

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

Patent No. 10,131,682

Ex Parte Reexamination Certificate Issued: January 4, 2021

Title: HYDROPHILIC LINKERS AND THEIR USES FOR CONJUGATION OF
DRUGS TO A CELL BINDING MOLECULES

Inter Partes Review No. IPR2022-01531

PETITIONER REPLY TO PATENT OWNER RESPONSE

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I. INTRODUCTION

Pursuant to 37 C.F.R. §42.23 and the Scheduling Order (Paper 26), Petitioner submits this Reply to the Patent Owner Response (“POR”; Paper 31).

II. CLAIM CONSTRUCTION

A. Construction of “Q-Y-T-Z” Terms

Despite now conceding that the T and Z claim terms can be met by a terminal vinyl sulfone group, Patent Owner contends that the Q and Y groups cannot. Patent Owner’s position is contrary to the DRP Decision, is unsupported by the intrinsic evidence, and should not be adopted.

1. The DRP Decision Dictates the Construction of the Q-Y-T-Z Terms.

While the Board may generally decide a matter without direction from the DRP or the Director after remand, Standard Operating Procedure 4 (“SOP 4”) caveats this with “unless that direction is specifically set forth in a Director or DRP order.” SOP 4(D), (E)(i). Here, the DRP carefully considered the intrinsic record and determined that when a linker contains a vinyl sulfone group, the vinyl should be mapped to Y or Z, and the sulfone mapped to Q or T. DRP Dec., 16. The DRP concluded that “such mapping satisfies the ‘enables reaction’ and ‘enables linkage’ requirements of claim 1.” *Id.* The DRP Decision thus unequivocally held that vinyl sulfone can satisfy both T-Z and Q-Y in claim 1. Furthermore, the DRP

Decision remanded “for further proceedings consistent with this opinion.” *Id.* (underline added).

To Petitioner’s understanding, the DRP Decision remains binding as the “law of the case,” thereby mooting Patent Owner’s argument that vinyl sulfone cannot satisfy Q-Y. *Cf. ArcelorMittal France v. AK Steel Corp.*, 786 F.3d 885, 888 (Fed. Cir. 2015) (holding that the lower court is bound by law of the case for the appellate court’s claim construction).

2. The DRP’s Decision regarding Vinyl Sulfone meeting Q-Y should be upheld.

Even if the DRP Decision is not formally binding, Patent Owner’s argument that vinyl sulfone cannot satisfy Q-Y should again be rejected. The claim language, intrinsic evidence, and precedent all support Petitioner’s position that Q-Y can be met by vinyl sulfone.

Patent Owner grasps for its desired construction by claiming that Y must “independently” enable the reaction (POR, 19-20), citing *Becton* for the proposition that separately listed claim elements must be mapped to distinct components (*id.*, 21). However, the rule laid out in *Becton* is not so black-and-white. In fact, the Federal Circuit has specifically noted that *Becton* “do[es] not create a per se rule that separately listed claim elements are distinct components...” especially where “[t]he specification contains no restrictive language and does not explicitly require that the claim inputs be separate.” *Google*

LLC v. EcoFactor, Inc., 92 F.4th 1049, 1058 (Fed. Cir. 2024) (vacating the lower tribunal's narrow construction stemming from its application of *Becton*).

The Federal Circuit has likewise declined to apply *Becton*'s rule where the specification "does not suggest that the claim terms require separate structures" (*Powell v. Home Depot U.S.A., Inc.*, 663 F.3d 1221, 1231 (Fed. Cir. 2011) (finding that two separately-listed claim limitations need not be met by distinct components)), and where not necessary to avoid the nonsensical result encountered in *Becton* (*Bot M8 LLC v. Sony Interactive Ent. LLC*, No. 2022-1569, 2023 WL 5606978, at *4 (Fed. Cir. Aug. 30, 2023) (affirming Board's construction not requiring that separate claim elements be met by distinct components). The Federal Circuit has similarly declined to apply *Becton* when not supported by the prosecution history. *Bot M8*, 2023 WL 5606978, at *4 (finding that the applicant's amendment after an Examiner rejection further distinguished *Becton*).

Here, neither the claim language itself, the specification, nor the prosecution history ever suggest that the vinyl moiety of a vinyl sulfone group cannot satisfy Y (or Z), with the sulfone satisfying Q (or T). To the contrary, as the DRP found, the intrinsic evidence supports the opposite conclusion, specifically that vinyl sulfone satisfies both the "enables linkage" and "enables reaction" claim terms. DRP Dec., 16; *see also* D.I., 36-37 (same).

Furthermore, Patent Owner's attempt to now define Y more narrowly than Z is nonsensical, unsupported by the claim language, specification, or prosecution history and does not merit application of *Becton*. Instead, as discussed below, the entirety of the intrinsic evidence supports Petitioner's (and the DRP's) construction.

(a) The claim language shows Y is broader than Z, not narrower.

In the claims, Y is a functional group that must “enable reaction” between the linker and a cell-binding agent (“CBA”), while Z is a functional group that must “enable linkage” between the linker and a drug via one of the enumerated bond types. As Patent Owner's expert admits, for Z to form a “linkage” via one of the listed bond types, a chemical reaction is necessarily required. Ex. 1063, 9:2-15:10. Z is therefore commensurate with Y in that they must both enable reaction between the linker and the drug/CBA, except that the reaction required for Z must form one of the specifically enumerated bond types, whereas in claim 1 Y can be satisfied via any chemical reaction (unlike for claim 20, as discussed further below).

Indeed, during reexamination the Examiner consistently characterized Y as a functional group “suitable for forming a bond between the [linker and the CBA]” (Ex. 1019, 19, 24), which matches the “enabling linkage” requirement for Z minus

the specific bond type required for Z. Accordingly, the relevant claim language defines Z more narrowly than Y.

Yet, Patent Owner turns the claim language upside down when conceding that the vinyl group in vinyl sulfone can satisfy Z, while insisting that the same vinyl group cannot satisfy Y. This makes no logical sense given that Y is broader than Z. Correctly interpreted, if the vinyl from vinyl sulfone can satisfy Z (as Patent Owner concedes), then the vinyl from vinyl sulfone must likewise be able to satisfy Y provided that linkage with a CBA is enabled.

(b) The specification further supports the Q-Y groups being met by vinyl sulfone.

