

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.

Case No. IPR2022-01531
U.S. Patent No. 10,131,682

**Patent Owner's Response
to Petition for *Inter Partes* Review
of U.S. Patent No. 10,131,682**

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EXHIBIT LIST

No.	Exhibit
2001	Declaration of Lawrence Nathan Tumey, Ph.D.
2002	<i>Curriculum vitae</i> of Lawrence Nathan Tumey, Ph.D.
2003	Maeda, H., et al., <i>Polymeric drugs for efficient tumor-targeted drug delivery based on EPR-effect</i> , European Journal of Pharmaceutics and Biopharmaceutics (2009) 71:3, 409-419.
2004	Adair, J.R., et al., <i>Antibody–Drug Conjugates – A Perfect Synergy</i> , Expert Opinion on Biological Therapy (2012) 12:9, 1191-1206
2005	Kovtun, Y.V., et al., <i>Antibody-Maytansinoid Conjugates Designed to Bypass Multidrug Resistance</i> , Cancer Research (2010) 70 (6): 2528–2537.
2006	Goldmacher, V., et al., <i>Antibody–Drug Conjugates: Using Monoclonal Antibodies For Delivery Of Cytotoxic Payloads To Cancer Cells</i> , Therapeutic Delivery (2011) 2:3, 397-416.
2007	Ducry, L., et al., <i>Antibody-Drug Conjugates: Linking Cytotoxic Payloads to Monoclonal Antibodies</i> , Bioconjugate Chemistry (2010) 21:1, 5–13.
2008	Carter P.J., Senter P.D., <i>Antibody-Drug Conjugates for Cancer Therapy</i> , Cancer Journal (2008) 14:3, 154-169.
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2013	Lopez-Jaramillo, F., et al., <i>Vinyl Sulfone: A Multi-Purpose Function in Proteomics</i> , Integrative Proteomics InTech (2012) 16:301-326.
2014	Acchione, M., et al., <i>Impact of Linker and Conjugation Chemistry on Antigen Binding, Fc Receptor Binding and Thermal Stability of Model Antibody-Drug Conjugates</i> , mAbs (2012) 4:3, 362-372.
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2017	Casi, G., <i>Antibody-Drug Conjugates: Basic Concepts, Examples, and Future Perspectives</i> , Journal of Controlled Release (2012) 161:2, 422-428.
2018	Li, L., et al., <i>Vinyl Sulfone Bifunctional Derivatives of DOTA Allow Sulfhydryl- or Amino-Directed Coupling to Antibodies. Conjugates Retain Immunoreactivity and Have Similar Biodistributions</i> , Bioconjugate Chemistry (2002) 13:1, 110–115.
2019	Ballini, R., et al., <i>Conjugate Additions of Nitroalkanes to Electron-Poor Alkenes: Recent Results</i> , Chemical Reviews (2005) 105:3, 933–972.
2020	Gallagher, S., et al., <i>Immunoblotting and Immunodetection</i> , Current Protocols in Cell Biology (2011) 52:6.2.1-6.2.28.
2021	Springer Nature, <i>Citation Details</i> , Retrieved May 24, 2023, from https://citations.springernature.com/item?doi=10.1007/BF00493477
2022	'682 Patent File History, Non-Final Office Action dated August 15, 2017
2023	U.S. Patent No. 5,094,848 (Brixner)

No.	Exhibit
2024	'682 Patent File History, Applicant Remarks and Response to Non-Final Office Action dated August 15, 2017
2025	Non-Final Office Action dated March 8, 2018
2026	WO1997/41897 (Lees)
2027	'682 Patent File History, Applicant Remarks and Response to Non-Final Office Action dated March 8, 2018
2028	'682 Patent File History, Final Office Action dated July 10, 2018
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2030	Widdison, W.C., et al., <i>Semisynthetic Maytansine Analogues for the Targeted Treatment of Cancer</i> , Journal of Medicinal Chemistry (2006) 49:14, 4392-4408.
2031	'682 Patent File History, Applicant Remarks and Response to Final Office Action dated July 10, 2018
2032	'682 Patent File History, Notice of Allowance
2033	'682 Patent Reexamination File History, IDS Form Signed by Examiner on September 10, 2020 Showing List of Considered References
2034	WO2009/134976 (Singh '976)
2035	Drawing by Dr. Ravi Chari in the November 14, 2024 Deposition
2036	Drawing by Dr. Ravi Chari in the November 14, 2024 Deposition
2037	Transcript of the November 14, 2024 Deposition of Dr. Ravi Chari
2038	Declaration of Lawrence Nathan Tumey, Ph.D., in Support of Patent Owner's Response to Petition for <i>Inter Partes</i> Review of U.S. Patent No. 10,131,682
2039	Declaration of June Ann Munford
2040	Appendix to Declaration of June Ann Munford
2041	Springer Nature, <i>Citation Details</i> , Retrieved Dec. 4, 2024, from https://citations.springernature.com/item?doi=10.1007/BF00493477

No.	Exhibit
2042	Dictionary of Science & Technology (2007) at 266.
2043	Encyclopedia of Chemistry (2005) at 113.
2044	McGraw-Hill Dictionary of Scientific and Technical Terms (2003) at 865.
2045	A Dictionary of Science (2010) at 339.

I. INTRODUCTION

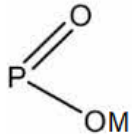
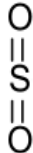
Patent Owner Hangzhou DAC Biotech Co. Ltd. ("DAC") hereby responds to Petitioner SynAffix B.V.'s ("Petitioner") Petition for IPR seeking cancellation of claims 1-17, 20-21, 24-26, and 29-34 of U.S. Patent No. 10,131,682 ("'682 patent," EX1001, EX1002) ("the challenged claims"). The Board should confirm the patentability of the challenged claims because Petitioner has not carried its burden of proving unpatentability of each of the challenged claims.

The challenged claims are directed to linker structures and related therapeutic drug conjugates (such as antibody-drug conjugates (ADCs)) that target specific cell populations (such as cancer cells) to treat diseases (such as cancer). The challenged independent claims fall into three classes based on their recited chemical formulas:

Claim	Structure	Formula
1	$Y-R_1-Q-R_2-T-R_3-R_4-Z$ $\begin{array}{c} \diagup \quad \diagdown \\ R_5 \quad R_6 \end{array}$	I
3, 24, 26	$Cb \left(R_1-Q-R_2-T-R_3-R_4-Drug \right)_q$ $\begin{array}{c} \diagup \quad \diagdown \\ R_5 \quad R_6 \end{array}$	II
20, 29, 30	$Y-R_1-Q-R_2-T-R_3-R_4-Drug$ $\begin{array}{c} \diagup \quad \diagdown \\ R_5 \quad R_6 \end{array}$	IV

The claimed linker structures and conjugates have advantageous hydrophilic properties achieved by incorporating polar phosphorus- or sulfur-based moieties into

the backbone of the linkers—namely, phosphinate, sulfone (also called sulfonyl), or sulfoxide, as shown below and designated as “Q” and “T” in the claimed formulas:

Phosphinate	Sulfone / Sulfonyl	Sulfoxide
		

EX1001, 2:53-4:23. The structural moieties forming the backbone of the linker (such as Q and T) are known in the art as “spacer elements.” EX2038, ¶¶55-58.

Among the three classes of claims, the “Formula I” claims claim hydrophilic linkers that also contain what are known in the art as “conjugation moieties” on each end of the linker that serve different functions, which are designated as “Y” and “Z” in the claimed formula. EX1002, 1:22-2:13 (claim 1); EX2038, ¶¶59-66. The claim language specifically defines “Y” as “a *functional group that enables reaction* of the hydrophilic linker with a *cell-binding agent*” (e.g., an antibody), and “Z” as “a *functional group that enables linkage* of the hydrophilic linker to a *cytotoxic drug*.” EX1002, 1:31-32, 1:40-45.¹

The “Formula IV” claims claim compounds containing the hydrophilic linker conjugated to a “Drug” on one end, with a conjugation moiety “Y” on the other end. EX1002, 4:12-13, 9:64-65, 11:2-3 (claims 20, 29, 30). As in claim 1, the Formula

¹ Emphases are added in this Response unless otherwise specified.

IV claims specifically define “Y” as “a *functional group that enables reaction* of the compound with a *cell-binding agent*” (e.g., an antibody). *Id.*

The “Formula II” claims claim therapeutic conjugates with the hydrophilic linker conjugated to a “Drug” on one end and a *cell-binding agent* or “Cb” on the other end of the linker. EX1002, 2:24-29, 6:40-45, 7:37-42 (claims 3, 24, 26).

As discussed below, the Petition is based on a glaring fallacy—that a vinyl functional group ($\text{CH}_2=\text{CH}-$) can satisfy the “Y” claim element and “enable[] reaction ... with a cell-binding agent.” Petitioner argues that the prior art discloses, teaches, or suggests compounds containing a vinylsulfone group ($\text{CH}_2=\text{CH}-\text{SO}_2-$), and maps vinylsulfone to both the claimed Y conjugation moiety and Q spacer element. Specifically, Petitioner divides the vinylsulfone functional group into two parts: vinyl ($\text{CH}_2=\text{CH}$) and sulfone (SO_2), and then maps only vinyl (without sulfone) onto Y and sulfone onto Q.

But Petitioner's expert (Dr. Ravi Chari) reversed course at deposition from what was written in his declaration accompanying the Petition and fully agreed with Patent Owner DAC and its expert's (Dr. Nathaniel Tumey) position. Specifically, Dr. Chari candidly admitted that: (1) vinyl and vinylsulfone are different functional groups (EX2037, 21:4-16); (2) vinyl alone cannot enable reaction of the compound with a cell-binding agent (*id.*, 20:17-21, 52:5-53:1); and (3) it is, instead, the sulfone part of the vinylsulfone that enables the reaction (*id.*, 21:17-22:9). In Dr. Chari's

unequivocal words when discussing the very prior-art compound that he relies, the “vinyl alone will not react”; “the only reactive group” is vinylsulfone, not vinyl. *Id.*, 52:16-53:1. Vinyl cannot possibly satisfy the claimed “Y” and the Petition fails.

Additionally, Petitioner also fails to show that its allegedly anticipatory prior art, namely, Morales-Sanfrutos and Straus (Ground 1) and Harris (Ground 2), discloses any “*cell-binding agent*” as required by the claims. Each of the challenged claims expressly recites a claim element of “cell-binding agent” that cannot be read out of the claims. Petitioner’s anticipation challenges fail for this additional reason.

Petitioner’s obviousness arguments based on Harris and Singh (Grounds 2-3) and Singh, Harris, and Bhakta or Snow (Grounds 4-5) also fail for additional reasons. Petitioner fails to demonstrate why a POSA would have been motivated to select specific prior-art teachings, and to modify or combine them to arrive at the claimed inventions. Petitioner’s arguments rely on impermissible hindsight to combine cherry-picked portions of broad and general prior-art disclosures, and unsupported and conclusory expert testimony that simply parrots the Petition’s arguments.

