivatized polysaccharide to one end and a protein to the other. *Id.* at 42. The Examiner found that NHS vinylsulfone anticipated formula 55 of the Specification, shown below:



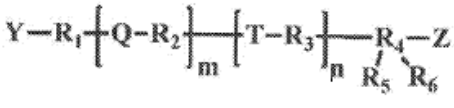
[3] Lees, Andrew, WO 97/41897, published November 13, 1997 (Ex. 2026, "Lees").

Id. at 42–43. Shown above is formula 55 of the Specification, which was encompassed by then-pending claim 1. Ex. 1001, p. 12, Figure 6.

In response, Applicant (now Patent Owner) amended claim 1 as follows to overcome the rejection.[4]

LISTING OF CLAIMS:

1. (Currently Amended) A hydrophilic linker of formula (I)



(I)

wherein:

Y represents a functional group that enables reaction of the hydrophilic linker with a cell-binding agent;

Q and T are either -P(=O)(OM)-, or -$S(O_2)$-, or -S(O)-;

m and n are integer from 0 to 5, but not 0 at the same time; provided that when m=1, n=0, Q is not -P(=O)(OM)-; ~~and~~ when n=1, m=0, T is not -P(=O)(OM)-; and when Q or T is -$S(O_2)$-, m and n are not 0;

Ex. 1018, 45. This amendment required that where claim elements Q or T were sulfone, integers m and n could not be zero. *Id.* Moreover, Applicant stated that the amendment was made to overcome Lees. *Id.* at 62 ("[C]laim 1 of the present application recites that when Q or T is -$S(O)_2$-, m and n are not 0, thereby excluding the above noted compound described in Lees."). *Id*. at 62. The Examiner subsequently allowed claim 1. *Id*. at 77.

3. Reexamination of '682 Patent

The '682 patent was reexamined and a reexamination certificate issued January 4, 2021. Ex. 1002 code (45). The reexamination resulted in the following determination:

> AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

[4] Only the relevant portion of the amended claim (now claim 1) is shown.

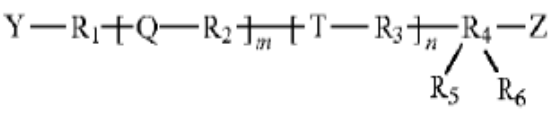
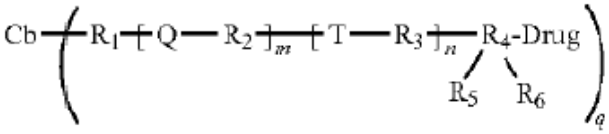
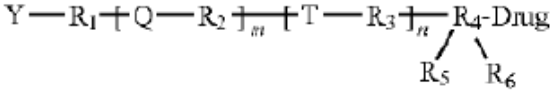
> Claims 1, 3, 18 and 20 are determined to be patentable as amended.
>
> Claims 2, 4-17, 19 and 21, dependent on an amended claim, are determined to be patentable.
>
> New claims 22-34 are added and determined to be patentable.

Id. at 1:13–21.

E. Challenged Claims

Petitioner challenges the patentability of claims 1–17, 20–21, 24–26, and 29–34 ("challenged claims") of the '682 Patent.[5] Pet. 1. The claims recite three types of linker structures that can be used to form antibody-drug conjugates, formulas I, II, and IV. These structures are shown in the table below along with the corresponding formula and the independent challenged claims that recite these structures:

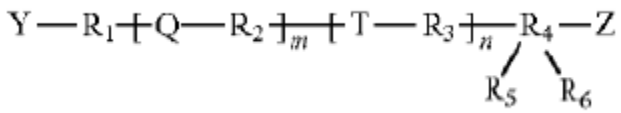
Table 1

Claim	Structure	Formula
1		I
3, 24, 26		II
20, 29, 30		IV

[5] All claims at issue were amended during reexamination, either directly or by dependency except claims 22–34, which were added during reexamination. Ex. 1002, 1:13–21.

Prelim. Resp. 5. The table above shows three types of linker structures, formula I, II, and IV, which can be used to form antibody-drug conjugates of the recited claims. *Id.*

Claim 1 of the '682 Patent is representative. The text of claim 1 pertinent to the parties' dispute[6] recites:

> 1. A hydrophilic linker of formula (I)
>
> 
>
> wherein:
>
> Y represents a functional group that enables reaction of the hydrophilic linker with a cell-binding agent;
>
> Q and T are either —P(═O)(OM)-, or —S(O_2)—, or —S(O);
>
> m and n are integers from 0 to 5, but not 0 at the same time; provided that when m=1, n=0, Q is not —P(═O)(OM)-; when n=1, m=0, T is not —P(═O)(OM)-; and when Q or T is —S(O_2)—, m and n are not 0;
>
> Z represents a functional group that enables linkage of the hydrophilic linker to a cytotoxic drug via a disulfide, thioether, thioester, hydrazone, ether, ester, carbamate, carbonate, secondary, tertiary, or quaternary amine, imine, cycloheteroalkane, heteroaromatic, alkoxime or amide bond; …

Ex. 1002, 1:22–2:14. Claim 1 is directed to structures represented by formula I, the basic hydrophilic linker. *Id.* Independent claims 3, 24, and 26 are directed to structures represented by formula II, wherein the linker is conjugated to a cell-binding agent and a drug. *Id.* at 2:14–3:12; 6:30–7:21; 7:28–8:25. Independent claims 20, 29, and 30 are directed to formula IV,

[6] The R groups are not central to the dispute in this matter. The full text of claim 1 is shown at Exhibit 1002, 1:22–2:14.

wherein the linker is conjugated to a drug. *Id.* at 4:3–5:3; 9:55–12:19. The challenged dependent claims recite additional structures or conjugates and their qualities or recite pharmaceutical compositions containing the structures. Ex. 1001, 49:10–55:29 (amended by dependency).

F. Prior Art and Asserted Grounds

Petitioner asserts that claims 1–17, 20–21, 24–26, and 29–34 are unpatentable on the following grounds:

Ground	Claim(s) Challenged	35 U.S.C. §[7]	Reference(s)/Basis
1	1–3, 6, 24–25, 33	§102(a)(1)	Morales-Sanfrutos[8] as evidenced by Straus[9]
2	1, 20–21, 29–31	§102(a)(1)/ §103(a)	Harris[10]
3	1–8, 10–12, 14–17, 20–21, 24, 26, 29–31	§103(a)	Singh,[11] Harris
4	9, 13	§103(a)	Singh, Harris, Bhakta[12]

[7] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284 (2011), amended 35 U.S.C. § 102 and § 103, effective March 16, 2013. Because the application from which the '682 patent issued was filed before this date, the pre-AIA version of § 102/§ 103 applies. *See* Prelim. Resp. 5.

[8] Julia Morales-Sanfrutos, et al., *Vinyl Sulfone Bifunctional Tag Reagents for Single-Point Modification of Proteins*, 75: J. ORG. CHEM., 4039–4047 (2010) (Exhibit 1005, "Morales-Sanfrutos").