Read as a whole, the '682 patent is structured to disclose and cover hydrophilic linkers that can link together one or more drug moieties to a cell-binding agent. The specification discloses Formulas I-IV, with Formula I covering the linker still possessing Y and Z groups, i.e., before the linker has reacted with either a drug or a CBA; Formula III covering the linker partially reacted to link with a CBA but not yet a drug; Formula IV covering the linker partially reacted to link with a drug but not yet a CBA; and Formula II covering the linker fully reacted to be linked with a CBA and a drug at opposite ends. *See, e.g.*, Ex. 1001, 3:1-4:35; *accord* D.I., 10-11.

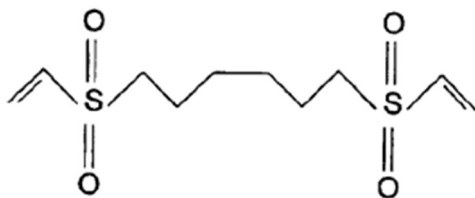
A POSA reading the specification would readily conclude that the linkers of Formula I are used to create the modified/conjugated molecules of Formulas III-IV,

which are then linked again to create the conjugates of Formula II, as depicted below:

Structure	Formula
$Y-R_1-\text{---}Q-R_2-\text{---}_m-\text{---}T-R_3-\text{---}_n-\text{---}R_4-Z$ $\begin{array}{c} \diagup \quad \diagdown \\ R_5 \quad R_6 \end{array}$	I
$Cb-\left(R_1-\text{---}Q-R_2-\text{---}_m-\text{---}T-R_3-\text{---}_n-\text{---}R_4-\text{Drug} \right)_q$ $\begin{array}{c} \diagup \quad \diagdown \\ R_5 \quad R_6 \end{array}$	II
$Cb-\left(R_1-\text{---}Q-R_2-\text{---}_m-\text{---}T-R_3-\text{---}_n-\text{---}R_4-Z \right)_q$ $\begin{array}{c} \diagup \quad \diagdown \\ R_5 \quad R_6 \end{array}$	III
$Y-R_1-\text{---}Q-R_2-\text{---}_m-\text{---}T-R_3-\text{---}_n-\text{---}R_4-\text{Drug}$ $\begin{array}{c} \diagup \quad \diagdown \\ R_5 \quad R_6 \end{array}$	IV

Ex. 1076, ¶4. Patent Owner's expert agrees. Ex. 1063, 89:9-90:18. Yet, Patent Owner's construction for Y would lead to the perverse result that a linker having a terminal vinyl sulfone for attaching a CBA would allegedly not meet the linkers of claim 1/Formula I, yet once reacted with a CBA via the vinyl group, the resulting conjugated linker would fall within claim 3/Formula II.

As a specific example, Patent Owner maintains that the bis vinyl sulfone linker depicted as



would not meet claim 1. POR, 14-15. Yet, when this same molecule is attached to a drug at one end and a CBA at the other end via reaction of each vinyl of the vinyl sulfone groups, the resulting conjugate would meet claim 3. Ex. 1063, 90:8-101:4.

Patent Owner's interpretation for Y thus contradicts the clear teachings in the specification that the linkers of Formula I are specifically intended for creating the conjugates of Formula II (via the intermediate conjugates of Formulas III and IV). The specification thus contradicts Patent Owner's interpretation for Y.

(c) The prosecution history further supports the DRP's and Petitioner's construction.

Patent Owner attempts to characterize Petitioner's argument as relying on a prosecution history disclaimer, arguing that the prosecution history fails to show a "clear and unmistakable" disclaimer because the Examiner allegedly never mapped Y to vinyl. POR, 19-23. Patent Owner is wrong on multiple fronts.

First, as noted above, it is Patent Owner that is trying to narrow the claims by importing an "independently" requirement for Y's "enables reaction" claim term to thereby exclude vinyl sulfone from satisfying Q-Y, while omitting any "independently" requirement for Z (Ex. 1063, 102:19-103:4) and conceding that vinyl sulfone meets the "enables linkage" requirement of the T-Z terms (POR, 19-

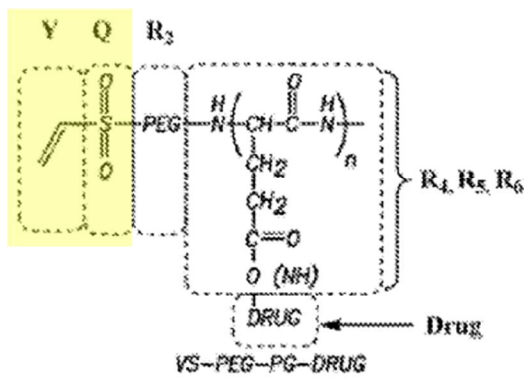
20, 22). Accordingly, it is Patent Owner's interpretation that narrows Y, not Petitioner's.

Second, Patent Owner is flat wrong when it claims that Y was never mapped to a vinyl group (*id.*, 23), because the Examiner did exactly that in the very first reexamination office action. Specifically, in addressing then-pending claim 20, the Examiner mapped the vinyl sulfone of WO'497 to the Q-Y group as follows:

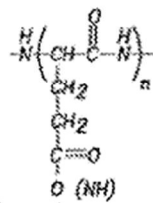
21. With respect to claim 20 in view of the Group I claim interpretation of variables R₁, R₂, R₃, and R₄ the VS¹-PEG-PG-DRUG of WO'497 (*i.e.*, Figure 2) is correlated to the instant

¹ VS represents a vinylsulfone moiety.

variables of **claim 20** (indicated below with the encircled dashed lines). The resulting representation depicted as:



- , where
- **instant Y** corresponds to **H₂C=CH-** of WO'497;
 - **instant R₁** (not depicted in the above representation) is **absent**;
 - **instant Q** corresponds to **-SO₂-** of WO'497;
 - **instant R₂** corresponds to **-PEG-** of WO'497;
 - **instant m** (not depicted in the above representation) corresponds to 1 of WO'497;
 - **instant T** is not depicted in the above representation since **instant n = 0**;
 - **instant R₃** is **absent**, and not depicted in the above representation since **instant n = 0**;
 - **instant n** (not depicted in the above representation) corresponds to 0 of WO'497;



- **instant R₄** corresponds to polymer carrier (PG), i.e., (i.e., ester/amide with 5 C atoms) of WO'497;
- **instant R₅** is **absent**;
- **instant R₆** is **absent**;
- **instant Drug** corresponds to **-DRUG** of WO'497 (e.g., doxorubicin) that is connected to the linker by an ester or amide bond.

Ex. 1019, 9-10 (highlighting added).