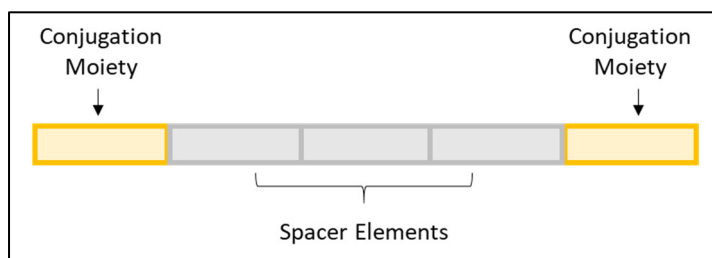
II. TECHNICAL BACKGROUND

Therapeutic drug conjugates, particularly antibody-drug conjugates (ADCs), have been used as drug delivery vehicles for treating cancer. EX2038, ¶¶48-52. These conjugates typically contain three building blocks:

- a targeting domain that can bind a specific cell population (*e.g.*, an antibody targeting and binding cancer cells),
- a therapeutic domain (*e.g.*, a cytotoxic drug), and
- a linker that covalently connects those two domains.

Id., ¶¶53-71. Because the conjugates contain a targeting domain (*e.g.*, an antibody) that recognizes and binds cancer-specific cellular markers, they can selectively target cancer cells and deliver a cytotoxic drug, thereby significantly increasing the efficacy of chemotherapies while minimizing off-site toxicity. *Id.*, ¶¶48-51.

The design of the linker in the conjugate impacts its efficacy; it can affect both the stability of the conjugate in the bloodstream and the efficient release of the drug in targeted cells. EX2038, ¶¶52, 55-71. The linker typically contains discrete components as depicted below. *Id.*, ¶55.



At each end of the linker are “conjugation moieties.” EX2038, ¶¶59-66; EX2010, 13.² Conjugation moieties are chemical functional groups that enable reaction with and/or linkage to the targeting domain (*e.g.*, an antibody) on one end

² EX2039, ¶¶36-39.

of the linker and the therapeutic domain (e.g., a cytotoxic drug) on the other end of the linker. EX2038, ¶¶59-66; EX2012, 523.³ As Dr. Chari admitted at deposition, enabling “linkage” and enabling “reaction” are two different requirements of the two different “Z” and “Y” conjugation moieties claimed in the '682 patent, respectively. EX2037, 16:20-18:14. As Dr. Chari admitted, linkage means “just to connect the link together You could say it's a covalent bond.” *Id.*, 15:18-16:3. Dr. Chari further admitted that a reaction, on the other hand, is the “the process to get that connection together.” *Id.*, 33:6-17; *see also id.*, 17:23-18:9.

Thus, as Dr. Tumey explains, while vinyl can serve as “Z” to enable linkage (consistent with the '682 patent prosecution history), vinyl cannot similarly serve as “Y” to enable reaction (as admitted by Dr. Chari). EX2038, ¶¶63-66, 72-76; EX2012, 488-489, 491; EX2013, 303-307⁴; EX2019, 933⁵. To drive the reactions, a conjugation moiety must have certain *functional properties*, such as specific electrophilic (electron accepting) reactivity to react with an antibody with specific nucleophilic (electron donor) moieties. EX2038, ¶¶59, 72-76. Absent the specific functional properties of the conjugation moiety, the linker will not react with the

³ EX2039, ¶¶44-47.

⁴ EX2039, ¶¶48-52.

⁵ EX2039, ¶¶73-76.

antibody. *Id.*

In between the conjugation moieties are “spacer elements.” EX2038, ¶¶55, 67-71; EX2011, 277.⁶ Spacer elements can affect the properties of the conjugate. For example, spacer elements can impart stability or solubility to the antibody-drug conjugate, as well as offset steric effects that arise from bulky antibody and drug components. EX2038, ¶¶67-71; EX2012, 523.

III. THE '682 PATENT

The '682 patent, titled “Hydrophilic Linkers and Their Uses for Conjugation of Drugs to Cell Binding Molecules,” issued on November 20, 2018, with twenty-one claims. EX1001. After *ex parte* reexamination, on January 4, 2021, the USPTO issued a reexamination certificate that amended independent claims 1, 3, 18, and 20, and added claims 22-34. EX1002. The '682 patent is entitled to a priority filing date of November 24, 2012, which Petitioner does not dispute. Pet. 19.

A. Challenged Claims

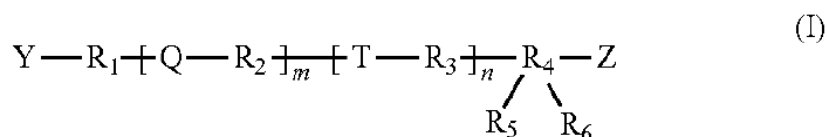
The challenged claims, as amended by the reexamination certificate, are reproduced in **Appendix A** of DAC's expert's declaration (EX2038). *See* EX1001, 48:31-55:29; EX1002, 1:16-12:40. The independent claims claim three classes of structures, Formulas I, II, and IV, shown below. EX2038, ¶¶106-111.

⁶ EX2039, ¶¶40-43.

Claim	Structure	Formula
1	$Y-R_1-Q-R_2-\text{---}_m-T-R_3-\text{---}_n-R_4-Z$ $\begin{array}{c} \diagup \quad \diagdown \\ R_5 \quad R_6 \end{array}$	I
3, 24, 26	$Cb-\left(R_1-Q-R_2-\text{---}_m-T-R_3-\text{---}_n-R_4-\text{Drug}\right)_q$ $\begin{array}{c} \diagup \quad \diagdown \\ R_5 \quad R_6 \end{array}$	II
20, 29, 30	$Y-R_1-Q-R_2-\text{---}_m-T-R_3-\text{---}_n-R_4-\text{Drug}$ $\begin{array}{c} \diagup \quad \diagdown \\ R_5 \quad R_6 \end{array}$	IV

Claim 1 is representative and reproduced below in pertinent part:

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;

The other independent claims are directed to structures of Formulas II and IV, wherein the linker is conjugated to a drug on one end and with “Y” on the other end (Formula IV: claims 20, 29, 30), or the linker is conjugated to a cell-binding agent and a drug (Formula II: claims 3, 24, 26).⁷

Notably, the claims define the conjugation moieties of the linker, Y and Z, by their *function*, with Y defined as “a *functional group* that *enables reaction with*” a cell-binding agent, and Z defined as “a *functional group* that *enables linkage to*” a cytotoxic drug. EX2038, ¶¶108-111; *see supra* at 3-4, 6 (Dr. Chari’s testimony regarding Y and Z). In contrast, other claimed elements, such as the spacer elements of the linker, Q, T, and R₁ through R₆, are defined by their structure, for example, with Q and T defined as –P(=O)(OM)–, –S(O₂)–, or –S(O)–. EX2038, ¶111.

The challenged dependent claims further specify the conjugation moiety Z (claim 2), the drug (claims 4-5, 8, 10, 14, 21), the cell-binding agent (claims 6-7), spacer elements (claims 25, 31-34), additional structural elements (claims 9, 12), or

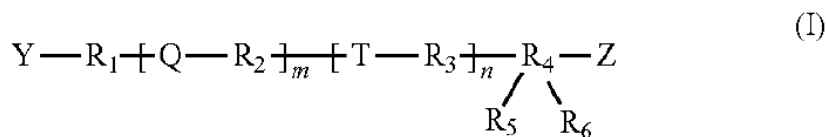
⁷ As to the challenged dependent claims: claim 2 depends from claim 1; claims 4-17 and 33 depend from claim 3; claims 21 and 34 depend from claim 20; claim 25 depends from claim 24; and claims 31-32 depend from claim 30.

the properties of the conjugate (claims 11, 13); dependent claims 15-17 are directed to pharmaceutical compositions comprising the claimed conjugate. EX2038, ¶112.

B. Specification

The '682 patent specification describes targeting and treating specific cell populations, such as cancer cells, using a selective cell-binding agent, such as an antibody, covalently conjugated to a therapeutic drug. *See, e.g.*, EX1001, 1:19-2:3 (discussing, *e.g.*, “[t]issue-selective drug delivery” and “selective permeation” of anticancer agents into tumor), 2:53-67; EX2038, ¶¶113-126. The specification describes prior attempts to achieve this goal through antibody-drug conjugates in which the antibody is conjugated to the drug via a linker. EX1001, 2:4-44. The specification observes that the “nature of the linker significantly affects the potency, selectivity and the pharmacokinetics of the resulting conjugates,” *id.*, 1:53-61, and states that the '682 patent's novel linkers address those concerns and the conjugates containing those linkers have advantageous properties. *Id.*, 2:45-67; EX2038, ¶¶115-116.

The components of the novel linkers of the '682 patent are distinct and serve different purposes; they are not interchangeable or overlapping. EX2038, ¶¶117-123. For example, in the hydrophilic linker of Formula I,



“Y” and “Z” are conjugation moieties, with the specification describing Y as a “*functional group*” that “*enables reaction*” of the linker with a “cell-binding agent,” such as an antibody (the targeting domain), and Z as a “*functional group*” that “*enables linkage*” of the linker to a “cytotoxic drug” (the therapeutic domain). EX1001, 3:11-23; 8:21-33; *id.*, 8:61-9:7, 13:51-63 (providing examples of the Y and Z functional groups); EX2038, ¶118. As in the claims, the specification defines the Y and Z functional groups in terms of their *function*, as a functional group that enables reaction or linkage. *Id.*

As in the claims, the specification defines the intervening structural elements between “Y” and “Z” in terms of their specific *structures*. EX2038, ¶119. For example, the specification describes “Q” and “T” as phosphinate, sulfonyl, and/or sulfoxide groups. EX1001, 2:53-55, 3:14-15, 8:23-24. R₁, R₂, R₃, R₄, R₅, and R₆ are likewise described in terms of structures. *Id.*, 3:24-43, 8:34-58. A POSA would have recognized that these intervening elements—known as “spacer elements”—are separate and distinct from the Y and Z conjugation moieties and serve different roles in the linker than the conjugation moieties. EX2038, ¶¶117-124.

The '682 patent describes the benefits of using the specific spacer elements Q

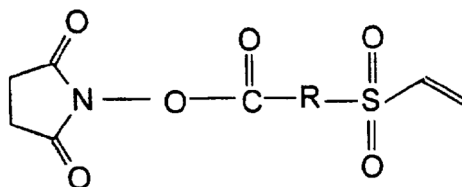
and T—“phosphinate, sulfonyl, and/or sulfoxide groups”—in therapeutic linkers. EX1001, 2:53-67. When combined with other components of the conjugates, these hydrophilic linkers advantageously “reduc[e] the aggregation of the conjugates,” “result[] in higher potency,” and allow the drug to be “retained inside the target cell after the drug-linker released from the conjugates.” *Id.*; EX2038, ¶116.