[9] W. Straus et al., *Unusual binding sites for horseradish peroxidase on the surface of cultured and isolated mammalian cells: Suppression of binding by certain nucleotides and glycoproteins, and a role for calcium*, 85: HISTOCHEMISTRY 277–286 (1986) (Ex. 1006, "Straus").

[10] J. Milton Harris, WO 95/13312, published May 18, 1995 (Ex. 1007, "Harris").

[11] Rajeeva Singh, et al., US 2010/0129314 A1, published May 27, 2010 (Ex. 1008, "Singh").

[12] Sunil Bhakta et al., US 2011/0301334 A1, published December 8, 2011 (Ex. 1011, "Bhakta").

Ground	Claim(s) Challenged	35 U.S.C. §[7]	Reference(s)/Basis
5	2, 25, 32–34	§103(a)	Singh, Harris, Snow[13]

Petitioner supports its allegations with the declarations of Ravi Chari, Ph.D. (Ex. 1003), and James Mullins, Ph.D. (Ex. 1012). Patent Owner supports its allegations in opposition with the declaration of Lawrence Nathan Tumey, Ph.D. (Ex. 2002).

II. ANALYSIS

A. Level of Ordinary Skill in the Art

The level of ordinary skill in the art at the time of the invention is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

> Petitioner alleges that an ordinarily skilled artisan of the '682 patent would have had a PhD degree in organic chemistry, biochemistry, medicinal chemistry and/or pharmacology, along with 1-2 years of relevant applied research and/or industry experience in the field of linkers and conjugates for biologically active molecules. Alternatively, a POSA would have had a Master's or Bachelor's degree in one of these same fields with, respectively, at least 3-5 or 5-7 years work experience. Such a person would have been familiar with protein/drug conjugates, including antibody-drug conjugates, the use of antibodies to selectively target cells and tissues associated with various diseases and conditions, linker design and selective attachment of the linker to proteins/antibodies and drugs, including targeted release of the drugs, as well as the need for water soluble

[13] Robert A. Snow et al., U.S. Pat. No. 5,414,135, issued May 9, 1995 (Ex. 1010, "Snow").

> conjugates for use with hydrophobic drugs, and methods for enhancing the potency of the protein/antibody-drug conjugates.

Pet. 18–19 (citing Ex. 1003 ¶¶ 23, 44–79). Patent Owner "adopts Petitioner's proposed level of skill in the art solely for the purposes of this Preliminary Response." *See* Prelim. Resp. 31.

Based on the information presented, we find that the asserted prior art itself is sufficient to demonstrate the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (prior art itself can reflect the appropriate level of ordinary skill in the art). To the extent a more precise definition is required, we apply Petitioner's unopposed proposed definition for purposes of determining whether to institute review because it is consistent with the disclosures of the asserted prior art references.

B. Claim Interpretation

In an *inter partes* review, the Board construes the terms of a patent claim "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." 37 C.F.R. § 42.100(b). Under that standard, claim terms generally are given their plain and ordinary meaning as would have been understood by the ordinarily skilled artisan at the time of the invention and within the context of the entire patent disclosure. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). We construe terms in controversy only to the extent necessary to resolve the controversy. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

1. Arguments

Petitioner did not propose any terms for interpretation. Pet. 24. Patent Owner proposes constructions for four terms. Prelim. Resp. 32–39. For purposes of deciding whether to institute, we find it necessary only to interpret claim terms referring to components "Y" and "Z" with regard to whether they must function independently or can work in concert with "Q" and "T."

Patent Owner proposes that "the claimed 'Y' term should be interpreted as a component distinct and separate from the other recited components, including 'Q' and 'T', of the claimed linkers" reflected in formulas I, II, and IV. *Id.* at 32 (citing Ex. 2001 ¶ 110; *Becton, Dickinson & Co. v. Tyco Healthcare Grp., LP*, 616 F.3d 1249, 1254 (Fed. Cir. 2010)). Patent Owner further proposes that "the 'Y' term should be construed as requiring that Y, as a functional group distinct from Q/T (and other claimed elements of the linker), ***independently enable*** the reaction of the linker with a cell-binding agent." *Id.* (citing Ex. 2001 ¶¶ 110–116) (emphasis original). Patent Owner argues that its interpretation is supported by the plain language of the claim, "enables reaction," such that "the Y structure by itself allows for the reaction between the linker (compound) and cell-binding agent to occur." *Id.* at 33 (citing Ex. 2001 ¶ 111). Patent Owner argues the Specification also supports this interpretation, and not that Y *works with* Q to enable reaction with a cell-binding agent; rather, all Y and Z must independently function. *Id.* at 32–33 (citing Ex. 2001 ¶¶ 112–115; Ex. 1001, 8:61–67, 48:30–43, 13:51–63). Patent Owner points out that the claims permit some embodiments of the linkers to have an optional intervening structure "R1" between components Y and Q, which would require Y to

function independently without assistance from Q in these embodiments. *Id.* at 33 (citing Ex. 2001 ¶ 112).

Patent Owner argues that claim term "Z" should likewise be construed as separate from other claim elements and to "***independently enable*** the reaction of the claimed linker with a ***cytotoxic drug***." *Id.* at 34 (citing Ex. 2001 ¶¶ 117–124) (emphasis original). Patent Owner argues that this interpretation is supported by the claim language and Specification, because both specify the types of chemical linkage the "Z" group must create with the cytotoxic drug, and because the claims permit some embodiments of the linkers to have optional intervening structures "R3" and "R4" between components T and Z that would require Z to function independently. *Id.* at 35–36 (citing Ex. 2001 ¶¶ 119–123; Ex. 1001, 8:61–67, 13:51–63).

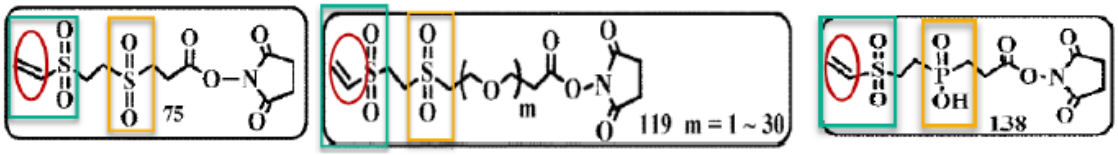
Patent Owner similarly argues that claim terms "Q" and "T" should be construed as separate from other structures, and that this interpretation is supported by the claim language and Specification. *Id.* at 36–37 (citing *Becton, Dickinson*, 616 F.3d at 1254; Ex. 2001 ¶¶ 125–129; Ex. 1001:3:14–15, 8:23–24). Patent Owner, through its declarant, argues that its proposed constructions of "Y," "Z," "Q," and "T" align with the understanding of the ordinarily skilled artisan at the time of the invention. *See, e.g.*, Ex. 2001 ¶¶ 110, 117, 124, 125.