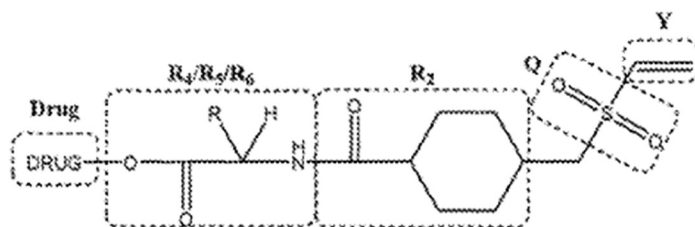
In response, the Applicant reiterated this mapping, and acknowledged the vinyl group as Y. *Id.*, 74-75. Applicant addressed this mapping/rejection not by disclaiming the scope of Q or Y, but instead by amending the claim, *inter alia*, to require that when Q or T is sulfone (i.e., “—S(O₂)—”), Y must be chosen from a

Markush group of bonds that excludes vinyl altogether. *Id.*, 51, 63-65, 75; *see also* Ex. 1002, 4:62-5:2.

Thus, just as the DRP found with Applicant's earlier amendments (DRP Dec., 11), the Applicant understood that Y was mapped to the vinyl of WO'497 (Ex. 1019, 63 ("...wherein Y is vinyl.")), and subsequently provided a disclaimer equal in scope to its amendments to claim 20 to avoid vinyl sulfone altogether. This amendment would have been wholly unnecessary had Applicant intended that "Y" not encompass the vinyl of a vinyl sulfone. *Cf.*, DRP Dec., 14-15 (finding that Applicant's amendment to overcome Lees, versus disclaiming vinyl sulfone as satisfying Q-Y/T-Z, indicates no disclaimer beyond the amendments).

Lastly, in rejecting claim 3 over PGPUB'053, the Examiner stated that "one skilled in the art would at once envisage the instantly claimed vinylsulfone species from a small genus of five well-delineated, thiol-reactive groups." Ex. 1019, 12-13. In response, the applicant stated:

The Examiner appeared to miss a portion in the proposed structure. It is presumed that the following structure was intended:



Id., 72. The Applicant went on to distinguish claim 3 based on its amendments to the R₂ group definition. *Id.* While focused on claim 3, the above exchange makes it clear that the Applicant—not the Examiner—again mapped Y to the vinyl group of vinyl sulfone. The above mapping is thus “more detail” from Applicant, not the Examiner. *See* DRP Dec., 14. Even if attributed to the Examiner in some way, the Applicant certainly never protested that vinyl sulfone was serving as the Q-Y groups in the precursor molecule leading to the conjugate covered by claim 3.

Aside from its express amendments, Patent Owner never identifies any alleged disclaimer limiting the scope of Y. Thus, the prosecution history confirms that Y, just like Z, was and should continue to be interpreted as encompassing the vinyl of vinyl sulfone unless otherwise prohibited (e.g., as in claim 20) for the same reasons found by the DRP (*id.*, 13-14; D.I., 18), which further counsels against the application of *Becton*. *See Bot M8*, 2023 WL 5606978, at *4 (finding that the applicant’s amendment after an Examiner rejection counseled against application of *Becton*).¹

¹ Patent Owner’s expert admitted that he did not review the entire prosecution history and was unaware that the Examiner mapped Y to vinyl. Ex. 1063, 25:7-26:8. His opinions regarding the interpretation of Y should thus be given little weight given that 37 C.F.R. §100(b) requires consideration of the prosecution history when interpreting claim terms.

B. Construction of “Cell-Binding Agent”

The Institution Decision and Patent Owner maintain that this term should be interpreted pursuant to an alleged definition in the specification stating:

The cell-binding molecule that comprises the conjugates and the modified cell-binding agents of the present invention may be of any kind presently known, or that become known, molecule that binds to, complexes with or reacts with a moiety of a cell population sought to be therapeutically or otherwise biologically modified.

Ex. 1001, 14:39-44 (highlighting added); D.I., 19-21; POR, 28. While it is unclear that this claim term must be construed to resolve the parties' disputes, Petitioner maintains that the above provision is not a definition of “cell-binding agent” as used in the claims.

First, the above passage is directed to a “cell-binding molecule,” not cell-binding agent. A cell-binding agent may be a part of the overall molecule, but when considered in the context of the '682 patent's Formula II, for example, the cell-binding agent is not itself a “molecule.” Ex. 1063, 56:8-12 (acknowledging that a molecule cannot be part of another molecule). Further, the passage above indicates that the cell-binding molecule comprises the conjugates and modified cell-binding agents of the invention, which refers to the reaction products of cell-binding agents with other moieties such as the hydrophilic linkers of Formula I and/or a drug to form the conjugates/modified cell-binding agents of Formulas II-IV.

In addition, the purported definition refers to cell populations “sought to be therapeutically or otherwise biologically modified.” Not only should the user’s intent not be a part of any construction of cell-binding agent, but further, the effect of therapeutically or biologically modifying a cell is the intended function of the drug linked to the conjugate, not an intended effect of the cell-binding agent itself.

To the extent this term requires interpretation/construction, it should be construed in accordance with the claim language itself: an agent that binds to cells. *Innova/Pure Water, Inc. v. Safari Water Filtration Sys.*, 381 F.3d 1111, 1115-1116 (Fed. Cir. 2004) (“[A] claim construction analysis must begin and remain centered on the claim language itself.”).

III. MORALES-SANFRUTOS ANTICIPATES CLAIMS 1-3, 6, 24-25, AND 33

Patent Owner contests Morales-Sanfrutos’ anticipation based on its construction of Y and cell-binding agent. Both arguments fail.²

² Petitioner notes that Patent Owner’s corresponding European patent 2922818 (Ex. 1078) was revoked by the EPO (Ex. 1079), in part over Morales-Sanfrutos (reference D6) (*id.*, 5, 22-23). Patent Owner appealed, submitting further amended claims under, *inter alia*, Auxiliary Request 6. Exs.1080-1081. The Boards of Appeal recently rejected the appeal in its entirety, again based in part on Morales-Sanfrutos (D6). Ex. 1082.

First, Y should be interpreted as set forth in the DRP's Decision for the reasons discussed *supra*, §II.A. Under this construction of Y, Patent Owner cannot and does not dispute that Morales-Sanfrutos discloses the Q-Y limitations. Moreover, even if Patent Owner's interpretation of Y were adopted, Morales-Sanfrutos still discloses Y because (1) vinyl alone can independently react to form a linkage with a CBA, and (2) the compounds of Morales-Sanfrutos can be mapped in the opposite direction where its vinyl sulfone constitutes the T-Z groups and the propargylamine group constitutes Y.