To this end, the '682 patent teaches “cell-binding agents” that are used to modify specific populations of cells (*e.g.*, targeting cancer cells using antibody-drug conjugates). EX1001, 14:38-15:32. The patent specifically defines a “***cell-binding agent***” as a “molecule that binds to, complexes with or reacts with a moiety of ***a cell population sought to be therapeutically or otherwise biologically modified.***” *Id.*, 14:42-44; EX2038, ¶¶125-126. Dr. Chari agreed at deposition that this definition is provided in the patent. EX2037, 51:24-52:4. Cell-binding agents include large molecular-weight proteins such as, *e.g.*, full length antibodies (polyclonal antibodies, monoclonal antibodies, dimers, multimers, multi-specific antibodies), single chain antibodies, and antibody fragments that selectively target and bind a specific cell surface antigen. EX1001, 14:45-15:32. Accordingly, a POSA reading the '682 patent would recognize that the cell-binding agent is intended to target (modify) a particular cell population (*e.g.*, an antibody binding a cell-specific antigen for that particular cell population). EX2038, ¶¶125-126. In other words, the claimed “cell-binding agent” does not indiscriminately bind cell populations that are not

targeted to be therapeutically or biologically modified, as this would undermine the purpose of the linker (and the conjugate). *Id.*

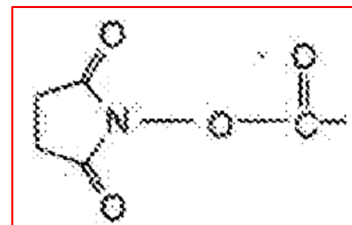
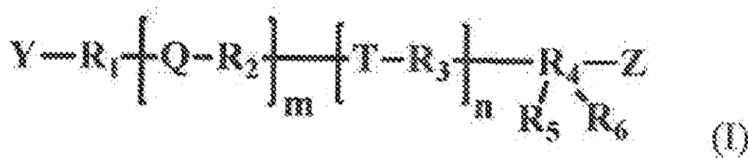
C. Prosecution History

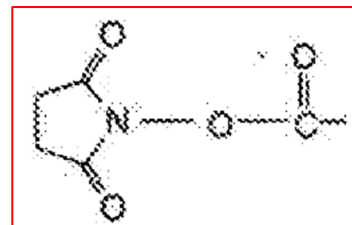
In an office action dated March 8, 2018, the Examiner rejected the then-pending claim 1 as allegedly anticipated by WO1997/041897 (“Lees”) (EX2026). EX1018, 42-43; EX2038, ¶¶128-133. Lees discloses the following structure with N-hydroxysuccinimide (NHS) ester on one end and vinylsulfone on the other end:



EX2026, 22. The Examiner stated that in the above structure “*the NHS portion represents a functional group that enables reaction* of the linker with a cell binding agent, and *the vinyl group enables linkage* of the linker to a cytotoxic drug” EX1018, 42-43. Thus, the Examiner mapped the *entire* reactive NHS ester group to “Y”, a “functional group that enables reaction ... with a cell binding agent,” and the vinyl group to “Z,” a functional group that “enables linkage ... to a cytotoxic drug.” *Id.*; EX2038, ¶129.

In response, the Applicant amended claim 1, including adding the limitation that “when Q or T is -S(O₂)-, m and n are not 0.” EX1018, 45. The Applicant observed that the Examiner mapped the above structure of Lees “to

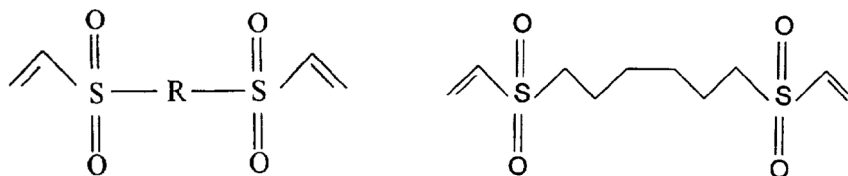


recited in claim 1 of the present application, where *Y* is , *Q* (or *T*) is -S(O₂)-, *m* (or *n*) is 1, *n* (or *m*) is 0, *R*₂(*R*₃) and *R*₄-*R*₆ are absent, and *Z* is .” EX1018, 62 (red box added for emphasis). The Applicant noted that “claim 1 of the present application recites that when *Q* or *T* is -S(O₂)-, *m* and *n* are not 0, thereby excluding the above noted compound described in Lees.” *Id.*

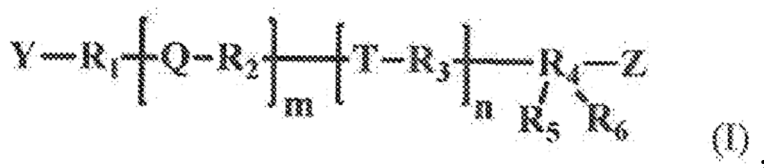
The Applicant thus restated the Examiner's mapping of *Z* to vinyl, and *Y* to the reactive NHS ester. EX2038, ¶¶130-131. The Applicant expressly mapped *Y* to the ***entire NHS ester*** (highlighted above in red box), making clear that *Y* correlates to the entire reactive functional group, not just the NHS moiety without the ester. *Id.* ***Neither the Examiner nor the Applicant mapped “Y” to only vinyl*** without the adjacent sulfone. *Id.* This is consistent with the specification's disclosure of figures including vinyl alone as *Z*. See EX1001. No figure in the specification discloses vinyl alone as *Y*.

Moreover, if *Y* could be mapped to vinyl only, the claim amendment requiring that “when *Q* or *T* is -S(O₂)-, *m* and *n* are not 0” would be insufficient to overcome

Lees. EX2038, ¶132. Specifically, Lees prominently discloses the following structures on the pages immediately preceding the page cited by the Examiner:



EX2026, 20-21. *If* (assuming) both Y and Z can be vinyl only without sulfone, then each of the above two structures of Lees would map to Formula I to anticipate the amended claim 1:



where Y and Z are each vinyl only, Q and T are each sulfone, m and n are 1 (not 0), R₁ and R₃-R₆ are absent, and R₂ is “R” or the C₆-alkylene linker in the above structures of Lees. EX2038, ¶132; EX2026, 20-21.

Therefore, the prosecution history shows the Examiner and the Applicant both understood that, unlike Z, “Y” by itself is a reactive “functional group that enables reaction of the hydrophilic linker with a cell-binding agent.” EX2038, ¶133; *see supra* at 3-4, 6 (Dr. Chari’s testimony regarding the same distinction).

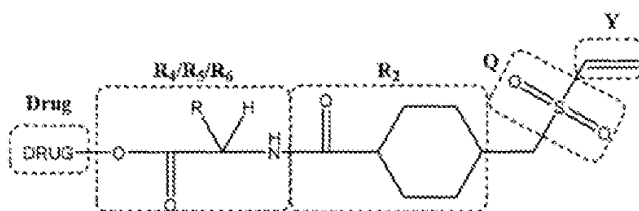
D. Reexamination

In 2019, a third party filed a reexamination request, raising numerous prior-

art-based challenges. After a thorough reexamination involving multiple office actions, in January 2021, the USPTO issued a reexamination certificate that amended claims 1, 3, 18, and 20 and added claims 22-34. EX1002.

During reexamination, in response to a lengthy office action (EX1019, 1-44; *id.*, 45-81), the patentee commented on a rejection against **claim 3** as follows:

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



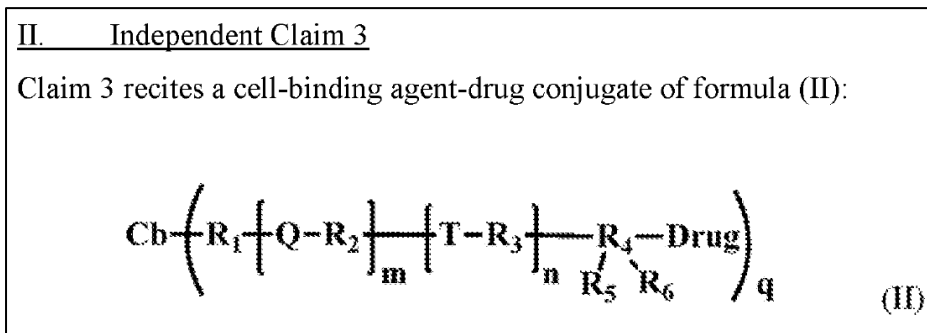
It is clear that in the above formula, the portion ***allegedly corresponding*** to R₂ in formula (II) of claim 3 of the present patent contains a cyclic structure. On the other hand, R₂ as defined in claim 3 of the present patent as amended does not encompass a cyclic structure.

For at least this reason, the above compound of US '053 does not meet all the requirements for formula (II) of claim 3 of the present patent.

EX1019, 72-73. Thus, in those remarks, the patentee pointed to the lack of clarity of the rejection and “presumed” that “[t]he Examiner ... intended” to describe a certain structure, without agreeing with the Examiner’s “alleged[]” mapping of that

presumed structure; and the patentee noted one of the reasons why the rejection fails, specifically stating that “[f]or at least this reason,” the prior art “does not meet all the requirements” of the claim. *Id.*; EX2038, ¶¶134-136.

Importantly, this rejection was directed to independent **claim 3**, reciting Formula II that does not even include any “Y” functional group:



EX1019, 68; EX2038, ¶135. This vague and ambiguous prosecution history relating to claim 3 does not disclaim or otherwise alter the claim language’s clear definition of “Y” recited in independent claims 1, 20, 29, and 30. EX2038, ¶¶135-136.

IV. PERSON OF ORDINARY SKILL IN THE ART

Solely for purposes of this IPR, DAC adopts Petitioner’s POSA. Pet. 18-19.

V. CLAIM CONSTRUCTION

In the Petition, Petitioner stated that it “does not currently believe that any claim terms require construction for purposes of deciding this Petition.” Pet. 24. After DAC filed its Preliminary Response (Paper 9), however, Petitioner disputed DAC’s proposed constructions and the parties exchanged briefing (Papers 11, 14-

16, 18, 22). After the Board initially denied institution, a Delegated Rehearing Panel (“DRP”) granted rehearing and the Board subsequently instituted review (Papers 23, 25). DAC believes that the following terms of the ’682 patent claims warrant construction:

- “Y represents a functional group that enables reaction ...” (claims 1, 20, 29, 30, and dependent claims); and
- “cell-binding agent” (all claims).

A. Legal Standard

Claim terms “are generally given their ordinary and customary meaning,” which “is the meaning that the term would have to a [POSA] at the time of the invention.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (en banc) (quotes and citation omitted). “[T]he claim construction inquiry ... begins and ends in all cases with the actual words of the claim.” *Renishaw PLC v. Marposs Societa’ per Azioni*, 158 F.3d 1243, 1248 (Fed. Cir. 1998). “[T]he claims themselves provide substantial guidance as to the meaning of particular claim terms,” *Phillips*, 415 F.3d at 1314, while the specification “is the single best guide to the meaning of a disputed term,” “informed, as needed, by the prosecution history,” *id.* at 1315 (quotes and citation omitted).

“There are *only two* exceptions to [the] general rule” that claim terms “are generally given their ordinary and customary meaning as understood by a [POSA]

when read in the context of the specification and prosecution history”: “1) when a patentee sets out a definition and acts as his own lexicographer, or 2) when the patentee disavows the full scope of a claim term either in the specification or during prosecution.” *Thorner v. Sony Comput. Entm’t Am. LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012).

The Board may also consider extrinsic evidence—*i.e.*, “evidence external to the patent and prosecution history,” but extrinsic evidence is “less significant than the intrinsic record.” *Phillips*, 415 F.3d at 1317 (quotes and citation omitted).

B. “Y represents a functional group that enables reaction ...” (claims 1, 20, 29-30, and dependent claims)

The dispute on the construction of “Y” turns on whether the claimed “Y” must by itself be *a functional group that independently enables reaction* with a cell-binding agent. As discussed below, the plain claim language requires that “Y” alone “represents *a functional group that enables reaction ...*,” meaning that it is “Y” that enables the reaction, not the combination of Y with some other claim elements such as Q or T as Petitioner contends. Nothing in the patent’s specification or prosecution history clearly and unmistakably disclaims that plain meaning of the claim language.