In response, Petitioner argues that Patent Owner's proposed construction for these terms is contradicted by both the Specification and the prosecution history. Pet. Prelim. Reply 4. Petitioner argues that "at least compounds 55, 75, 99, 119 and 138 contradict Patent Owner's position." *Id.*

(citing Figures 6 and 8–10[14] of the Specification). Petitioner argues that "the vinyl group of the terminal vinyl sulfone moiety corresponds to Z for all five compounds, and the sulfone group corresponds to Q in all five compounds (and/or T in compounds 55 and 99)." Petitioner argues that its proposed designations must be correct because otherwise, these compounds and the compounds created by linking to a "Drug" do not fall within the scope of the challenged claims. *Id.* at 5 (citing *National Steel Car. Ltd. v. Canadian Pacific Railway, LTD.*, 357 F.3d 1319, 1336 n.19 (Fed. Cir. 2004)).

Petitioner further argues that Patent Owner's current interpretations do not reconcile with statements made during patent prosecution or reexamination, where Patent Owner identified a vinyl group as both Z and Y and vinyl sulfone as the combination of TZ and QY. *Id.* at 6–7 (citing Ex. 1018, 36–43; Ex. 1019, 72).

Patent Owner responds that compounds 75, 119, and 138 do not contradict the proposed constructions because they do not disclose a vinyl group alone as Z, but rather a vinyl sulfone. PO Sur-reply. 4. Patent Owner provides a diagram, reproduced below, to explain its proposed designations for compounds 75, 119 and 138.



PO Sur-reply, 4. Patent Owner's diagram, reproduced above, provides its proposed designations for compounds 75, 119 and 138. *Id.* Patent Owner states:

[14] We note that compound 75 appears in Figure 7 of the Specification. *See* Ex. 1001, 13 (Figure 7).

> [C]ompounds 75, 119, and 138 do not contradict DAC's proposed constructions at least because those compounds do not disclose a vinyl group alone as Z. Rather . . . each of those compounds include a vinyl sulfone as Z (green rectangle) and a distinct sulfonyl or POOH group as Q (yellow rectangle).

Id. Patent Owner notes that it is undisputed that vinyl alone cannot react with either cell-binding agents or cytotoxic drugs. *Id.* (citing Prelim. Resp., 44). Patent Owner does not dispute that compounds 55 and 99, under Patent Owner's constructions, do not fall within claim 1, but argues that neither is a preferred embodiment and that the intrinsic evidence supports its claim construction. *Id.* at 4–5 (citing *SIMO Holdings Inc. v. Hong Kong uCloudlink Network Tech. Ltd*., 983 F.3d 1367, 1378-1379 (Fed. Cir. 2021); *TIP Sys., LLC v. PBG, Inc.*, 529 F.3d 1364, 1373 (Fed. Cir. 2008)). Patent Owner further argues that the statements cited by Petitioner in the patent examination and reexamination were instances in which Applicant repeated the Examiner's proposed identifications, prior to arguing against them, and not statements in which Applicant advocated for those designations. *Id.* at 6–7.

In further response, Petitioner argues that by identifying "putative Z and Q groups in each of 75, 119, and 138, going so far as to include a graphic highlighting each group in each compound[,] PO strongly implies that compounds 75, 119 and 138 fall within the claims." Pet. Resp. Brief 1. Petitioner argues that claim 1 does not cover compounds 75, 119 and 138 even under Patent Owner's designation because claim 1 requires Q and T to both be present when Q is sulfone or phosphinate as neither m nor n can be zero in that instance. *Id.*

Patent Owner responds that its proposed identifications are not inconsistent but rather remain consistent across all the claims, and that

Petitioner is interjecting new, narrowing claim constructions when "m" and "n" terms have not been construed. PO Resp. Brief 1.

2. Analysis

To interpret the identification of "Y," "Z," "Q," and "T," we begin with how each term is used in the claims. *Phillips*, 415 F.3d at 1313. We need not reach the issue of whether the preamble is limiting for purposes of deciding institution. *See Vivid Techs*., 200 F.3d at 803 ("[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy."). Claim 1 recites the following about these terms:

> Y represents a functional group that enables reaction of the hydrophilic linker with a cell-binding agent;
>
> Q and T are either —P(═O)(OM)-, or —S(O_2)—, or —S(O);
>
> . . .
>
> Z represents a functional group that enables linkage of the hydrophilic linker to a cytotoxic drug via a disulfide, thioether, thioester, hydrazone, ether, ester, carbamate, carbonate, secondary, tertiary, or quaternary amine, imine, cycloheteroalkane, heteroaromatic, alkoxime or amide bond; […]

Ex. 1002, 1:22–2:14.

There is no dispute about the function of moieties Y or Z; both parties agree that these groups enable connection of the linker to a cell-binding agent (Y) or a cytotoxic drug (Z). *See* Pet. 22–23; Prelim. Resp. 32–36. The parties likewise agree that Q and T are defined as being one of three chemical compounds: sulfone, sulfonide, or phosphinate. *See* Pet. 22; Prelim. Resp. 36–37.

The central issue for interpretation is whether Y or Z must act independently or whether they can act in concert with an adjoined Q or T compound, as alleged by Petitioner. *See, e.g.*, Pet. 30–31 ("To illustrate,

comparing Claim 1's formula (I) and one embodiment of Morales-Sanfrutos' compound 2 shown in column 2(a) of Table B2 above, Y is vinyl (–CH=CH2), R1 is absent, m =1, Q is sulfonyl (–S(O2)– . . .", alleging "[v]inyl groups adjacent to a sulfone moiety are known in the art to react with functional groups present in cell-binding agents (e.g., at thiol groups)", citing Ex. 1003 ¶ 86; Ex. 1005, 4043–44). As explained below, and as further discussed in our analysis of Petitioner's Grounds, we conclude that Y and Z must independently enable their respective chemical reactions because Patent Owner (as Applicant) disclaimed embodiments in which Y or Z was adjoined to a sulfone compound with no *additional* adjacent sulfone, sulfoxide or phosphinate, in order to distinguish Lees.[15] *See* Ex. 1018, 42–43 (Examiner's rejection), 62 (Applicant's amendment and comments).

The language of claim 1 provides that "Y represents a functional group that enables reaction of the hydrophilic linker with a cell-binding agent" and "Z represents a functional group that enables linkage of the hydrophilic linker to a cytotoxic drug . . . ." As Patent Owner notes, our case law holds that when a claim identifies components individually, this implies that they are distinct components. Prelim. Resp. 32 (citing *Becton, Dickinson*, 616 F.3d at 1254). However, "enables reaction" and "enables linkage" do not clearly explain whether the Y or Z group catalyzes the entire reaction or merely facilitates it, as Petitioner suggests, by working in concert with an adjacent group that is necessary for the reaction to occur. *See, e.g.*, Pet. 28–32 (identifying Y as vinyl, Q as sulfone, and relying on presence of both groups for reaction ("[v]inyl groups adjacent to a sulfone moiety are

[15] As we decide this case on the merits, we do not reach Patent Owner's argument on discretionary denial under 35 U.S.C. § 325(d).

known in the art to react with functional groups present in cell-binding agents (e.g., at thiol groups))"). We note, as Patent Owner argues, the claim cites optional intervening structures such as "R1" or "R4," which would require that Y or Z act without the assistance of neighboring compounds in those embodiments. *See* Pet. 33, 35. As analysis of the claims does not alone resolve this issue, we turn to the intrinsic evidence for additional information. *Phillips*, 415 F.3d at 1313.