Finally, even though claim 1 does not require a CBA, HRP is in fact a cell-binding agent under any proffered interpretation of that term. Straus expressly teaches this, and Patent Owner has not shown otherwise.

A. Morales-Sanfrutos Reads on Claim 1 even under Patent Owner's Construction of Y.

1. Vinyl alone is a functional group that can link to a CBA.

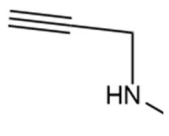
Patent Owner asserts that a terminal vinyl sulfone cannot satisfy Q-Y because "vinyl itself cannot enable reaction with a cell-binding agent" and thus does not meet the Y limitation. POR, 39. Even if Patent Owner's construction for Y is adopted, the art cited in the Petition (e.g., Morales-Sanfrutos and Harris) still satisfies Y. *Axonics, Inc., v. Medtronic, Inc.*, 75 F.4th 1374, 1380-84 (Fed. Cir. 2023).

As explained by Dr. Chari (Ex. 1076, ¶¶5-10), Dondoni describes the

conjugation of vinyl groups to thiol-bearing cysteine residues on bovine serum albumin (BSA) using “a longer wavelength light at 365 nm which is known to cause minimum photodamage to the living cells and organisms.” Ex. 1064, 11447 (Scheme 3). BSA is a known CBA. *Id.*, ¶8. Accordingly, vinyl alone is a reactive functional group that links to CBAs under physiologically-acceptable conditions, irrespective of an adjacent sulfone. *Id.*, ¶11. Although Dr. Chari did not consider such reactions schemes during his deposition since that was not an original focus of the Petition, the vinyl group in Morales-Sanfrutos nonetheless meets Patent Owner’s new interpretation for Y. *Id.*

2. Morales-Sanfrutos’ Compounds Map to Claim 1 in Both Directions.

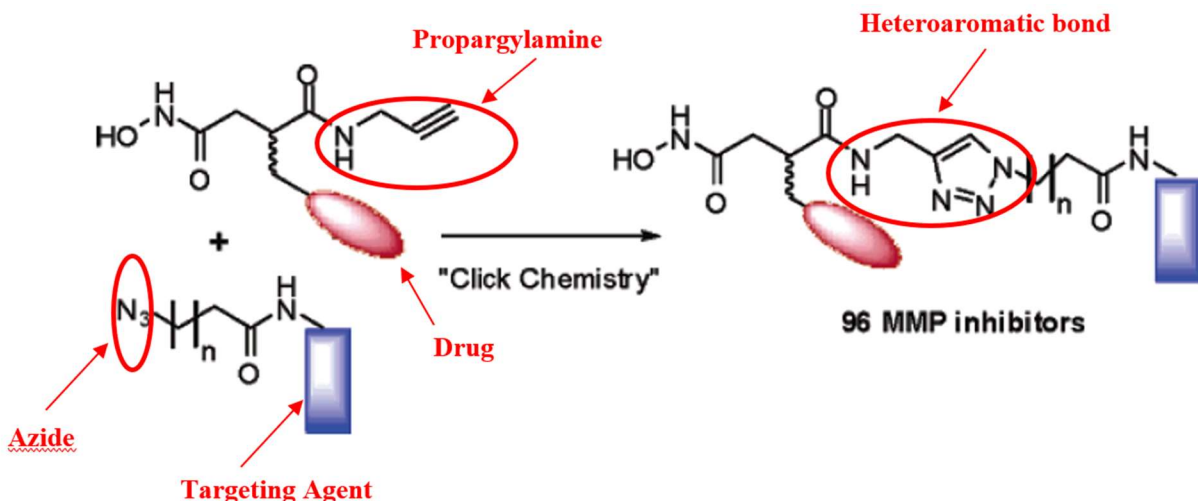
As shown in the Petition, certain Morales-Sanfrutos compounds can be mapped in either direction to satisfy claim 1. Pet., 28-31, Table B2 (compound mapping 2(a)-2(c), 4(a)-4(b), 5(a)-5(b)). In the embodiments of compounds 2(a)-2(b), 4(a), and 5(a), the vinyl sulfone maps to Q-Y, and propargylamine (i.e.,



, which includes both alkynyl and amine moieties) maps to Z.

Vinyl sulfone linkages to CBAs and functionalizing drugs with azides were known to a POSA. Ex. 1003, ¶¶54-56, 87; *see also* Ex. 1076, ¶¶15, 33. Further, the reactions between the azides and alkynyl moieties propargylamine group, as taught by Morales-Sanfrutos, were also well-known (referred to as “Click Chemistry”).

Ex. 1003, ¶87; Ex. 1076, ¶¶13-17. For example, the synthesis of anti-cancer MMP inhibitors via Click chemistry reaction of propargylamine and azide groups, resulting in a heteroaromatic bond, has been reported:

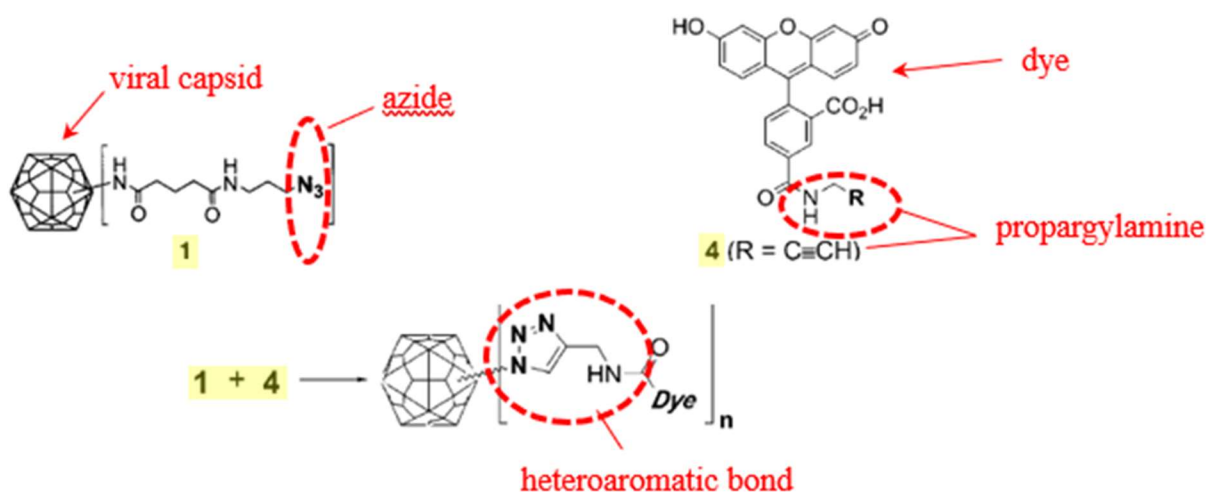


Ex. 1068, 3821; *see also* Ex. 1076, ¶¶16-17. Accordingly, propargylamine groups satisfy the Z limitation because they enable linkages to drugs via, e.g., heteroaromatic bond linkages (D.I., 40).