1. The claims themselves support DAC’s construction.

Claim construction “must begin and remain centered on the language of the

claims themselves.” *Brookhill-Wilk 1, LLC v. Intuitive Surgical, Inc.*, 334 F.3d 1294, 1298 (Fed. Cir. 2003) (quotes and citation omitted). Here, the claims that recite “Y” each expressly define “Y” as “a **functional group that enables reaction**” of the hydrophilic linker (claim 1), or the compound (claims 20, 29, 30), with a cell-binding agent, without referring to any other claim element to enable that reaction. EX1002, 1:31-32, 4:12-13, 9:64-65, 11:2-3. The claim language thus requires that Y itself be a functional group that independently enables the reaction with a cell-binding agent. EX2038, ¶¶138-141. A functional group that is unable to enable that reaction would not satisfy the claims’ requirement of “Y”. *Id.* Petitioner’s expert agrees. Dr. Chari testified that whereas “[t]he Y variable ... is defined as a functional group that enables reaction of the hydrophilic linker with a cell-binding agent,” the Q variable is “defined and are selected from -P(=O)(OM)-, or -S(O₂)-, or -S(O)-.” EX1003, ¶¶25-26.

In addition to the plain meaning of the “Y” claim term, “the context in which [that] term is used” in the claims is also “highly instructive.” *Phillips*, 415 F.3d at 1314. The claimed Formulas I and IV each depict Y at one end of the linker, adjacent to “R₁” that can be absent or a non-reactive alkyl group, among others, which is in turn adjacent to “Q” (or “T”, if Q and R₂ are both absent).

Formula I	Formula IV
$Y-R_1-Q-R_2-T-R_3-R_4-Z$ $\begin{array}{c} \diagup \quad \diagdown \\ R_5 \quad R_6 \end{array}$	$Y-R_1-Q-R_2-T-R_3-R_4-\text{Drug}$ $\begin{array}{c} \diagup \quad \diagdown \\ R_5 \quad R_6 \end{array}$

As discussed above in Section III, the claims recite the spacer elements of the claimed linkers, including R₁, Q, R₂, and T, as separate and distinct elements from the Y conjugation moiety. EX2038, ¶111. For example, the claims do not recite that Y and Q (or T) together “enables reaction” with a cell-binding agent; rather, the claims define Q and T structurally as phosphinate, sulfonyl, or sulfoxide; and define Y functionally as a “functional group” that “enables reaction” with a cell-binding agent. EX1002, 1:22-34, 4:3-15, 9:55-67, 10:60-11:5; EX2038, ¶¶139-140. The claims also recite an optional intervening structure, “R₁”, located between and physically separating Y from Q (and T). EX2038, ¶141. Thus, Q is not always directly adjacent to Y and, in the presence of an R₁ group that can be a non-reactive alkyl group, any effect of Q on Y would be eliminated. *Id.*

“Where a claim lists elements separately, ‘the clear implication of the claim language’ is that those elements are ‘distinct component[s]’ of the patented invention.” *Becton, Dickinson & Co. v. Tyco Healthcare Grp., LP*, 616 F.3d 1249, 1254 (Fed. Cir. 2010) (quoting *Gaus v. Conair Corp.*, 363 F.3d 1284, 1288 (Fed. Cir. 2004)). Here, the claims themselves make clear that the claimed “Y” element is a distinct and separate component from the other recited components, including

“Q” and “T”, of the claimed formulas, and that Y, not Q or T, is the claimed “functional group that enables reaction” with a cell-binding agent. EX2038, ¶¶138-141.

2. The specification supports DAC's construction.

DAC's construction is also supported by the specification. As in the claims, the specification consistently and repeatedly defines Y as “a functional group that enables reaction” with a cell-binding agent. EX1001, 3:12-13, 4:14-15, 8:21-22. The specification describes the Y functional group as specifically attracted to and independently reactive with certain chemical groups present in a cell-binding agent and provides examples of reactive functional groups as Y. *Id.*, 8:61-67, 13:51-63, 14:8-10; EX2038, ¶¶142-144. For example, the specification states that “cell-binding agents bearing an amino or hydroxyl substituent can react with cross linkers bearing *an N-hydroxysuccinimide (NHS) ester*, cell-binding agents bearing a thiol substituent can react with cross linkers bearing *a maleimido or haloacetyl group*,” and “cell-binding agents bearing a carbonyl substituent can react with cross linkers bearing *a hydrazide or a hydroxylamine*,” EX1001, 13:54-60, and that a POSA “can readily determine which linker to use based on the known *reactivity* of the available functional group on the cell-binding agent,” *id.*, 13:61-63.

Nothing in the specification redefines or alters the plain meaning of the claims requiring that “Y” by itself be a functional group that independently enables reaction

with a cell-binding agent. *Thorner*, 669 F.3d at 1365-66; *Phillips*, 415 F.3d at 1316. And none of the compounds from the patent's figures relied upon by the Board in instituting review had vinyl alone as Y. Paper 25 at 6-7. The vinyl alone is Z, as it is linked to a drug, not reacted with a cell-binding agent.

3. The prosecution history supports DAC's construction.

DAC's construction is also consistent with the prosecution history. A party "seeking to invoke prosecution history disclaimer bears the burden of proving the existence of a *clear and unmistakable* disclaimer" *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1063-64 (Fed. Cir. 2016) (quotations and citation omitted).

There is no clear and unmistakable prosecution disclaimer of the "Y" term. As discussed in Section III.C, when describing the rejection over Lees, the Examiner and the Applicant mapped "Z" to vinyl, but *never mapped "Y" to vinyl*. EX1018, 42-43, 62. Rather, consistent with the claims' requirement that Y be "a functional group that enables reaction" with a cell-binding agent, the Examiner and the Applicant mapped the entire reactive NHS ester group to Y. *Id.*; EX2038, ¶145.

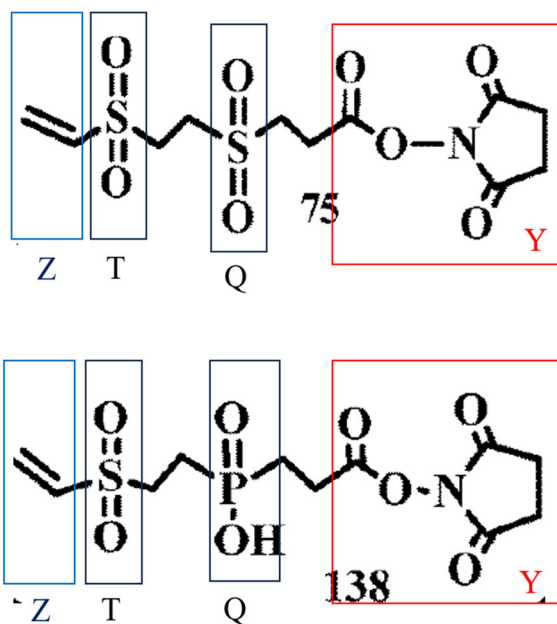
The mapping of vinyl to "Z" does not disclaim or alter the meaning of "Y", a distinctly different claim term. EX2038, ¶¶145-146. Here, the claims use different words to define Y and Z: Y is "a functional group that enables *reaction*" of the linker "*with a cell-binding agent*," whereas Z is "a functional group that enables *linkage*" of the linker "*to a cytotoxic drug*" via certain chemical bonds. EX1002,

1:31-32, 1:40-45. And the specification describes “Y” and “Z” differently, never equating the two different functional groups. *Compare* EX1001, 8:61-67, *with id.*, 9:1-7; EX2038, ¶146; EX2037, 15:23-16:3, 22:4-9, 33:6-14 (Dr. Chari confirming the different meanings of “linkage” and “reaction”). “Different claim terms are presumed to have different meanings.” *Bd. of Regents of Univ. of Texas Sys. v. BENQ Am. Corp.*, 533 F.3d 1362, 1371 (Fed. Cir. 2008) (citing *CAE Screenplates Inc. v. Heinrich Fiedler GmbH & Co.*, 224 F.3d 1308, 1317 (Fed. Cir. 2000)). The mapping of vinyl to only “Z”, not to the different claim term “Y”, is not a clear and unmistakable disclaimer of the meaning of “Y”.

As also discussed in Section III.C, allowing Y to be mapped to only vinyl of a vinylsulfone, without sulfone, would render claim 1 anticipated by two other compounds expressly disclosed in Lees. EX2038, ¶132. Petitioner's construction of “Y”—where vinyl alone may be mapped to Y—would improperly construe the claims “as encompassing the prior art that was ... disclaimed during prosecution.” *Kinik Co. v. Int'l Trade Comm'n*, 362 F.3d 1359, 1365 (Fed. Cir. 2004).

DAC's construction does not exclude the disclosed embodiments of the '682 patent. EX2038, ¶¶147-148. For example, during prosecution, the Applicant cited disclosed Examples, including Examples 75 and 138, as support for the amendments of claim 1. EX1018, 59. As illustrated below, under DAC's construction of “Y” to require a functional group that independently enables reaction with a cell-binding

agent (an NHS ester highlighted in red box below), and the Examiner's mapping of vinyl to "Z" (highlighted in blue box below), claim 1 covers both Examples 75 and 138. EX2038, ¶147.



Additionally, Examples 55, 99, and 119 all have a vinyl as the Z, and an NHS ester as the Y.⁸ EX2038, ¶148.

Petitioner also cites a rejection of independent *claim 3* to support its flawed construction of "Y". Paper 18 at 12. As discussed in Section III.D, however, unlike claim 1, claim 3 does not even recite nor require "Y", and the patentee's remarks

⁸ Examples 55 and 99, each with a vinylsulfone on the left and an NHS ester on the right, without an additional sulfone in the linker, are not covered by claim 1. EX2038, ¶148.

regarding the rejection of claim 3—including the “presumed” structure that the Examiner might have “intended” when rejecting claim 3 that does not recite “Y”—were at best ambiguous. EX2038, ¶¶134-136, 149. Where, as here, the alleged prosecution disclaimer is “ambiguous” or “amenable to multiple reasonable interpretations,” courts have consistently “declined to apply the doctrine of prosecution disclaimer.” *Omega Eng’g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1324-25 (Fed. Cir. 2003) (“[W]e have thus consistently rejected prosecution statements too vague or ambiguous to qualify as a disavowal of claim scope.”); *Core Wireless Licensing S.A.R.L. v. LG Elecs., Inc.*, 880 F.3d 1356, 1367 (Fed. Cir. 2018); *Avid Tech., Inc. v. Harmonic, Inc.*, 812 F.3d 1040, 1045-46 (Fed. Cir. 2016).

4. The extrinsic evidence supports DAC’s construction.

The extrinsic evidence, including the testimony of Petitioner’s expert, further supports DAC’s construction. During deposition, Dr. Chari agreed to a definition of “functional group” as “a specific identifiable group of atoms within a molecule that directly contributes to its characteristic chemical properties and reactivity.” EX2037, 10:5-11. Contemporaneous technical dictionaries⁹ provide similar definitions of “functional group” (EX2038, ¶¶150-151):

⁹ EX2039, ¶¶88-101.

- EX2042: “[A] group of atoms that reacts as a single unit and determines the properties and structure of a class of chemicals.”
- EX2043: “The functional group is an atom (or a group of atoms) that has similar chemical properties whenever it occurs in different compounds. It defines the characteristic physical and chemical properties of families of organic compounds.”
- EX2044: “An atom or group of atoms, acting as a unit, that has replaced a hydrogen atom in a hydrocarbon molecule and whose presence imparts characteristic properties to this molecule.”
- EX2045: “The group of atoms responsible for the characteristic reactions of a compound.”