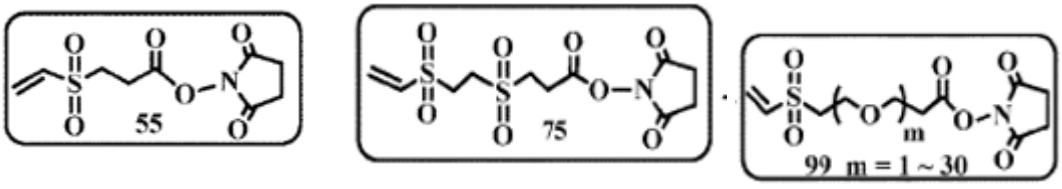
> Y, Z, Q, and T are defined in the Specification as follows:
>
> Y represents a functional group that enables reaction with a cell-binding agent; Q and T are either —P(═O)(OM)-, or —S(O_2)—, or —S(O)— ; Z represents a functional group that enables linkage of a cytotoxic drug via a [assorted compounds including thiols].

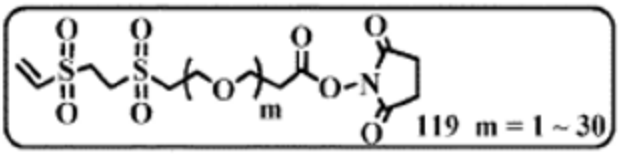
Ex. 1001, 3:12–23. This definition is similar to the language in claim 1 and does not provide additional helpful information.

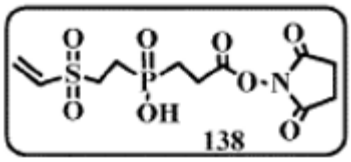
Petitioner points us to embodiments in the Specification that Petitioner alleges support its argument that Y or Z can act in concert with Q or T:

> [T]he '682 patent discloses exemplary formula (I) compounds that contain a vinyl functional group located adjacent a sulfone moiety, and shows their reaction with a thiol (–SH) functional group. EX1001, Figs. 7-10 (showing compound 75, compound 99, compound 119 and compound 138, respectively).

Pet. 31. The disclosure of these compounds along with compound 55 is discussed in Section I.D(1) *supra*. These compounds are additionally reproduced as excerpts from the Specification:



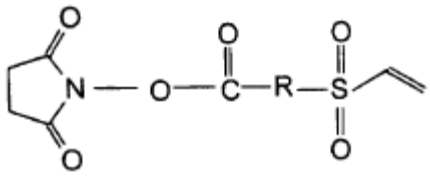




Shown above are compounds 55, 75, 99, 119, and 138 from Figures 6–10 of the '682 patent. Ex. 1001, 12–15. We acknowledge Petitioner's assessment of these compounds as to the Y, Q, T, and Z groups represented and as to whether they fall under claim 1 as amended during prosecution. *See* Pet. 31; Pet. Prelim. Reply 4–5; Pet. Resp. Brief 1.

We additionally consider the patent's prosecution history as intrinsic evidence. A patent's prosecution history "facilitates claim construction by revealing the intended meaning and scope of technical terms and may even trump the weight of specification language in some circumstances." *TDM Am., LLC v. U.S.*, 85 Fed. Cl. 774, 788 (Fed. Cl. 2009) (citing *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 804 (Fed. Cir. 1999)). For example, "an applicant's amendment accompanied by explanatory remarks can define a claim term by demonstrating what the applicant meant by the amendment." *Personalized Media Cmmc'ns, LLC v. Apple Inc.*, 952 F.3d 1336, 1340 (Fed. Cir. 2020). Thus, "like the specification, the prosecution history can act like a dictionary." *Hemphill v. McNeil-PPC, Inc.*, 25 F. App'x 915, 918 (Fed. Cir. 2001) (non-precedential).

As summarized in Section I.D(2) *supra*, during examination, the Examiner issued a rejection of claim 1 based on a disclosure in Lees of N-hydroxysuccinimide vinyl sulfone, copied below.

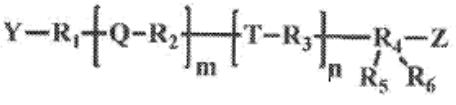


Ex. 1018, 42–43. The Examiner found that Lees discloses NHS vinyl sulfone as a heterobifunctional linker used to attach a derivatized polysaccharide to one end and a protein to the other and found that this compound anticipated formula 55 of the Specification, which was encompassed by claim 1. *Id.* at 42–43.

In response, Applicant amended claim 1 as follows in the relevant portion of the claim to overcome the rejection.

LISTING OF CLAIMS:

1. (Currently Amended) A hydrophilic linker of formula (I)



(I)

wherein:

Y represents a functional group that enables reaction of the hydrophilic linker with a cell-binding agent;

Q and T are either -P(=O)(OM)-, or -$S(O_2)$-, or -S(O)-;

m and n are integer from 0 to 5, but not 0 at the same time; provided that when m=1, n=0, Q is not -P(=O)(OM)-; ~~and~~ when n=1, m=0, T is not -P(=O)(OM)-; and when Q or T is -$S(O_2)$-, m and n are not 0;

Ex. 1018, 45. The amendment specified that where claim elements Q or T were sulfone, integers m and n could not be zero. *Id.*; *see also id.* at 62 (". . . claim 1 of the present application recites that when Q or T is -$S(O)_2$)-, m and n are not 0, thereby excluding the above noted compound described in Lees"). The Examiner subsequently allowed claim 1. *Id.* at 77.

Patent Owner's language accompanying its claim amendments makes clear that the amendments were meant to overcome Lees' disclosure of a

terminal vinyl sulfone group as the group that "enables linkage of the hydrophilic linker to a cytotoxic drug." *See* Prelim. Resp. 24–25 (discussing amendment over compound in Lees that is identical to compound 55 disclosed in Figure 6 of the '682 patent); *Personalized Media*, 952 F.3d at 1340 (explaining relevance of an applicant's remarks accompanying claim amendments during prosecution to interpret "what the applicant meant by the amendment").

In light of the amendment made to exclude the compound described in Lees, we are not persuaded by Petitioner's argument that Y or Z of claim 1 could be interpreted to comprise a vinyl group adjacent to a sulfone without additional Q and T groups, as required by the phrase "when Q or T is —$S(O_2)$—, m and n are not 0."[16] Patent Owner's amendment disclaimed compounds in which the terminal group is vinyl sulfone without one or more adjacent Q and T groups. Ex. 1018, 45, 62; *see Schriber–Schroth Co. v. Cleveland Trust Co.*, 311 U.S. 211, 220–21 (1940) ("It is a rule of patent construction consistently observed that a claim in a patent as allowed must be read and interpreted with reference to claims that have been cancelled or rejected, and the claims allowed cannot by construction be read to cover

[16] We note that Patent Owner alleges that Petitioner's citation to this same phrase raises new claim construction arguments. *See* PO Resp. Brief 1 (citing Pet. Resp. Brief 1). We are not persuaded as Patent Owner has cited to this same phrase in its arguments under 35 U.S.C. § 325, in arguing that Applicant's amendment adding this phrase rendered Petitioner's assertion of Harris as a prior art reference a duplicative argument. Prelim. Resp. 20–24 (regarding the rejection in Lees, "The claims were amended to overcome these rejections and subsequently allowed by the Examiner.") Petitioner's application of the term here is identical and we discern no need to further interpret the meaning.

what was thus eliminated from the patent."); *cf. Graham v. John Deere Co*., 383 U.S. 1, 33, 86 S. Ct. 684 (1966) (ruling, in addressing the invalidity of the patents in suit, that "claims that have been narrowed in order to obtain the issuance of a patent by distinguishing the prior art cannot be sustained to cover that which was previously by limitation eliminated from the patent"); *see also Omega Eng'g, Inc. v. Raytek Corp*., 334 F.3d 1314, 1325 (Fed. Cir. 2003) (noting that a prosecution history disclaimer requires a "clear disavowal" of claimed subject matter to attach).