Alternatively, compounds 2(c), 4(b), and 5(b) were mapped to Formula I in the opposite direction, with vinyl sulfone mapping to T-Z and Morales-Sanfrutos' propargylamine mapping to Y. *See* Ex. 1003, ¶84. A POSA readily appreciated propargylamines as capable of linking to cell-binding agents (Ex. 1076, ¶18), and vinyl sulfones as capable of attaching to thiol-modified drugs, as admitted by Patent Owner's expert (Ex. 1063, 9:2-8, 24:18-25:6, 36:12-18, 78:17-22).

For example, viral capsids, which the '682 patent teaches as among its CBAs (Ex. 1001, 14:45-15:26), bind to the surface of host cells (Ex. 1071, 258

(“the phage capsid . . . remain bound to the [host] cell surface)), and Wang (Ex. 1072, 3192) describes the conjugation of an azide-modified viral capsid with a dye bearing a propargylamine moiety via a heteroaromatic bond using CuAAC:



The above figure again shows the heteroaromatic bond forming from the reaction between an azide and the alkynyl of propargylamine. Thus, even if Patent Owner’s definition of Y is applied, Morales-Sanfrutos’ compounds 2(c), 4(b), and 5(b) still anticipate claim 1.

Lastly, contrary to the Patent Owner’s assertions (POR, 44), a POSA would appreciate that Click chemistry reaction conditions are suitable for the purpose of generating functionally active biological conjugates. (Ex. 1076, ¶¶19-21). The art expressly teaches examples of using conjugates created from copper-catalyzed reactions in living organisms, and reports their therapeutic effectiveness in suppressing tumor growth in *in vivo*. *Id.*

B. Morales-Sanfrutos Discloses the Claimed CBA.

Patent Owner again argues that claim 1 requires the disclosure of a CBA (POR, 45), without addressing the Board's contrary finding on this point (D.I., 37). With no new arguments presented, the Board's preliminary decision should stand.

Nonetheless, Morales-Sanfrutos discloses a CBA, as preliminarily found by the Board. D.I., 38. Indeed, Straus expressly teaches that HRP binds to the surfaces of specific cell populations (Ex. 1006, 1, 5, 7; Figs. 1-14), and a POSA would have readily appreciated Straus's teachings as applying to HRP binding in living cells. Ex. 1075, ¶¶10-15, 20, 23.

Patent Owner's argument that certain of Straus' experimental results were conducted on cells that had been dried and treated with methanol and paraformaldehyde (POR, 36) is meritless. Straus' techniques are known as cell "fixation," which preserves cells in their natural state precisely so that binding experiments can be subsequently conducted. *Id.*, ¶¶16-20.

As a POSA understood (*id.*, ¶¶19-21), "fixation is one of the most critical steps in immunostaining" and "the goal of fixation is to preserve cells and tissues in a life-like manner." Ex. 1074, 55. Fixation "helps to prevent artifactual diffusion of cell components, . . . and avoids decomposition of the tissue" and Straus' techniques are widely used. *Id.*, 56.

Consistent with a POSA's understanding, Straus expressly states that its

fixation techniques were necessary to avoid “background” adsorption, and to prevent the washing away of key surface proteins that would otherwise skew the results. Ex. 1006, 6. Straus concludes that its fixation technique was “sufficient to study the binding of HRP to the cell surface.” *Id.* This merely confirms what a POSA already knew, namely that Straus’ techniques were common in binding studies to preserve (i.e., “fix”) cells so that the binding experiments could be conducted with minimal artifacts,³ and with the understanding that such results were indicative of cell-binding in their natural (i.e., living) state. Ex. 1075, ¶23.

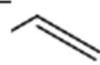
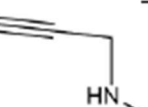
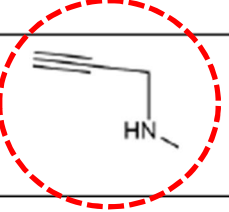
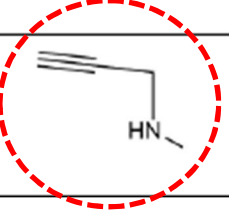
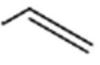
C. Morales-Sanfrutos Discloses Claim 2

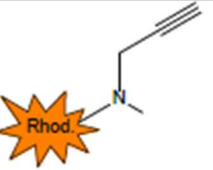
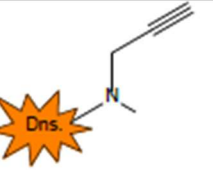
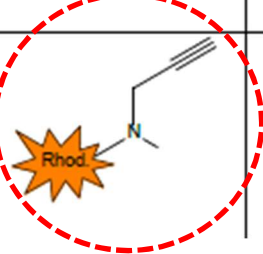
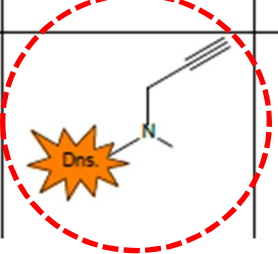
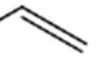
The Institution Decision questioned Petitioner’s identification of claim 2’s limitations in Morales-Sanfrutos, pointing to a perceived inconsistency in Petitioner’s identified Z groups between claims 1 and 2. D.I., 41-42. The Board misapprehends Petitioner’s argument.

The Petition identified the Z group from Morales-Sanfrutos in Table B2, excerpted below:

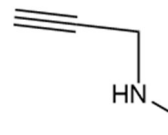
³ Patent Owner also highlights Straus’ mention of potential “artifacts” (POR, 37), but fails to mention Straus’ explanations regarding why they did not affect the results, which actually strengthen Straus’ credibility. Ex. 1075, ¶22.

Table B2

Morales-Sanfrutos' Compounds 1-2 (Table B1)				
'682 (I)	Compound 1	Compound 2		
		(a)	(b)	(c)
Y				
Z				

'682 (I)	Compound 4		Compound 5	
	(a)	(b)	(a)	(b)
Y				
Z				

Pet., 28-29 (circles added). Patent Owner recognized as much. POR, 41-42 (blue oval annotations). As indicated by both parties' annotations to Table B2, the



Petition consistently identified the propargylamine group (i.e., which is found in Morales-Sanfrutos' Compounds 2, 4, and 5 (with attached rhodamine and dansyl groups for compounds 4 and 5, respectively).