Therefore, a POSA would understand that, as a “functional group that enables reaction” with a cell-binding agent, “Y” itself as a single unit must be capable of and responsible for the recited reaction. EX2038, ¶151. As Dr. Chari admitted, a POSA would understand, for example, vinyl and vinylsulfone are different functional groups with different properties, and vinylsulfone is “much more reactive” than vinyl. EX2037, 19:15-17, 21:11-16. As Dr. Chari unequivocally testified, vinyl “won’t react by itself” because it is “not reactive,” and “you need” the “sulfone” moiety to “activate the vinyl sulfone” to “enable[e] the reaction” because “vinyl alone will not react.” *Id.*, 19:18-21:3, 21:17-22:9, 52:16-53:1. Dr. Chari also consistently identified the more reactive vinylsulfone, not just vinyl alone, as the “Y” functional group. *Id.*, 48:6-49:12, 52:5-53:1. The extrinsic evidence thus

convincingly demonstrates that DAC's proposed construction of the "Y" claim term is the correct construction. EX2038, ¶¶150-152.

C. "cell-binding agent" (all claims)

In the Institution Decision, the Board adopted DAC's proposed construction of "cell-binding agent" as "[a] molecule that binds to, complexes with or reacts with a moiety of a cell population sought to be therapeutically or otherwise biologically modified." Paper 25 at 20-21. The Board should maintain that construction.

Lexicography governs the interpretation of "cell-binding agent" and this term should be construed as the patentee defined it in the specification: a "molecule that binds to, complexes with or reacts with a moiety *of a cell population sought to be therapeutically or otherwise biologically modified.*" EX1001, 14:39-44; EX2038, ¶¶153-157; EX2037, 51:24-52:4. The inventor described the "cell-binding agent" based on its ability to interact with specific cell-associated molecules (*e.g.*, "a moiety of a cell population") that are intended to be targeted with the claimed conjugates (*e.g.*, "sought to be therapeutically or otherwise biologically modified"). EX1001, 14:43-44; *id.* 14:45-15:32 (listing "large molecular weight proteins" and other biological and chemical molecules, preferably monoclonal antibodies). The inventor's definition should be given effect. *Phillips*, 415 F.3d at 1316.

Claims must be interpreted in light of the specification and doing otherwise results in interpreting the term "cell-binding agent" in a manner divorced from the

specification. *Phillips*, 415 F.3d at 1324. Here, the specification specifies that the cell-binding agent-drug conjugates of the “present invention” target specific cell populations including for therapeutic purposes. EX1001, 14:39-44 (“cell-binding molecule that comprises the conjugates and the modified ***cell-binding agents of the present invention***”); 1:7-9 (“The ***present invention*** relates to the preparation of novel hydrophilic linkers used for the conjugation of a drug, in particular, a cytotoxic agent to a biological molecule”). “When a patent ... describes the features of the ‘present invention’ as a whole, this description limits the scope of the invention.” *Verizon Servs. Corp. v. Vonage Holdings Corp.*, 503 F.3d 1295, 1308 (Fed. Cir. 2007).

Accordingly, a “cell-binding agent” should not be interpreted, as Petitioner suggests, to encompass any molecule that could potentially bind to cells under highly artificial conditions, such as those used in Straus. EX2038, ¶¶156-157. As discussed below in Section VI.A, Straus discloses “unusual binding sites” on cells that were previously dried and chemically treated with cold methanol, for an enzyme (HRP) that is used in the art as a reporter and ***not once*** as a cell-targeting agent as contemplated by the ’682 Patent. EX2038, ¶¶82-85, 157. Petitioner’s broad interpretation of “cell-binding agent” untethered to the patent’s definition effectively reduce the “cell-binding agent” to a moiety that is not used to target cell populations, contrary to the inventor’s definition of this term in the ’682 patent. *Id.*, ¶157.

VI. PETITIONER FAILS TO PROVE UNPATENTABILITY

Each of Petitioner's Grounds fails to prove unpatentability. Pet. 3.

A. **Ground 1: Petitioner Fails to Show Morales-Sanfrutos and Straus Anticipate Claims 1-3, 6, 24-25, and 33.**

To prove anticipation, Petitioner must demonstrate that “the four corners of a *single*, prior art document describe *every* element of the claimed invention” as “*arranged or combined in the same way* as in the claim.” *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369-70 (Fed. Cir. 2008). Petitioner's Ground 1 fails.

First, Petitioner's arguments are based on its flawed construction of “Y” that allows it to map vinyl alone to Y. As Petitioner's expert admitted, vinyl does not (and cannot) enable reaction of the linker with a cell-binding agent.

Second, as a separate and independent reason why Ground 1 fails, Morales-Sanfrutos does not disclose any cell-binding agent, a claim element recited by all the challenged claims. Petitioner attempts to incorporate alleged teachings of Straus to fill that fatal gap of Morales-Sanfrutos. But such reliance on a second reference is improper as a matter of law. Moreover, even assuming Petitioner may rely on Straus, Straus does not demonstrate that the modified HRP of Morales-Sanfrutos is a cell-binding agent, under *either* Petitioner's *or* DAC's construction of that term.

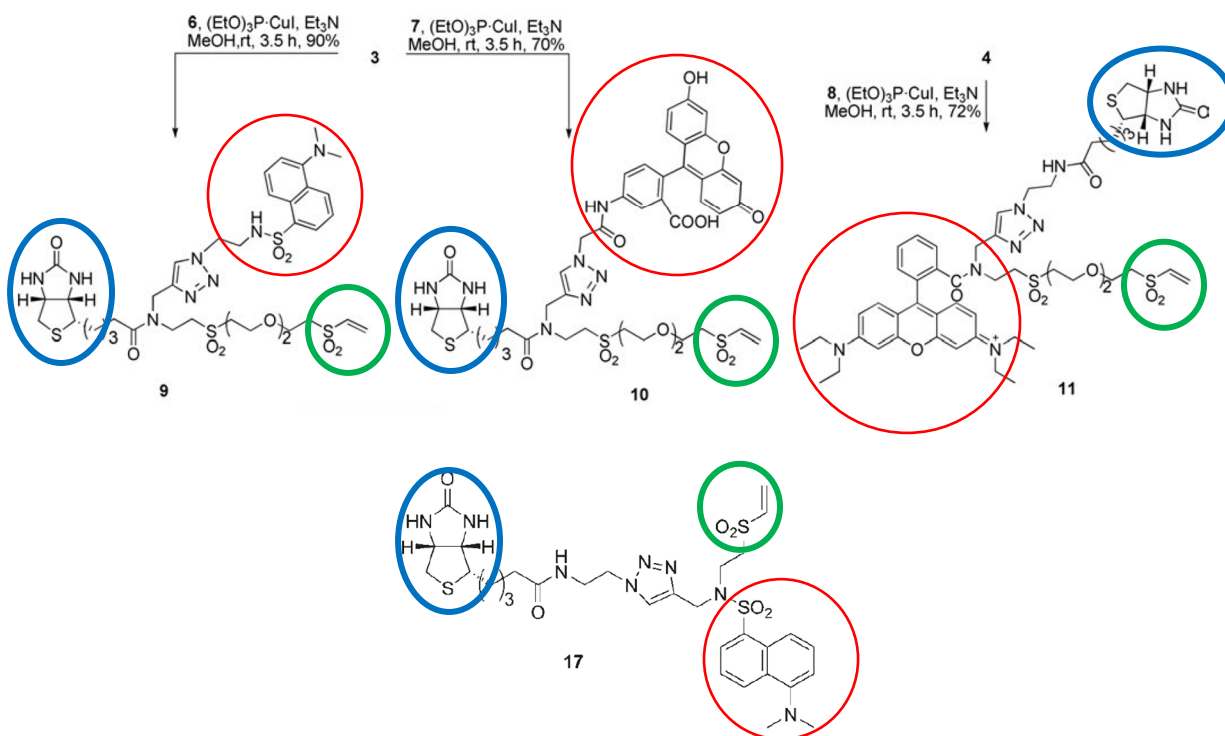
None of claims 1-3, 6, 24-25, and 33 is anticipated by Morales-Sanfrutos as evidenced by Straus. Indeed, Petitioner admits that both references were previously

considered by the Examiner during reexamination of the '682 patent (Pet. 8, 10), and the claims were deemed patentable over this art. EX2033 (Examiner signing IDS listing Morales-Sanfrutos and Straus).

1. Morales-Sanfrutos (EX1005)

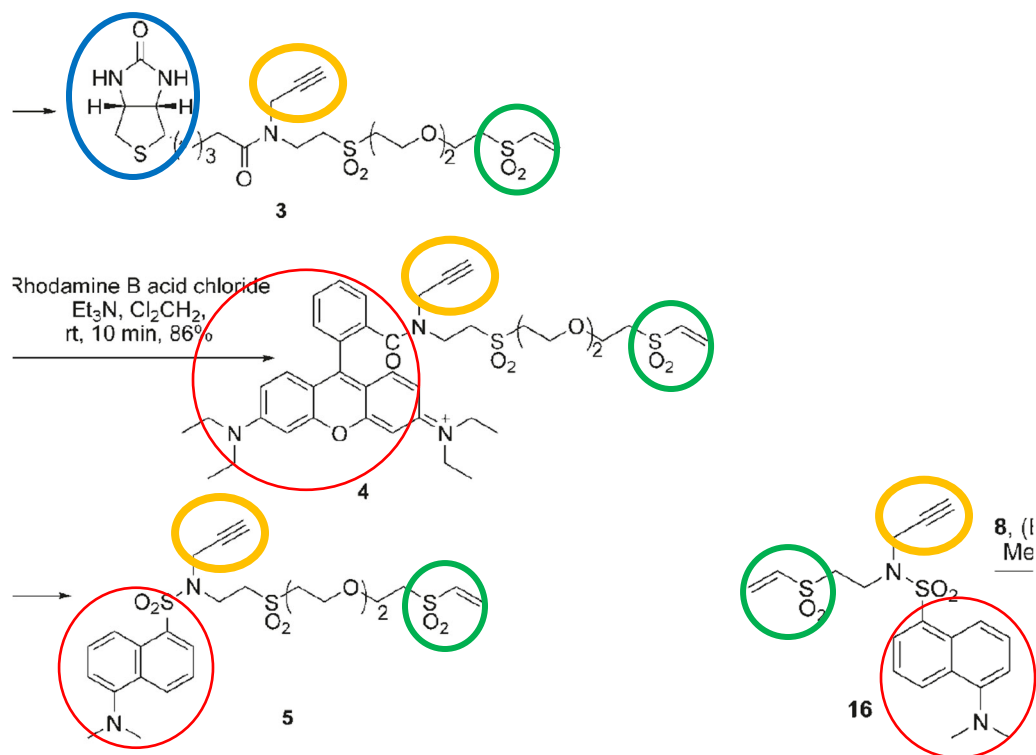
Morales-Sanfrutos does not disclose *any* of the claimed hydrophilic linkers or cell-binding agent-drug conjugates. EX2038, ¶¶77-81, 159-168. Rather, it discloses a reporter system for visualizing the activity of biomolecules in *in vitro* assays. *Id.*

Specifically, Morales-Sanfrutos discloses “bifunctional tag single attachment point reagents (BTSAP),” such as compounds **9-11** and **17** (below), containing a biotin tag (annotated below with blue circles), a fluorescent tag (red circles), and an “electrophilic vinyl sulfone group” that “function[s] as a reactive linking group” (green circles). EX1005, 4039-4040. Morales-Sanfrutos explains that vinylsulfone (not vinyl alone) “is an appealing function for protein conjugation through the Michael-type addition with the amine and thiol groups present in the proteogenic residues under mild conditions that are compatible with their biological function.” *Id.*, 4040. Thus, Morales-Sanfrutos discloses that vinylsulfone—not vinyl alone—is a reactive functional group that enables reaction with a protein for conjugation. EX2038, ¶161.