We therefore interpret claim 1 to exclude compounds in which the sole terminal group is vinyl sulfone without one or more adjacent Q and T groups. With this understanding, we agree with Petitioner that claim 1 does not read on embodiments 55, 75, 99, 119, and 138 because Applicant relinquished such subject matter during prosecution to obtain allowance. However, the existence of embodiments in a patent that are not covered by a claim's construction is permissible when supported by the intrinsic evidence. *See, e.g.*, *TIP Sys., LLC v. Phillips & Brooks/Gladwin, Inc*., 529 F.3d 1364, 1373 (Fed. Cir. 2008) (construing claim terms to exclude an embodiment and stating "the mere fact that there is an alternative embodiment disclosed in the '828 patent that is not encompassed by district court's claim construction does not outweigh the language of the claim, especially when the court's construction is supported by the intrinsic evidence"); *SIMO Holdings Inc.*, 983 F.3d at 1378–1379 (reviewing cases construing claim terms in manner not including all embodiments, and construing claim to exclude some embodiments, but not preferred embodiment).

Turning back to the claims with the above-gained information from the prosecution history, we find Patent Owner's proposed interpretations of Y and Z as separate functional groups to be consistent with the language in

the claims and in the Specification for the disclosed embodiments within the scope of claim 1 as amended during prosecution. Specifically, we interpret Y and Z to independently enable their respective reactions, without assistance from an adjoining Q or T. In this regard, we are persuaded by the testimony of Patent Owner's declarant regarding the understanding of one of ordinary skill in the art of the meaning of the claim terms and context of their use. *See* Ex. 2001 ¶¶ 110–124; *see also* Prelim. Resp. 34–36, providing citations to Specification. We additionally find that the claim term definitions should be consistent across all claims. *See Phillips*, 415 F.3d at 1315 ("[b]ecause claim terms are normally used consistently throughout the patent, the usage of a term in one claim can often illuminate the meaning of the same term in other claims," citing *Rexnord Corp. v. Laitram Corp*., 274 F.3d 1336, 1342 (Fed. Cir. 2001); *CVI/Beta Ventures, Inc. v. Tura LP*, 112 F.3d 1146, 1159 (Fed. Cir. 1997). We apply these interpretations in analyzing the Petitioner's grounds.

C. The Patentability Challenges

1. Ground Based on Morales-Sanfrutos as Evidenced by Straus

A patent claim is unpatentable under 35 U.S.C. § 102 if a prior art reference "discloses every claim limitation." *In re Montgomery*, 677 F.3d 1375, 1379 (Fed. Cir. 2012). In this section, we apply that standard to assess whether Petitioner shows sufficiently, for purposes of institution, that the subject matter of claims 1–3, 6, 24, 25, and 33 is anticipated by the disclosure of Morales-Sanfrutos as evidenced by Straus. Pet. 24–37.

a) Morales-Sanfrutos (Ex. 1005)

Morales-Sanfrutos is titled "Vinyl Sulfone Bifunctional Tag Reagents for Single-Point Modification of Proteins." Ex. 1005, 4039. Morales-Sanfrutos describes the "synthesis of vinyl sulfone derivatized bifunctional

tag single attachment point reagents (BTSAP) bearing biotin and a fluorescent tag" and use of the proteins to introduce detectable labels using chemical reactions occurring at the electrophilic vinyl sulfone group. *Id.* Morales-Sanfrutos teaches that the tags can be coupled to Horse Radish Peroxidase (HRP) by conjugating HRP by incubation with the vinyl sulfone derivatized bifunctional tags to make labeled proteins, such as HRP-11. *Id.* at 4046.

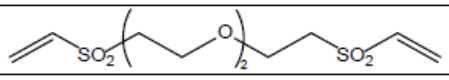
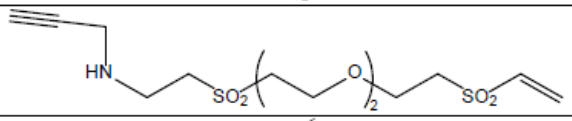
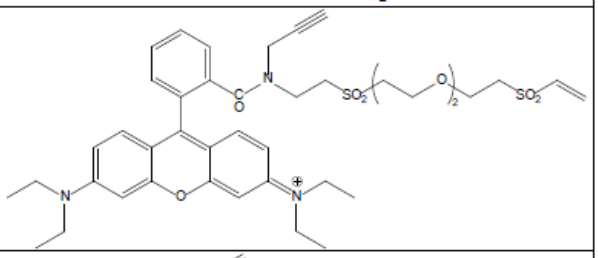
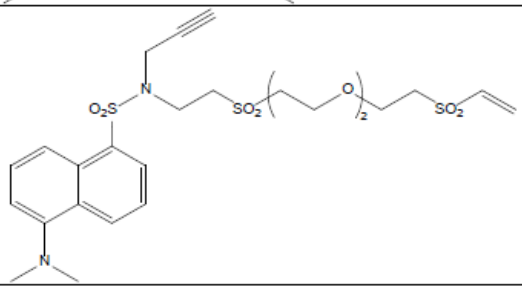
b) Straus (Ex. 1006)

Straus is titled "Unusual Binding Sites for Horseradish Peroxidase on the Surface of Cultured and Isolated Mammalian Cells." Ex. 1006, 1. Straus is a study of binding sites for horseradish peroxidase (HRP). *Id.* Petitioner alleges that Straus discloses that HRP has been show to bind at specific sites in cells such as macrophages, fibroblasts, mast cells and endothelial cells. Pet. 36; *see* Ex. 1006, 1.

c) Petitioner's allegations of anticipation

Petitioner alleges that Morales-Sanfrutos discloses four bifunctional vinyl sulfone poly(ethylene glycol) ("PEG") derivatives falling within formula I as recited by certain challenged claims of the '682 patent. Pet. 26–28 (citing Ex. 1005, 4041 (Scheme I), 4043–44 (Scheme 2)). Petitioner lists the four compounds in Table B1 of the Petition, reproduced below:

Table B1

Cmpd	Bifunctional PEG Cross-linkers
1	
2	
4[4]	
5[3]	

Pet. 27. Reproduced above is Table B1 from the Petition providing formulas of four linker compounds disclosed in Morales-Sanfrutos. *Id.* Through its declarant, Dr. Chari, Petitioner explains that the four disclosed compounds of Morales-Sanfrutos meet the limitations of claim 1 in multiple ways. *Id.* at 28–31 (citing Ex. 1003 ¶¶ 82–84). In these compounds, Petitioner identifies sulfone groups as Q and T and vinyl groups as Y and Z. *Id.* Dr. Chari states that "[v]inyl groups located adjacent to a sulfone moiety are known in the art as functional groups that can react with functional groups present in cell-binding agents (e.g., at thiol groups)." Ex. 1003 ¶ 86 (citing Ex. 1005, 4043–44). Petitioner argues that Morales-Sanfrutos discloses that its compounds can complex to HRP easily ("click attachment through Michael-type addition") and that the vinyl sulfone groups at the ends of the linkers can react selectively toward amines or thiols easily – without byproducts and in mild conditions – to attach to a cell. Pet. 9 (citing Ex. 1005, 4043–44; Ex.