Such propargylamine groups are art-recognized, with reports on “the peculiar reactivity of the *propargylamine moiety*” and descriptions of using propargylamines in copper(I)-catalyzed cycloaddition reactions with azides. Ex. 1076, ¶14.

Moreover, propargylamine groups enable the linkage required for Z (or Y). As noted with respect to claim 1, the alkynyl moiety (i.e., the triple-bonded carbons) can react with azide-functionalized drugs, as expressly disclosed in Morales-Sanfrutos. Pet., 31-32. Yet propargylamine also possesses an amino group, as required for claim 2. Incidentally, the amine can likewise form a linkage with a drug resulting in a tertiary amine bond, as Morales-Sanfrutos illustrates for biotin (*id.*, 32 (Table B1, compound 2)), although claim 2 does not require this. Ex. 1076, ¶22-25.

In sum, Petitioner consistently identified Morales-Sanfrutos' propargylamine group as Z in Table B2, and this group satisfies both claims 1 and 2 by having the capability to form heteroaromatic linkages with drugs through its alkynyl moiety (claim 1), and comprising an amino group (claim 2). This is all claim 2 requires, and Patent Owner does not argue otherwise (POR, 48-49).

Further, with no dispute that vinyl sulfone meets T-Z, Compounds 2(c), 4(b),

and 5(b) disclosed in Table B2 also satisfy all limitations of claim 2, with claim 2 met because the vinyl (as Z) reacts with thiol-containing cytotoxic drugs to form a thioether bond (*see, e.g.*, Ex. 1008, ¶¶[0007], [0101]-[0102], [0132]-[0134]).

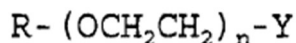
Morales-Sanfrutos' Compounds 2, 4, and 5 thus anticipate claims 1-2 when read in either direction, even if Patent Owner's interpretation of Y were adopted.

IV. HARRIS ANTICIPATES AND RENDERS OBVIOUS CLAIMS 1, 20-21, AND 29-31

A. Harris Anticipation

Patent Owner primarily attacks Harris' anticipation based on its interpretation of Y (POR, 50-51, 53), which was addressed above (*supra*, §II.A). Patent Owner also argues that "a POSA would not 'at once envisage the claimed arrangement or combination' of the elements of Formula I" because Harris' disclosure is allegedly so broad. POR, 54-55.

The Harris passage quoted by Patent Owner references the following formula



and expressly identifies vinyl sulfone and haloethyl sulfone as potential Y groups, while expressly identifying vinyl sulfone, haloethyl sulfone, methyl, and hydrogen as potential R groups. Ex. 1007, 19:10-30; Claims 24-28. With two expressly-identified groups for Y and four for R, this amounts to at most 8 combinations. Moreover, Harris expressly identifies "PEG *bis* vinyl sulfone" as a useful

bifunctional linker for connecting multiple biologically-active molecules. Ex. 1007, 16:37-17:5. Given the above express disclosures, a POSA could at once envisage the *bis* vinyl sulfone linkers relied on for Harris' anticipation.

Patent Owner makes a similar argument (POR, 58) regarding Harris' heterobifunctional linkers (Pet., 42). Yet Harris discloses linkers having vinyl sulfone on one end and an amino-reactive moiety on the other that can react with the cysteine or lysine groups in proteins. Ex. 1007, 17:23-37; Claims 36-37. This satisfies claim 1's requirement that Y merely enable linkage to the CBA. Moreover, Harris expressly identifies nine possibilities (*id.*, 18:5-15), one of which is the NHS-ester group relied on by Petitioner for claims 20 and 29 (Pet., 42; Ex. 1003, ¶¶109-110). Thus, Harris' disclosure is sufficiently express and apparent to a POSA.

1. Cell-Binding Agent

Patent Owner complains that Harris does not disclose a CBA, and argues that claims 1, 20, and 29 require such a disclosure. POR, 56, 59. However, these claims only require a functional group that *enables* reaction with a CBA, and Harris discloses groups such as the vinyl of its terminal vinyl sulfone and NHS ester which are functional groups for attaching to proteins. This is all claims 1, 20 and 29 require. D.I., 37. Harris further teaches that its linkers can attach to thiols on biologically active molecules such as polypeptides and proteins via the vinyl

group, illustrating additional express disclosure of the claimed functionality for Y. Ex. 1007, 16:4-17:8, 17:21-23, 18:29-19:5, 19:31-34, 20:1-30; Claims 33-34; *see also* Pet. 42-43 (discussing NHS ester attachment to CBAs).

2. Claims 30-31

Patent Owner notes that claim 30 requires the presence of both Q and T (e.g., two sulfones, not just one as with claims 20 and 29). Petitioner concedes that Harris' heterobifunctional linkers would not meet claim 30 (or claim 31) for this reason. However, Harris' *homobifunctional* linkers having two sulfones (e.g., Harris' PEG *bis* vinyl sulfone) still meet claims 30 and 31 (Pet., 40-44), which Patent Owner does not separately challenge (POR, 59-60).

B. Harris-Based Obviousness

Patent Owner again argues that Harris is non-analogous art (POR, 52-53), yet fails to address the Board's contrary finding (D.I., 56-58). Harris specifically teaches "dumbbell structures" that link pharmaceuticals to proteins. Ex. 1007, 18:31-19:1; *see also id.*, 16:34-17:8, Claims 33-34. Moreover, Patent Owner admits that Harris' linkers anticipate claim 1, aside from the argument regarding Y. *See* POPR, 25 (explaining how Harris' linkers are the same as those disclosed by Lees); POR, 14-15 (admitting that Lees' structures map to claim 1). The "dumbbell structures" taught by Harris thus fall squarely within the '682 patent's field of endeavor.

Harris also teaches that its linkers are water soluble, hydrolytically stable, and produce stable linkages with thiol groups. Ex. 1007, 19:31-34, 20:1-30.

Harris' linkers "enable otherwise insoluble molecules to pass into solution when conjugated with the derivative." *Id.*, 19:34-37; *see also* Pet., 5-7, 39-44. Similarly, the '682 patent seeks linkers that are usefully soluble in water (Ex. 1001, 13:7-12), exhibit less aggregation in water (*id.*, 2:25-49, 60-62), and conveniently react with thiol groups on CBAs and/or drugs to form thioether linkages (*id.*, 1:7-15, 2:21-24, 3:19-20, 3:59-60, 8:61-9:7, 12:6-10, 12:21-25), specifically including, *inter alia*, sulfones (*id.*, 13:7-12).