EX1005, 4041-4042.

Morales-Sanfrutos describes the chemical synthesis of the BTSAP reagents from “alkyne vinyl sulfone derivatized tags (AVST),” such as compounds **3-5** and **16** (below), containing vinylsulfone (annotated with green circles) and an alkyne (orange circles) that may react with an azide in another molecule via a copper-catalyzed reaction for “click CuAAC attachment of a second azide functionalized tag.” EX1005, 4039-4040.

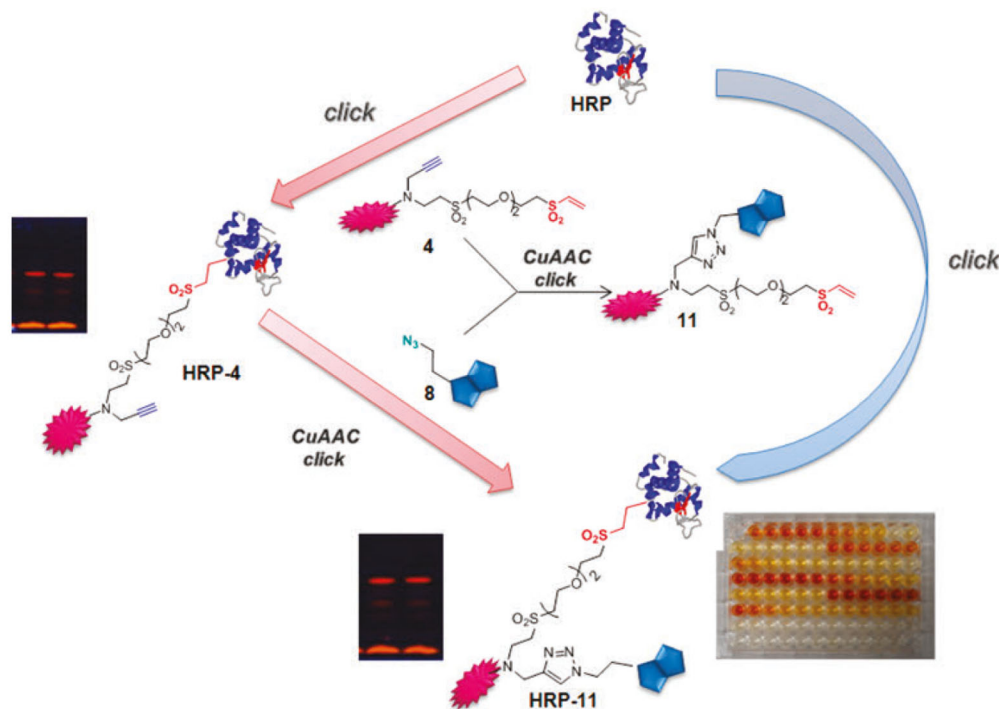


EX1005, 4041-4042 (Schemes 1 and 3); *see also id.* (Schemes 2-3 depicting copper-catalyzed reactions of AVST compounds).

Morales-Sanfrutos notes that “copper catalyst is toxic for living organisms and induces degradation of the structures of the biomolecule in vitro.” EX1005, 4040; *id.*, 4043 (“the problem of the use of copper in bioconjugation whose toxicity for living organisms and potential to induce degradation of the structure of the biomolecule in vitro are important drawbacks”); *accord* EX2037, 33:18-34:8. Thus, Morales-Sanfrutos describes the alkyne in its AVST compounds as reacting to a small-molecule “azide derivative of a second tag,” ***not to any protein or biomolecule***, “while leaving unreacted the vinyl sulfone group for the ulterior

coupling with biomolecules.” EX1005, 4040; *id.* 4041-4042 (Schemes 2-3); EX2038, ¶163.

Morales-Sanfrutos does not disclose any group other than vinylsulfone as a functional group enabling reaction with horseradish peroxidase (“HRP”), a peroxidase enzyme. EX2038, ¶164. For example, in Scheme 4 (below), Morales-Sanfrutos discloses the reaction of HRP with compound **4** (having both vinylsulfone and alkyne) that provided a labeled **HRP-4**, with vinylsulfone enabling the reaction of compound **4** with HRP, while leaving the alkyne intact for a subsequent reaction with compound **8**, a small-molecule azide-labeled biotin.



EX1005, 4044. Nowhere does Morales-Sanfrutos disclose that the alkyne in the AVST compounds (or in HRP-4) enables any reaction with a protein such as HRP;

only the vinylsulfone enables the reaction to HRP. EX2038, ¶165; EX1005, 4040 (“vinyl sulfone is an appealing function for protein conjugation through the Michael-type addition with the amine and thiol groups present in the proteogenic residues under mild conditions that are compatible with their biological function”); *accord* EX2037, 30:5-32:2 (Dr. Chari admitting that Morales-Sanfrutos does not disclose reacting alkyne to any cell-binding agent).

Morales-Sanfrutos also does not disclose a “cell-binding agent.” EX2038, ¶166. It describes labeling the peroxidase enzyme HRP with its BTSAP reagents “to generate a dual **reporter group** (i.e., fluorescence and **peroxidase activity**) that may be also coupled to any recognition system” via the biotin tag. EX1005, 4042. Morales-Sanfrutos refers to the labeled HRPs as a “dual reporter” with “fluorescence and peroxidase activity,” meaning the HRP functions as a reporter through its peroxidase activity, not through binding to any specific cell populations. *Id.*, 4039, 4043; EX2038, ¶¶166-167.

A POSA would not understand HRP to be a cell-binding agent; rather, a POSA would understand HRP to be a reporter as disclosed by Morales-Sanfrutos. EX2038, ¶168; EX1005, 4041 (“HRR has been coupled to other molecules to **use the peroxidase activity as a reporter**”). Specifically, HRP is a peroxidase enzyme that catalyzes oxidation of organic substrates by hydrogen peroxide, and it is widely utilized in cell-free biochemistry assays (*e.g.*, western blotting, ELISA) to detect

proteins, not as a cell-binding agent. EX2038, ¶168.

2. Straus (EX1006)

Straus, a decades-old publication from 1986, titled “*Unusual binding sites* for horseradish peroxidase on the surface of cultured and isolated mammalian cells,” does not establish that the HRP described in Morales-Sanfrutos is a cell-binding agent, as Petitioner argues. EX2038, ¶¶82-85, 169-172.

Straus studies the binding of HRP to previously dried and chemically treated cells under highly artificial conditions. *Id.* Straus discloses that “[b]inding sites for horseradish peroxidase (HRP) with unusual properties, were detected on the surface of cultured and isolated cells after the cells (*on the cover slips*) had been *quickly dried, fixed in cold methanol, and post-fixed in a paraformaldehyde solution.*” EX1006, 277. Straus emphasizes the “[i]mportance” of the “*initial treatment of dried cells with cold methanol,*” which it describes as “essential to attain a strong binding of HRP to the cell surface.” *Id.*, 279; *id.*, 282 (“The initial treatment of dried cells with cold methanol was essential to obtain a strong binding of HRP to the plasma membrane and to prevent a significant ‘background’ adsorption of HRP.”). Straus reports that in cells “without having been first dried, the reaction for the surface-bound HRP was relatively weak.” *Id.* As Petitioner’s expert Dr. Chari admitted, drying cells and treating them with methanol would cause the cells to die, and such conditions are not the conditions for cell-binding as contemplated by the

'682 patent. EX2037, 24:22-27:3.

As discussed in Section V.C, the '682 patent defines a “cell-binding agent” as a “molecule that binds to, complexes with or reacts with a moiety *of a cell population sought to be therapeutically or otherwise biologically modified.*” EX1001, 14:39-44. Straus does not demonstrate HRP as having the ability to target or bind specific cell populations to allow the therapeutical or biological modification of such cells. EX2038, ¶¶169-172.

Instead, Straus merely states that “[b]inding sites for [HRP], with *unusual properties*, were detected on the surface of cultured and isolated cells” that were previously dried, treated with methanol, and fixed in a paraformaldehyde solution, EX1006, 277, indicating that HRP’s ability to bind cells is atypical and unusual. EX2038, ¶172. Straus also describes various limitations of its study, including the presence of artifacts, which further underscore the uncertainty of its purported conclusions. EX1006, 283-284; EX2038, ¶172. Straus’s teachings regarding HRP’s purported cell-binding activity are not mainstream, well-known, or relied upon. EX2038, ¶¶82, 172. Rather, HRP is routinely used (*e.g.*, in *cell-free* assays) as a reporter to detect the presence of a protein. *Id.*

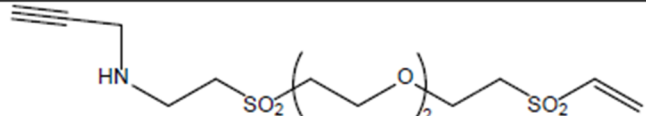
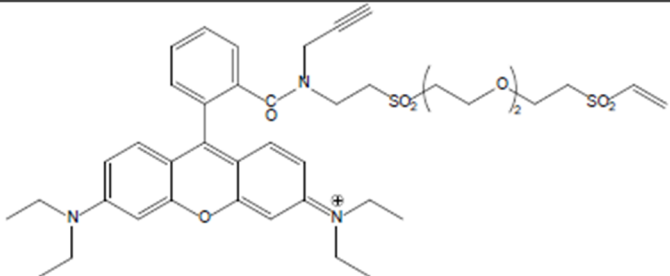
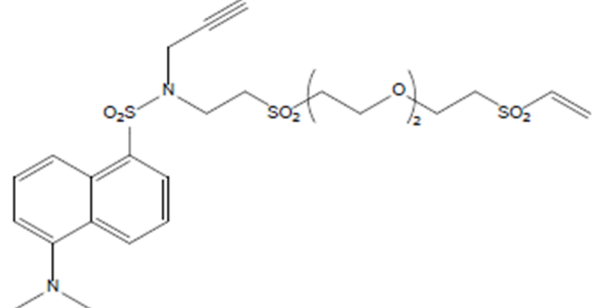
3. Claim 1

Claim 1 recites a hydrophilic linker of Formula I with specific limitations on the individual components of Formula I.

Structure	Formula
$Y-R_1-\text{[Q]}-R_2-\text{[T]}-R_3-\text{[R}_4\text{]}-Z$ $\swarrow \searrow$ $R_5 \quad R_6$	I

To prove anticipation, Petitioner must show that the separate and distinct elements (*e.g.*, Y, Q, T, Z) of the above formula are expressly or inherently disclosed in a single prior-art reference, and that all those distinct elements are arranged in the prior art as in the '682 patent claims. *Net MoneyIN*, 545 F.3d at 1369-70. Moreover, to the extent Petitioner relies on any inherent disclosures of the prior art, “inherency may not be established by probabilities or possibilities.” *In re Montgomery*, 677 F.3d 1375, 1380 (Fed. Cir. 2012) (cleaned up).

Petitioner asserts that four compounds (1, 2, 4, and 5 in Table B1, reproduced below) disclosed in Morales-Sanfrutos each anticipate claim 1. Pet. 27. Petitioner's arguments fail for several reasons. EX2038, ¶¶173-183.