1003 ¶¶ 54–57). Petitioner highlights Morales-Sanfrutos' statement that vinyl sulfone chemistry is particularly useful because of its high efficiency, ease of reaction, and stability in water relative to prior methods. *Id.*

In other words, Petitioner relies on Morales-Sanfrutos as evidenced by Straus to argue anticipation of the limitation of claim 1 that specifies that the linker comprises a cell-binding agent, moiety Z. *Id.* (citing Ex. 1006, 277; Ex. 1003 (Chari Declaration), ¶¶ 59, 90). Petitioner also points out that claim 1 does not require actual conjugation of the formula (I) compound to a cytotoxic drug, but rather "requires only that Z be a functional group that enables reaction with a cytotoxic drug via any one of the many identified bond types, including thioether and heteroaromatic bonds." Pet. 31.

Among other arguments, Patent Owner argues that Morales-Sanfrutos does not anticipate claim 1 because Petitioner's identification of vinyl as Y and Z and the sulfones as Q and T in the compounds does not meet these claim elements as properly construed. Prelim. Resp. 41–44. Patent Owner argues that Y and Z are separate groups and it is "improper to map a single prior art structure—Morales-Sanfrutos' singular vinyl sulfone structure—onto both as Petitioner has done." *Id.* at 42. Patent Owner argues that because vinyl sulfone is the reactive functionality (e.g., YQ together), as the skilled artisan also understood, it is improper to map Y and Z to vinyl alone. *Id.* Patent Owner further argues with regard to compounds 2, 4, and 5 of Morales-Sanfrutos, the limitation "when Q or T is sulfonyl (-S(O2)-), 'm and n are not 0,'" is not met because only one Q or T is present when the groups are correctly identified. *Id.* at 45.

For the reasons discussed above regarding claim interpretation of Y, Z, Q and T, Patent Owner has the better argument for claims 1 and 2. Specifically, Y and Z are independent groups that function without reliance

on a neighboring group, e.g., sulfone. As all of Petitioner's compounds in this ground for claims 1 and 2 rely on sulfone to assist vinyl to enable the reaction above, Petitioner is unlikely to prevail in establishing that Morales-Sanfrutos discloses the Y or Z limitations and has therefore not established a reasonable likelihood of prevailing in showing that the disclosures of Morales-Sanfrutos in light of Straus anticipate claims 1 and 2.

With regard to claims 3, 6, 24, 25, and 33 we are persuaded by Patent Owner's argument that Petitioner's assignment of sulfone for the Q moiety is incorrect because that group becomes complexed to HRP through a vinyl-sulfone mediated reaction, making a derivatized protein, e.g., HRP-11. Prelim. Resp. 48 (citing Ex. 1005, 4046). In this structure, sulfone is no longer an independent group available to be identified as Q because it has been complexed to the Cb moiety, making the Q moiety limitation not shown in the HRP-11 conjugate. Thus, Petitioner has not established a reasonable likelihood of prevailing in showing that Morales-Sanfrutos discloses the Q limitation and has therefore not established a reasonable likelihood of prevailing in showing that the disclosures of Morales-Sanfrutos in light of Straus anticipate claims 3, 6, 24, 25, and 33.[17]

[17] Although Petitioner did not address this argument on reply, to the extent Petitioner were to succeed in persuading us that the sulfone group in the derivatized protein is not complexed and remains available for identification as a Q moiety, we would regardless deny institution of claims 3, 6, 24, 25, and 33 under 35 U.S.C. § 314(a). We are permitted, but never required, to institute *inter partes* review when a petitioner meets the threshold for institution. *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2140 (2016) ("[T]he agency's decision to deny a petition is a matter committed to the Patent Office's discretion."); *Harmonic Inc. v. Avid Tech., Inc*., 815 F.3d 1356, 1367 (Fed. Cir. 2016) (explaining that, under § 314(a), "the PTO is permitted, but never compelled, to institute an IPR proceeding"). If we were to find a reasonable basis on claims 3, 6, 24, and 25, Petitioner would have

2. Ground Based on Harris

a) Harris (Ex. 1007)

Harris is titled "Water Soluble Active Sulfones of Poly(ethylene glycol)." Ex. 1007, 1 code (54). Harris discloses methods for synthesizing a PEG derivative that is activated with a sulfone moiety. *Id.*, code (57, Abstract). Harris teaches that vinyl and halo-ethyl are conjugation moieties that can couple with sulfone groups to a linker. *Id.* 6:8–14; 7:8–11. The PEG can have more than one vinyl sulfone attached to become PEG *bis* vinyl sulfone, and used as a linker or spacer to attach a biologically active molecule to a surface or to attach more than one such biologically active molecule to the PEG molecule." *Id.* at 16:24–17:5. Harris discloses n-hydroxylsuccinimide ester and conjugates of biological molecules with reactive thiol moieties that are water soluble. *Id.* at 17:34–18:13.

b) Petitioner's allegations of anticipation

In this section, we apply the anticipation standard set forth in II.C.1. (*see In re Montgomery*, 677 F.3d at 1379) to assess whether Petitioner shows sufficiently, for purposes of institution, that the subject matter of claims 1, 20, 21, and 29–31 would have been anticipated by the disclosure of Harris.

Petitioner argues that Harris teaches a hydrophilic linker satisfying formula I because it discloses PEG derivatives with two sulfone moieties

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established in part only 1 of 5 grounds, and does not have a reasonable likelihood of prevailing for the remaining 23 claims. Although we do not look strictly at precise percentages of institutable grounds and/or claims, this case presents a clear instance where the benefits of holding a trial to resolve the challenges having a reasonable likelihood would be overwhelmed by the burden of addressing the challenges having no reasonable likelihood.

and contains all moieties of formula I. Pet. 37–44. For claim 1, Petitioner alleges

> the vinyl and halo-ethyl groups located adjacent to sulfone moieties in Harris are equivalent to Y or Z of formula (I) because they are known in the art as functional groups that react with thiol moieties, which are present in both cell-binding agents (e.g., antibodies) and cytotoxic drugs, and react to form thioether linkages.

Id. at 39.