Accordingly, Harris is also pertinent to the problems sought to be addressed by the '682 patent. *Innovention Toys, LLC v. MGA Entm't, Inc.*, 637 F.3d 1314, 1321 (Fed. Cir. 2011) ("If a reference disclosure has the same purpose as the claimed invention, the reference relates to the same problem."). Harris is thus analogous art.

V. SINGH IN VIEW OF HARRIS RENDERS CHALLENGED CLAIMS 1, 3-8, 10-12, 14-17, 20-21, 24, 26 AND 29-31 OBVIOUS

Patent Owner's arguments for Ground 3 regarding Y fail for the same reasons already discussed. Patent Owner's non-cumulative Ground 3 arguments are further addressed below.

A. It Was Obvious to Incorporate Vinyl Sulfone in Singh's Linkers

Patent Owner argues that Singh never discloses vinyl sulfone linkers, and that

there was no motivation to include vinyl sulfone in Singh's linkers. POR, 61-65.

The record demonstrates otherwise.

As the Petition noted (Pet., 47-48), Singh's expressly-drawn linkers include maleimide or halo acetamides reactive groups instead of vinyl/vinyl sulfones. However, Singh states that its "preferred linking groups are thiol or disulfide bonds" (Ex. 1008, ¶[0132]), and discloses thiol-containing maytansinoid drugs (*id.*, ¶[0136]) and thiol-containing monoclonal antibodies ("mAb~SH") (*id.*, Fig. 17). Singh then teaches three moieties (maleimide, halo acetamide, and vinyl sulfone) for forming linkages to thiol (i.e., sulfhydryl or SH) groups. *Id.*, ¶[0134].

Singh thus teaches the use of vinyl sulfones as but one of three options for achieving the preferred thiol-based linkage resulting in a thioether bond. *Id.* And since Singh discloses both drugs and CBAs with reactive thiols, a POSA could easily envisage the substitution of vinyl sulfones for the maleimides/halo acetamides depicted in Singh's expressly-drawn molecules. Pet., 48-49.

As noted in the Petition, further motivation and a POSA's reasonable expectation of success for making these substitutions was further bolstered by Harris, which, as noted above (*supra*, §IV.A) discloses bis vinyl sulfones for linking various biologically-active molecules such as pharmaceuticals and proteins. *See* Ex. 1076, ¶¶31, 33-39. Harris teaches vinyl sulfone's beneficial qualities as improving water solubility to bring less-soluble entities into solution, and providing for

convenient thiol-based reactions resulting in hydrolytically stable bonds. Pet., 49-53. That Harris' linkers are very similar to those of Singh (POR, 64) further supports the reasonable expectation of success a POSA would have had in making the substitutions already expressly suggested by Singh (Ex. 1008, ¶[0134]).

While Patent Owner attempts to make much of Dr. Chari's testimony that the inventors in Singh (including Dr. Chari) did not need vinyl sulfone (POR, 61), he was referring to the commercial embodiment underlying that work (Ex. 1076, ¶¶26-30). However, when dealing with more hydrophobic drugs, or when the PEG chain must be kept short, Dr. Chari explains that indeed a POSA would recognize the benefits of incorporating vinyl sulfone (*Id.*, 30), just as Singh itself discloses (Ex. 1008, ¶[0134]). The test for obviousness under *KSR* is not that the substitution will or must be made in every situation, but merely that there is a rationale for making the combination. Singh together with Harris clearly provided that rationale for the reasons identified above.

In regard to the Board's concerns whether a thioether-bond-forming reactive functionality (e.g., vinyl sulfone) would bond with the same CBA or drug as an amide-bonding forming reactive functionality (e.g., an NHS ester), Harris and Snow both expressly disclose that vinyl sulfones react with amines on proteins. Ex. 1010, col. 22, lines 31-35; Ex. 1007, 28 lines 17-21.

B. Claim 2

A POSA would also envisage the substitution of Harris' related sulfonyl functionalities (e.g., PEG *bis*-vinyl sulfone discussed above;

$\text{CH}_2=\text{CH}_2-\text{S}(\text{O})_2-(\text{CH}_2-\text{CH}_2-\text{O})_n-\text{S}(\text{O})_2-\text{CH}=\text{CH}_2$) as thiol-reactive groups for the maleimide depicted as the Y group in Singh's expressly-drawn linkers to obtain their aforementioned benefits (Pet., 50), thus meeting the limitations of claim 2 (i.e., two sulfones as Q and T, with one vinyl (from a vinyl sulfone) as Y, and maleimide as Z). Ex. 1076, ¶¶31-32.