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

(a) “Y” and “Q”

Petitioner attempts to map each of the above compounds to the elements of Formula I. Pet. 28-30 (Table B2). In doing so, Petitioner divides the vinylsulfone in Morales-Sanfrutos' compounds in half—mapping the vinyl to Y and the sulfone to Q. But, as discussed in Section V.B, the claimed “Y” group must be a functional group that independently enables reaction with a cell-binding agent. As Dr. Chari unequivocally testified, vinyl itself cannot enable reaction with a cell-binding agent and thus it does not meet the “Y” limitation; rather, the entire vinylsulfone must be mapped to “Y” because it is the sulfone that enables the reaction (and vinyl enables

the linkage, which is what is required by “Z” not “Y”). EX2037, 19:15-22:9, 48:12-49:12, 52:16-53:1; EX1003, ¶¶103, 107 (Dr. Chari relying on prior-art disclosures of “vinyl sulfone” groups).

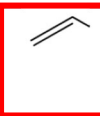
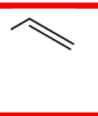
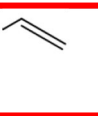
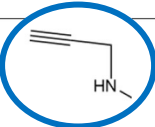
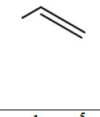
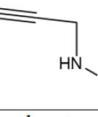
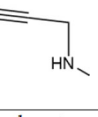
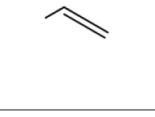
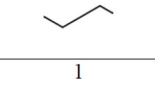
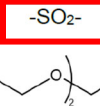
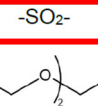
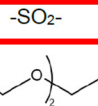
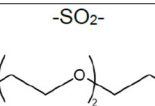
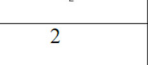
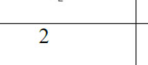
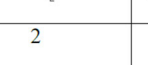
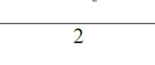
Once the entire vinylsulfone is mapped to Y (as required by the claim's definition of Y), Morales-Sanfrutos does not disclose any compound with a separate sulfone that can be mapped to Q. EX2038, ¶¶176-178. Claim 1 requires that when Q or T is -S(O)₂- (sulfone), “m and n are not 0.” EX1002, 1:38-39.

The same vinylsulfone cannot be mapped to both Y and Q. In *Hopkins*, for example, the Board rejected the argument that “a single structure may satisfy two limitations in a claim” because the claims at issue recited terms that “are separate and distinct.” *Hopkins Mfg. Corp. v. Cequent Performance Prods., Inc.*, IPR2015-00613, Paper 9 at 11-12 (PTAB Aug. 7, 2015). Here, too, the claimed Y and Q are separate and distinct (as discussed above). It is improper to map a single prior-art structure—Morales-Sanfrutos' singular vinylsulfone structure—onto both, as Petitioner has done.

Petitioner's argument that claim 1 “does not require actual conjugation to a cell-binding agent” (Pet. 31) does not remedy the deficiency in Petitioner's analysis. As discussed, by Petitioner's own expert's admission, ***vinyl alone does not enable reaction of the Formula I linker***. EX2037, 52:16-53:1. Instead, the vinyl must be part of a vinylsulfone to be sufficiently reactive because the sulfone is what enables

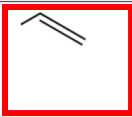
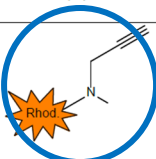
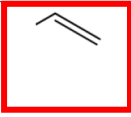
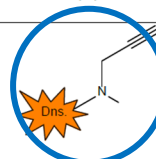
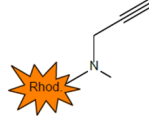
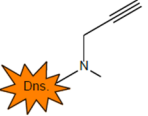
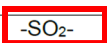
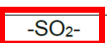
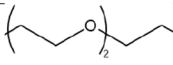
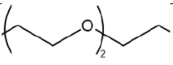
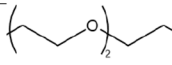
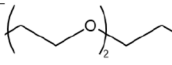
the reaction. *Id.*, 22:1-3. But Petitioner does not map vinylsulfone to Y. If Petitioner did, then Petitioner would fail to demonstrate that Q was disclosed in Morales-Sanfrutos.

Accordingly, Petitioner's mapping in 1, 2(a), 2(b), 4(a), and 5(a) of Table B2 (reproduced below) fail at least because vinyl does not meet the claim's requirement for Y and, once the entire vinylsulfone is mapped to Y, the claim element Q would be missing in each compound, as highlighted in red boxes below.¹⁰ EX2038, ¶¶176-178.

Morales-Sanfrutos' Compounds 1-2 (Table B1)				
'682 (I)	Compound 1	Compound 2		
		(a)	(b)	(c)
Y				
Z				
R ₁	absent ⁵	absent	absent	
m	1	1	1	1
Q				
R ₂				
p	2	2	2	2

¹⁰ Petitioner acknowledges that another sulfone group in Compound 5 belongs to a “dansyl” group and is therefore irrelevant to this analysis. *See* Pet. Tables B1-B2.

n	1	1	1	1
T	-SO ₂ -	-SO ₂ -	-SO ₂ -	-SO ₂ -
R₃	absent		CH ₂	absent
R₄	absent	absent	CH ₂	absent

'682 (I)	Compound 4		Compound 5	
	(a)	(b)	(a)	(b)
Y				
Z				
R₁	absent		absent	
m	1	1	1	1
Q		-SO ₂ -		-SO ₂ -
R₂				
p	2	2	2	2
n	1	1	1	1
T	-SO ₂ -	-SO ₂ -	-SO ₂ -	-SO ₂ -
R₃		absent	absent	absent
R₄	absent	absent		absent

Petitioner's mapping of 2(c), 4(b), and 5(b) also fail. EX2038, ¶¶179-183. Petitioner fails to demonstrate that "the four corners" of Morales-Sanfrutos "describe every element of the claimed invention" in the same "arrange[ment] as in the claim." *Net MoneyIN*, 545 F.3d at 1369-70; *see also Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1325, 1332 (Fed. Cir. 2010) ("The way in which the elements are

arranged or combined in the claim must itself be disclosed, either expressly or inherently, in an anticipatory reference.”).

In each of 2(c), 4(b), and 5(b), Petitioner maps a moiety containing an *alkyne* group (shown above, highlighted with blue circles) to Y, a functional group that *enables reaction* of the linker *to a cell-binding agent*. But Petitioner ignores that Morales-Sanfrutos never discloses, expressly or inherently, the alkyne reacting with any biomolecule (such as HRP), much less any cell-binding agent; Morales-Sanfrutos only discloses the alkyne reacting with small-molecule azide-containing tags (such as biotin or fluorescence tags) in the presence of a copper catalyst. *See* Section VI.A.1. As Dr. Chari confirmed, Morales discloses reaction of the alkyne only with an azido group (also called azide) in biotin and other small molecules that are *not* cell-binding agents. EX2037, 30:5-32:2.

Indeed, Morales-Sanfrutos describes the reaction of alkyne in its compounds to a small-molecule “azide derivative of a second tag,” not to any biomolecule (*e.g.*, HRP), “while leaving unreacted the vinyl sulfone group for the ulterior coupling with biomolecules.” EX1005, 4040; *id.* 4041-4042 (Schemes 2-3). In Scheme 4, Morales-Sanfrutos discloses the reaction of HRP with compound **4** (having both vinylsulfone and alkyne) that yielded compound **HRP-4**, with vinylsulfone enabling the reaction of compound **4** with HRP, while leaving the alkyne intact for a subsequent reaction with compound **8**, an azide-labeled biotin.

Moreover, the alkyne in Morales-Sanfrutos' compounds is designed to react with an azide in a small-molecule compound, which must be catalyzed by a copper catalyst. EX2038, ¶¶165, 181. Morales-Sanfrutos repeatedly emphasizes that "copper catalyst is toxic for living organisms and induces degradation of the structures of the biomolecule in vitro." EX1005, 4040; *id.*, 4043 ("the problem of the use of copper in bioconjugation whose toxicity for living organisms and potential to induce degradation of the structure of the biomolecule in vitro are important drawbacks"). Dr. Chari confirmed that a POSA was moving away from copper catalysts due to the toxicity. EX2037, 33:18-34:8. Thus, mapping the alkyne in Morales-Sanfrutos' compounds to Y for reaction with a cell-binding agent (*e.g.*, a large biomolecule), as Petitioner has done, is directly contrary to Morales-Sanfrutos' teachings. EX2038, ¶¶165, 181.

Morales-Sanfrutos also does not disclose any biomolecule, much less any cell-binding agent, that has an azide that can react with an alkyne. EX2038, ¶182. The HRP disclosed in Morales-Sanfrutos does not contain any azide and thus cannot react with the alkyne in Morales-Sanfrutos' compounds. *Id.* Morales-Sanfrutos does not disclose any compound using alkyne as the functional group that enables reaction with any cell-binding agent. *Id.*, ¶¶179-183.

(b) "Cell-Binding Agent"

Morales-Sanfrutos as evidence by Straus does not disclose any "cell-binding

agent” as required by claim 1. EX2038, ¶¶184-189.

Petitioner argues that claim 1 does not require a cell-binding agent because the claim “does not require actual conjugation” to this agent. Pet. 31. Petitioner’s interpretation should be rejected. Claim 1 requires that Y be “a *functional group that enables reaction* of the hydrophilic linker *with a cell-binding agent.*” The asserted prior art must disclose or identify “a cell-binding agent” with an appropriate group that can react with the claimed “Y”. Absent such disclosure, the claim limitation is not fully met by the asserted prior art to establish anticipation. EX2038, ¶185.

As discussed above in Section VI.A.1-2, neither Morales-Sanfrutos nor Straus discloses HRP as a cell-binding agent. Morales-Sanfrutos does not disclose any “cell-binding agent” as it does not disclose or even suggest that HRP binds to any cells. EX2038, ¶186. As noted in Section VI.A.1, Morales-Sanfrutos specifically describes HRP as a reporter that functions through its peroxidase enzymatic activity, *not* through binding to any cells. EX1005, 4039, 4043; EX2038, ¶¶166-168.

Petitioner instead relies on a different reference, Straus, for alleged prior-art teaching of HRP as a “cell-binding agent.” Pet. 36. But Petitioner’s reliance on Straus for “a very specific teaching, not for any light [Straus] shed on what [Morales-Sanfrutos] would have meant to those skilled in the art,” is improper and “contrary to settled law.” *Studiengesellschaft Kohle, m.b.H. v. Dart Indus., Inc.*, 726 F.2d 724,

727 (Fed. Cir. 1984); *accord Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1335 (Fed. Cir. 2002) (“Although we have permitted the use of additional references to confirm the contents of the allegedly anticipating reference, we have made clear that anticipation does not permit an additional reference to supply a missing claim limitation.” (internal citation omitted)). Here, as noted, Morales-Sanfrutos expressly describes HRP as a peroxidase reporter for *in vitro* biological assays, not for binding to any cells. In contrast, as discussed in Section VI.A.2, Straus describes “unusual” binding of HRP to previously dried and methanol-treated cells under highly artificial conditions. EX2038, ¶¶169-172. Petitioner does not use Straus “to confirm the contents of” Morales-Sanfrutos, but instead relies on Straus “to supply a missing claim limitation,” which is legally impermissible. *Teleflex*, 299 F.3d at 1335; EX2038, ¶187.