Petitioner relies on the same rationale for claims 20, 21, and 29–31, identifying teachings in Harris regarding use of pharmaceuticals such as penicillin conjugated by thiols attached to PEG derivatives for "Drug" disclosed by the '682 patent for formula (IV) and identifying disclosures in Harris teaching elements of the dependent claims. *Id.* at 40–42 (citing Ex. 1007, claims 33–34, 6:28–31, 7:23–28, 16:34–18:15, 19:10–12, Abstract; Ex. 1008 ¶ 144, Figures 7–12, 46–52; Ex. 1009, Figure 3; Ex. 1003 ¶¶ 106–113 (e.g., "Drug is a pharmaceutical linked via a thioether linkage to an ethylene group resulting from reaction of the thiol-containing drug with the vinyl sulfone.")).

c) Patent Owner's arguments

Patent Owner again argues that Petitioner improperly maps a single prior art element to two distinct claim elements. Prelim. Resp. 50–51. Patent Owner argues that vinyl and halo-ethyl are conjugation moieties that require attachment to sulfone to form vinyl sulfone or halo-ethyl sulfone to enable reactivity and are therefore not independently active. *Id.* at 50. Patent Owner argues that Petitioner's mapping of the structural elements is deficient and relies on Harris's use of vinyl sulfone as a conjugation moiety. *Id.* at 53.

For the reasons discussed above regarding claim interpretation of Y and Z, Patent Owner has the better argument. Specifically, Y and Z are independent groups that function without reliance on a neighboring group, e.g., sulfone. As all of Petitioner's compounds in this ground rely on sulfone to assist vinyl as described above, Petitioner is unlikely to prevail in establishing that Harris discloses the Y or Z limitations and has therefore not established a reasonable likelihood of prevailing in showing that the disclosures of Harris anticipates claims 1, 20, 21, and 29–31.

d) Petitioner's allegations of obviousness

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). In this section, we determine whether Petitioner shows sufficiently, for purposes of institution, that claims 1, 20, 21, and 29–31 would have been rendered obvious by Harris.

Petitioner argues that claim 1 is obvious over Harris because "Harris' basic structure suggests each element of formula (I) of claim 1" and the skilled artisan would have been motivated to prepare bis vinyl sulfones with multiple lengths of ethyleneoxy subunits as Harris discloses "because Harris teaches that such bifunctional PEGS are water soluble, hydrolytically stable, selective for coupling with thiol moieties, and form stable thioether linkages with proteins and pharmaceuticals." Pet. 39 (citing Ex. 1007). Petitioner argues Harris' disclosures of how to make PEG bis vinyl sulfones would have given an ordinarily skilled artisan a reasonable expectation of success in making the claimed subject matter. Regarding claims 20, 21, and 29–31,

Petitioner argues that the same motivation to make the claimed subject matter and the reasonable expectation of success in doing so apply likewise for these compounds. *Id*. at 42–43.

e) Patent Owner's arguments

Patent Owner argues that, in addition to containing deficient allegations of how the artisan would have combined structures in Harris to achieve the linker of formula I and why the combination would have been made in the manner claimed, Petitioner's allegations nonetheless contain the same mapping of elements Y, Z, and Q to rely on the activity of vinyl sulfone rather than as individual elements. Prelim. Resp. 51–54.

For the reasons discussed above regarding claim interpretation of Y and Z, Patent Owner has the better argument. Specifically, Y and Z are independent groups that function without reliance on a neighboring group, e.g., sulfone. As all of Petitioner's compounds in this ground rely on sulfone to assist vinyl as described above, Petitioner is unlikely to prevail in establishing that Harris discloses the Y or Z limitations and has therefore not established a reasonable likelihood of prevailing in showing that the disclosures of Harris render claims 1, 20, 21, and 29–31 obvious.

3. Ground Based on Singh and Harris

a) Singh (Ex. 1008)

Singh is titled "Potent Conjugates and Hydrophilic Linkers." Ex. 1008, code (54). Singh discloses modifying linkers used to bind drugs to cell binding agents by incorporating a polyethylene glycol spacer. *Id.*, code (57, Abstract). Singh discloses that a drug can be linked to a cell-binding agent using a disulfide bond if the linker molecule contains a reactive chemical group that will react with the cell binding agent. *Id.* ¶ 144.

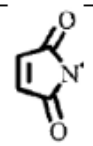
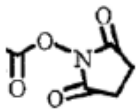
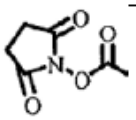
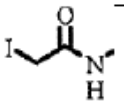
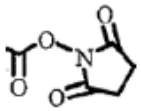
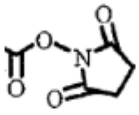
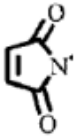
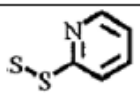
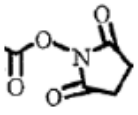
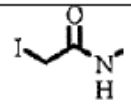
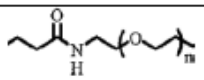
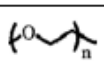
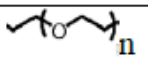
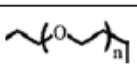
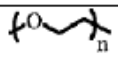
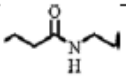
In this regard, Singh discloses N-Succinimidyl esters and N-sulfosuccinimidyl esters. *Id.*

b) Petitioner's allegations of obviousness

In this section, we determine whether Petitioner shows sufficiently, for purposes of institution, that claims 1–8, 10–12, 14–17, 20–21, 24, 26, and 29–31 would have been rendered obvious by the combination of Singh and Harris.

Regarding claims 1 and 2, Petitioner argues that Singh teaches bifunctional PEG cross-linkers that contain "each element of claim 1, save Q and T." Pet. 44. Petitioner provides Table C1, reproduced below, to illustrate how Singh's PEG cross-linkers meet the elements of claim 1 except for Q and T.

Table C1

	Singh's Compounds (Table A1)				
'682 (I)	**1**		**2**	**3**	
	(a)	**(b)**		**(a)**	**(b)**
Y					
Z					
R_1	absent	absent	absent	absent	absent
R_2					
p	n=1-2000, 1-100, 1-14, 1-4	n=1-2000, 1-100, 1-14, 1-4	n=1-14	n=1-2000, 1-100, 1-14, 1-4	n=1-2000, 1-100, 1-14, 1-4
R_3	absent	absent	absent	absent	absent
R_4	absent		absent	absent	

Id. at 46–47. Table C1 lists Petitioner's proposed mapping of claim 1 elements to Singh's PEG cross-linkers. *Id.*

Petitioner argues that Singh "expressly suggests the use of vinyl sulfones as a thiol-reactive functionality and teaches their equivalence to maleimide and haloacetamides for this purpose." *Id.* at 48 (citing Ex. 1008 ¶ 134; Ex. 1003 ¶ 124). Petitioner alleges that the ordinary artisan would have been motivated to replace the functionalities disclosed in Singh with a vinyl sulfone group, "resulting in Q or Q and T each being a sulfone group, and Y, or Y and Z, each being a vinyl group." *Id.* at 49 (citing Ex. 1003

¶ 125). Petitioner argues that Harris's disclosure of hydrophilic PEG derivatives comprising one or two sulfone moieties that are useful for conjugating two biologically-active molecules with reactive thiol moieties would have provided motivation for numerous reasons including the advantages of hydrophilicity. *Id.* at 49–52 (citing Ex. 1007, claims 33–34, 3:28–35, 6:12–15, 14:1–7, 16:34–17:5, 18:5–30, 19:10–15, 19:24–37, 21:26–28:34, 29:1–22, 30:3–29, Abstract; Ex. 1008 ¶ 134, Figures 50–51; Ex. 1003 ¶¶ 126–134).