VI. CHALLENGED CLAIMS 9 AND 13 ARE OBVIOUS IN VIEW OF SINGH, HARRIS, AND BHAKTA

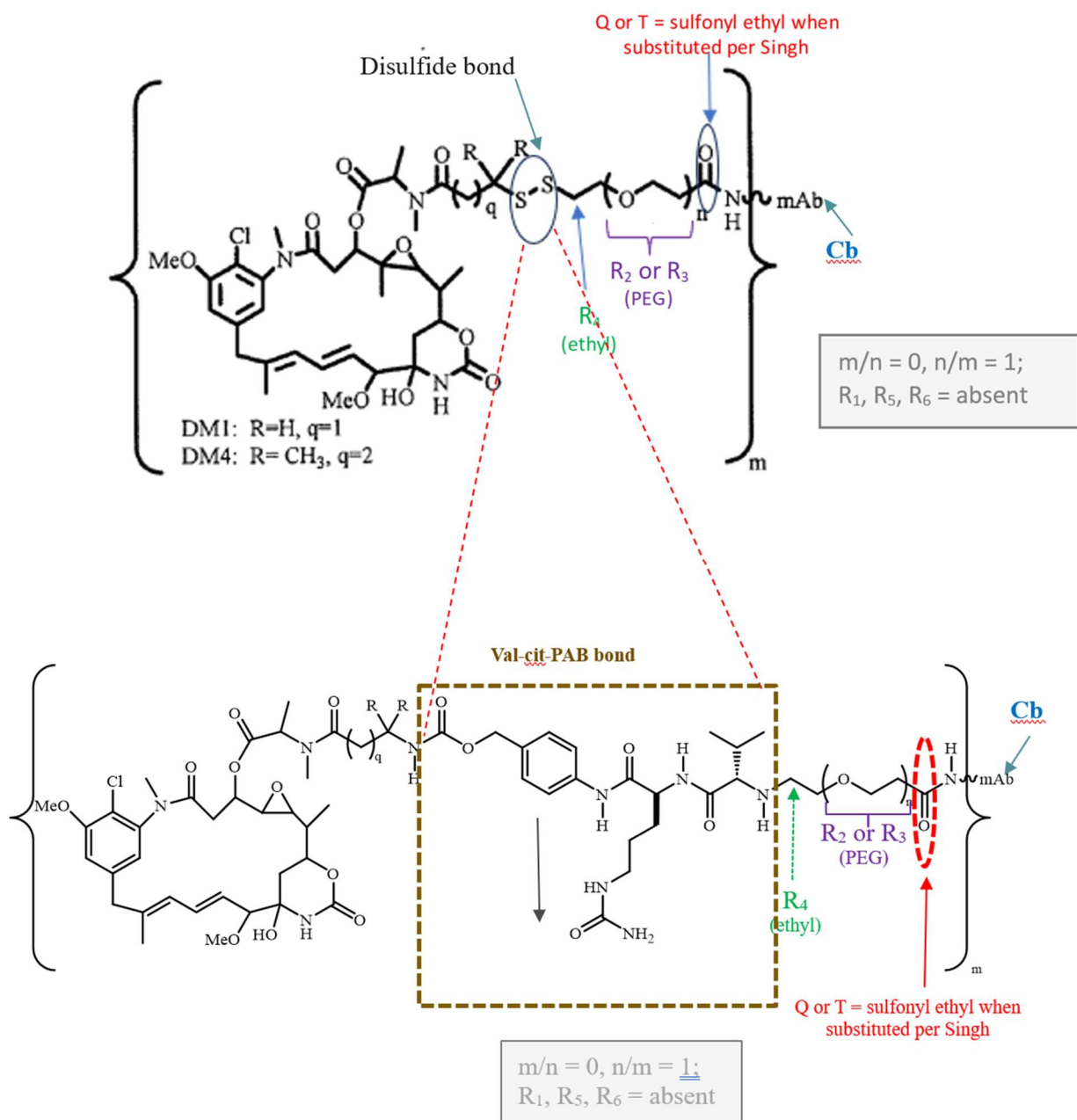
Patent Owner alleges that Petitioner does not explain which starting compound of Singh is being modified, which 'disulfide linkage' is being replaced, and whether the modified compound would still meet all the limitations of claim 9 and 13, including the structural elements of Formula II. POR, 68.

However, Tables C2 and C3 list only a single Singh CBA-drug conjugate having a PEG-containing crosslinker with a cleavable disulfide linkage. Pet., (59) (compound 4), 66 (compound 3⁴). Petition Ground 4 merely proposed modifying

⁴ Petition Table C3 inadvertently contained a numbering error such that Table C2's compound 4 was labeled "3" in Table C3. However, the last entries in Tables C2

Singh's compound 4 by (i) replacing the amide bond forming group (such as N-hydroxysuccinimide) with sulfonyl ethyl (described at Pet. 66) and (ii) substituting the disulfide-drug bond with Bhakta's val-cit-PAB-drug bond satisfies all the limitations of claims 9 and 13, which is depicted below for easier visualization:

and C3 are identical, and this is the only compound that has a disulfide linkage and is the subject of Ground IV.



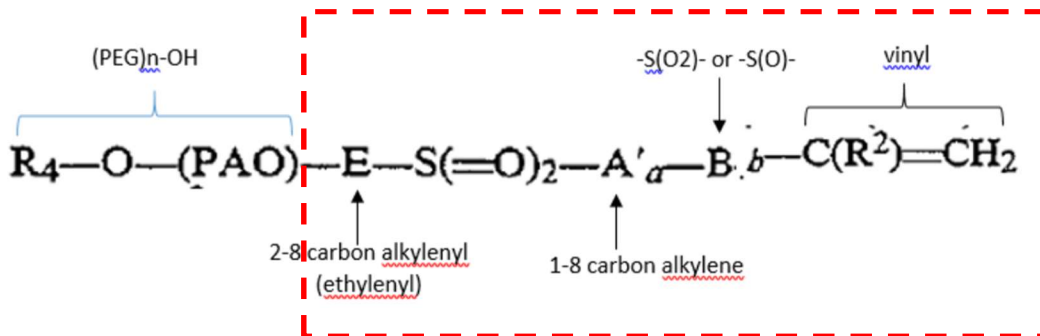
Disulfide linkages and val-cit peptide linkages are functionally equivalent because they are cleavable *in vivo*, thereby permitting drug release from the CBA-drug conjugate. Ex. 1003, ¶¶179-181. Further, cleavage of Bhakta's val-cit-PAB linker by a tumor-associated protease results in specific drug release at target cells.

Id. The Petition set forth the motivation and reasonable expectation of success in making the above substitutions. Pet., 63-67 (sulfonyl substitution), 72 (val-cit substitution).

VII. CHALLENGED CLAIMS 2, 25 AND 32-34 ARE OBVIOUS OVER SINGH IN VIEW OF HARRIS AND SNOW

Patent Owner alleges that the Ground 5 arguments are based on impermissible hindsight (POR, 70), while the Board questioned why the amide groups were included in the substitution of the maleimides (D.I., 71-72).

Snow discloses PEG-vinyl sulfone conjugates such as:



The box above shows that the bis sulfone portion can be *directly* coupled to PEG (i.e., “PAO”) with the “E” group between PEG/PAO and the nearest sulfone.

Snow’s conjugates are reactive with thiols on proteins (Ex. 1010, 9:58-63).

Thus, Snow’s thiol-reactive vinyl bis-sulfone compounds teach direct coupling from the bis-sulfone section to the PEG without any need for amide linkages as found in Singh’s bismaleimide PEG linkers. *E.g.*, Pet. 13, Table A1, Entries 1, 4. The intervening amide linkages were encompassed in the substitution schemes outlined at Petition pages 75-76 because they are a result of the maleimide

attachment, yet are unnecessary when joining sulfone-containing compounds to PEG, as evidenced by Snow connection above where E is merely a 2-8 carbon alkylenyl. Ex. 1076, ¶¶36-39. Nor are the substitutions hindsight, given the known improvement to hydrophilicity from PEG-bis-sulfone compounds, as taught by Harris.

Respectfully submitted,

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CERTIFICATE OF WORD COUNT

The undersigned certifies that the foregoing Reply complies with the requirements of 37 C.F.R. §42.24. Excluding the portions exempted by 37 C.F.R. §42.24(c), the Petition contains **5,555** words as counted by the word processing system used to prepare it.

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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing PETITIONER
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