Regarding claims 20–21 and 29–31, Petitioner argues Singh discloses PEG drug linkers that may be attached to a cell binding agent to provide conjugate molecules. Pet. 54 (citing Ex. 1008 ¶¶ 14, 80). Petitioner argues that these linkers "overlap with and suggest compounds of formula (IV)." *Id.* at 54 (citing Ex. 1003 ¶¶ 137–151). With regard to the elements at issue, Petitioner argues that

> Singh's Z group also meets at least the Q variable of '682's formula (IV) because Singh discloses vinyl sulfone—a reactive functionality that forms thioether bonds—as one of only three such groups (along with haloacetamide and maleimide). EX1008, ¶[0134]. In this case, Y of formula (IV) is vinyl, Q is sulfonyl, m=1 and, as permitted by the claims, R1 is absent from Singh's compound of formula (1).

Id. at 54–55 (citing Ex. 1008 ¶¶ 134, 138); *see also* Table C2 diagrams showing how Petitioner maps the elements at issue to challenged claims when substituted). Petitioner alleges the PEG compounds differ only from the challenged claims because Q and T are absent. *Id.* at 59. Petitioner argues the ordinarily skilled artisan would have been "motivated to substitute thiol reactive groups that can react with a cysteine in a cell-binding agent . . . and/or the reactive functionality forming the thioether bond" to Singh's drug with vinyl sulfone or other sulfones as taught by

Harris because of the advantages of using vinyl sulfones taught in both Singh and Harris. *Id.* at 60 (citing Ex. 1003 ¶¶ 148–149). Petitioner argues the skilled artisan would have had a reasonable expectation of success in making the claimed subject matter. *Id.* (citing Ex. 1003 ¶ 150).

c) Patent Owner's arguments

Among other arguments, Patent Owner argues that Petitioner's allegations again incorrectly map the independent function of the Y group to the combined Q-Y vinyl sulfone group because Y is an independent moiety not reliant on the function of Q. Prelim. Resp. 54–59. Patent Owner also argues that Petitioner's allegations of obviousness and motivation to combine lack merit. *Id.* at 56–57.

For the reasons discussed above regarding claim interpretation of Y and Z, Patent Owner has the better argument. Specifically, Y[18] is an independent group that functions without reliance on a neighboring group, e.g., sulfone. As all of Petitioner's compounds in this ground rely on sulfone to assist vinyl to be reactive, Petitioner is unlikely to prevail in establishing that Harris discloses the Y limitations and has therefore not established a reasonable likelihood of prevailing in showing that the disclosures of Harris render claims 1, 20, 21, and 29–31 obvious. Accordingly, we agree with Patent Owner that Petitioner has not established a reasonable likelihood of prevailing in showing that the combination of Singh and Harris renders claims 1–8, 10–12, 14–17, 20–21, 24, 26, and 29–31 obvious.

[18] We confine our decision on this ground to the lack of disclosure of the Y moiety as Petitioner's evidence regarding the Z moiety would in one or more instances meet the standard for institution of trial. *See* Ex. 1008 ¶ 144.

4. Ground Based on Signh, Harris, and Bhakta

a) Bhakta (Ex. 1011)

Bhakta is titled "Water Soluble Active Sulfones of Poly(ethylene glycol)." Ex. 1007, code (54). Bhakta discloses a PEG derivative that is "activated with a sulfone moiety for selective attachment to thiol moieties on molecules and surfaces. It is water soluble, hydrolytically stable, and forms stable linkages with thiol moieties." *Id.*, code (57, Abstract).

b) Petitioner's allegations of obviousness

In this section, we determine whether Petitioner shows sufficiently, for purposes of institution, that claims 9 and 13 would have been rendered obvious by the combination of Singh, Harris, and Bhakta.

Petitioner relies on Singh and Harris for the alleged disclosures of Y and Z as discussed above in regards to the Ground based on Singh and Harris. Pet. 70–71. Petitioner does not identify any other teaching in Harris or in Singh that discloses moiety Y for the claims challenged in this ground, and relies on Bhakta only to teach conjugates claimed by dependent claims 9 and 13.

c) Patent Owner's arguments

Patent Owner argues that this ground fails for the same reasons as in the Ground based on Singh and Harris because claims 9 and 13 depend from claim 3. Prelim. Resp. 59.

We agree for the reasons stated in our analysis of the Ground based on Singh and Harris regarding the lack of evidence supporting a Y moiety as construed. Accordingly, Petitioner has not established a reasonable likelihood of prevailing in showing that the combination of Singh, Harris, and Bhakta renders claims 9 and 13 obvious.

5. Ground Based on Singh, Harris, and Snow

a) Snow (Ex. 1010)

Snow is titled "Vinyl Sulfone Coupling of Polyoxyalkylenes to Proteins." Ex. 1010, code (54). Snow discloses polyalkylene oxide vinyl sulfone reagents and a method for using them in hydrated media for the modification of proteins. *Id.*, code (57, Abstract).

b) Petitioner's allegations of obviousness

In this section, we determine whether Petitioner shows sufficiently, for purposes of institution, that claims 2, 25, and 32–34 would have been rendered obvious by the combination of Singh, Harris, and Snow.

Petitioner relies on Singh and Harris for the alleged disclosures of Y and Z as discussed above in regards to the Ground based on Singh and Harris. Pet. 73. Petitioner argues that the ordinary artisan would have been "motivated to replace at least one of the maleimide-containing arms in Singh's bifunctional bis-maleimide PEG crosslinking agent with the bis-vinyl sulfone group of Snow" to enhance hydrophilicity of the PEG linkers, and would have had a reasonable expectation of success in doing so. *Id.* at 74. Petitioner provides diagrams to reflect the proposed substitutions for formulas (I) and (IV).[19] *Id.* at 75–76.

c) Patent Owner's arguments

Patent Owner argues that this ground fails for the same reasons as in the Ground based on Singh and Harris because each of the alleged claims depends from a claim challenged in that ground. Prelim. Resp. 59.

[19] A diagram for Formula (III) is also provided, though claims meeting the structure of this formula are not at issue.

We agree for the reasons stated in our analysis of the Ground based on Singh and Harris regarding the lack of evidence supporting a Y moiety as construed. Accordingly, Petitioner has not established a reasonable likelihood of prevailing in showing that the combination of Singh, Harris, and Snow renders claims 2, 25, and 32–34 obvious.

III. CONCLUSION

As discussed above, we have determined that Petitioner has not established a reasonable likelihood of prevailing with respect to any claims. Thus, we do not institute an *inter partes* review.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314(a), the Petition is *denied* as to all challenged claims, and no *inter partes* trial is instituted.

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