Even assuming Petitioner may rely on Straus, Petitioner fails to demonstrate that the HRP in Morales-Sanfrutos is a cell-binding agent, under *either* DAC’s *or* Petitioner’s construction of that term. EX2038, ¶188. Regarding the “cell-binding agent” limitation, Petitioner asserts in a single conclusory sentence that “HRP is a known cell-binding agent,” citing page 277 of Straus and two paragraphs (59 and 90) of its expert declaration. Pet. 36.

Paragraph 90 of the declaration repeats the same conclusory sentence as the Petition, EX1003, ¶90, and thus is entitled to no weight. Paragraph 59 merely states

that “Straus discloses that the [HRP] enzyme *may* bind to the surface of a variety of cells, including macrophages, fibroblasts, mast cells and endothelial cells,” citing page 277 of Straus without further explanation. EX1003, ¶59.

The cited portion of Straus states that “[t]he occurrence of mannose-specific binding sites for horseradish peroxidase (HRP) in macrophages, fibroblasts, mast cells and endothelial cells of rat tissues has been demonstrated earlier by a *cytochemical method*,” and that “[i]n the present *cytochemical study*, binding sites for HRP with unusual properties were detected at the surface of cultured and isolated cells.” EX1006, 277. Straus does not provide detailed information on those earlier studies, including whether the cells were treated and/or studied under artificial conditions. EX2038, ¶189. For the “present” study, as discussed in Section VI.A.2, Straus describes a cytochemical method that involves highly artificial conditions, such as drying the cells, treating them with cold methanol, and fixing them in a paraformaldehyde solution. As discussed above, Straus does not establish that HRP is a cell-binding agent. EX2038, ¶¶82-85, 169-172. Rather, Straus emphasizes the “[i]mportance” of the “initial treatment of dried cells with cold methanol.” EX1006, 279, 282. Straus’ disclosures demonstrate the opposite—that HRP does not necessarily and inherently bind cells under normal physiological conditions. Moreover, in view of the highly artificial conditions used by Straus, a POSA would not have looked to Straus to inform their understanding of Morales-Sanfrutos.

EX2038, ¶189.

Petitioner's proffered evidence is inadequate to support either express or inherent anticipation by Morales-Sanfrutos and Straus for these additional reasons.¹¹

4. Claim 2

Morales-Sanfrutos and Straus do not anticipate claim 2 for the same reasons provided for claim 1, and for additional reasons below. EX2038, ¶¶190-192.

For claim 2, Petitioner cites Morales-Sanfrutos' compound 2 and argues that compound 2 has an *amino* group that can be mapped to Z, and that "biotin may be attached to this amino group *via an amide bond*." Pet. 32. Petitioner's arguments fail for at least two reasons. EX2038, ¶¶191-192.

First, as shown in Petitioner's Table B2, 2(a) and 2(b) map a group containing amino and alkyne to Z. Pet. 28. As discussed above for claim 1, however, Petitioner's mapping in 2(a) and 2(b) fail at least because vinyl does not meet the claim's requirement for Y and, once the entire vinylsulfone is mapped to Y, Q would be missing in compound 2. EX2038, ¶191.

Second, as the Board noted (Paper 25 at 41-42), Petitioner's analyses of claim 1 and its dependent claim 2 are internally inconsistent. EX2038, ¶192. For claim 1,

¹¹ As also discussed above in Section VI.A.2, DAC's expert Dr. Tumey identifies many reasons to doubt Straus's proffered teachings.

Petitioner argues that “Z is the *alkynyl* group” in compound 2 (Pet. 30), and that the alkynyl can react with an azide group in biotin to form a linkage (Pet. 31-32). For claim 2, it argues that the *amino* group in compound 2 is mapped to Z, and that biotin is attached to that *amino* via an amide bond (Pet. 32). In view of Petitioner's inconsistent analysis for claims 1 and 2, its invalidity arguments against claim 2 fail as a matter of law.

5. Claims 3, 6, 24, 25, and 33

Claims 3 and 24 recite cell-binding agent-drug conjugates of Formula II, and claims 6, 25, and 33 each depend from one of these claims.

Structure	Formula
$\text{Cb} - \left(\text{R}_1 - \text{Q} - \text{R}_2 - \text{T} - \text{R}_3 - \text{R}_4 - \text{Drug} \right)_q$ $\text{R}_5 \quad \text{R}_6$	II

Petitioner argues that **HRP-11**—a compound containing a modified HRP—discloses every limitation of this formula. Pet. 33-36. Petitioner maps HRP-11 to the elements of Formula II, arguing that the HRP moiety in HRP-11 is a cell-binding agent. *Id.* Petitioner's arguments fail at least because, as discussed above for claim 1 (Section VI.A.3.b), Morales-Sanfrutos and Straus does not disclose any cell-binding agent under either DAC's or Petitioner's construction of that term. EX2038, ¶¶193-194.

B. Ground 2: Petitioner Fails to Show Harris Anticipates or Renders Obvious Claims 1, 20-21, and 29-31.

In Ground 2, Petitioner asserts that claims 1, 20-21, and 29-31 are anticipated by or obvious over Harris. Petitioner's challenges fail for at least the same reasons discussed above for Ground 1 and for the following reasons. EX2038, ¶¶195-224.

1. Harris (EX1007)

Harris, a decades-old patent application from 1995, discloses poly(ethylene glycol) ("PEG") derivatives "*activated with a sulfone moiety* for selective attachment to thiol moieties on molecules and surfaces," and that "[t]he PEG derivative is useful for *modifying the characteristics of substances* including modifying biologically active molecules *and surfaces for biocompatibility*." EX1007, Abstract. As discussed below, Harris does not disclose or render obvious *any* of the claimed hydrophilic linkers or related compounds. EX2038, ¶¶88-91, 196-203.

Harris discloses *active sulfone* moieties such as vinylsulfone and haloethyl sulfone—not just vinyl or haloethyl—having the reactivity to allow reaction of the PEG linkers with thiol moieties. EX2038, ¶¶197-200. For example, Harris discloses:

Specific sulfone moieties for the activated polymers of the invention are those having at least two carbon atoms *joined to the sulfone group -SO₂-* with a reactive site for thiol specific

coupling reactions on the second carbon from the sulfone group.

... [T]he *active sulfone moieties* comprise *vinyl sulfone*, the active ethyl sulfones, including the *haloethyl sulfones*, and the thiol-specific active derivatives of these sulfones....

EX1007, 7:3-22; *id.*, 9:37-10:1 (“active sulfone functional group”); *id.*, 11:8-17 (defining “functional group”). Harris identifies the entire vinylsulfone and haloethyl sulfone as the reactive groups. That is because, consistent with Dr. Chari’s testimony, it is the sulfone that enables the reaction. EX2037, 22:1-3. Harris also explains that haloethyl sulfone is in fact a *precursor* of vinylsulfone in the thiol-coupling reaction:

[B]ased on the observable reaction kinetics as shown in Example 3, ... the chloroethyl and other activated ethyl sulfones and reactive derivatives are *converted to PEG vinyl sulfone*, and ... *it is the PEG vinyl sulfone or derivative thereof that is actually linked to the thiol moiety*.

EX1007, 14:15-21; *id.*, 17:21-23; EX2038, ¶199.

As discussed above for Ground 1, vinyl alone does not satisfy “Y”. In view of Harris’ disclosures, a POSA would also understand that haloethyl sulfone (not just haloethyl) would be mapped to Y. EX2038, ¶200.

As discussed below, when the vinylsulfone or haloethyl sulfone is mapped to Y, Petitioner’s invalidity arguments fail because the claimed “Q” is then absent in the alleged prior art. EX2038, ¶201.

For its obviousness challenge (Grounds 2-5), Petitioner also fails to establish that Harris is analogous art for the '682 patent. *Sanofi-Aventis Deutschland GmbH v. Mylan Pharms. Inc.*, 66 F.4th 1373, 1380 (Fed. Cir. 2023) (reversing invalidity holding because patent challenger did not meet its burden to establish analogousness of prior-art reference). Harris is not from the same field of endeavor as the '682 patent's inventions as Harris does not relate to the field of therapeutic drug conjugates. EX2038, ¶¶202-203.

Rather, Harris "relates to active derivatives of poly(ethylene glycol) and related hydrophilic polymers and to methods for their synthesis for ***use in modifying the characteristics of surfaces and molecules.***" EX1007, 1:2-6. Harris' disclosure about pharmaceuticals is general and non-specific, where it states that "almost any substance could be modified." EX1007, 18:34-19:2; EX2038, ¶202. Yet it does not specifically teach conjugation of a drug to an antibody or other cell-binding agent for treating diseases. EX2038, ¶202. Accordingly, Harris relates to a different field of endeavor.

Nor is Harris reasonably pertinent to the problem facing the '682 patent's inventor. As explained in the '682 patent, "there is a critical need to improve methods for conjugating drugs/cytotoxic drugs to carriers (cell binding molecules) that minimize the amount of aggregation and thereby allow for as high a drug loading as possible through application of a hydrophilic cross-linker." EX1001, 2:45-49. As

Harris does not teach therapeutic linkers, much less linkers that solve the identified need, it is not reasonably pertinent to this problem. EX2038, ¶203.

Therefore, Petitioner has not even met its burden to qualify Harris as prior art. *See Sanofi*, 66 F.4th at 1380.

2. Claim 1

Claim 1 recites a Formula I linker.

Structure	Formula
$Y-R_1-Q-R_2-\text{---}_m-T-R_3-\text{---}_n-R_4-Z$ $\swarrow \searrow$ $R_5 \quad R_6$	I

Anticipation. Petitioner argues that claim 1 is anticipated by “Harris’ basic structure” of $R-(OCH_2CH_2)_n-Y$, where R and Y are allegedly “vinyl sulfone and/or halo-ethyl sulfone,” and Harris “discloses PEG derivatives comprising **two** sulfone moieties.” Pet. 38 (emphasis in original). Petitioner then maps “Y” of the claimed formula to “vinyl” or “halo-ethyl”, and “Q” to “sulfonyl” of the same active sulfone moiety from Harris. Pet. 38-39. Here, again, Petitioner misreads the claims and art and improperly maps a single active sulfone group (*e.g.*, vinylsulfone or haloethyl sulfone) to two separate and distinct claim elements (Y and Q). EX2038, ¶¶204-207.

As discussed in Section VI.B.1, Harris describes vinylsulfone and haloethyl sulfone (not just vinyl and haloethyl) as the reactive functional group for conjugation

reaction. EX2038, ¶206. Harris discloses coupling the “*active sulfone moieties*” to the PEG linker allows the linker to “coupl[e]” with thiol moieties in other molecules. *E.g.*, EX1007 6:8-14. Petitioner effectively concedes this. *See, e.g.*, Pet. 7, 39. Thus, Harris’ sulfone moieties (vinylsulfone or haloethyl sulfone) are the claimed “Y” group and necessary to enable that group’s reactivity because the sulfone is what enables the reaction; they cannot be mapped to the separate, distinct spacer element Q. EX2038, ¶¶205-207.

Petitioner makes no other attempt to argue that Harris discloses the separate and distinct Q element. Indeed, Harris merely discloses PEG linkers without any sulfone as spacer elements, and with “one or more active sulfone” conjugation moieties at the end of the linker for reacting with thiol in other molecules. EX1007, 6:11; EX2038, ¶207. Harris therefore does not disclose all elements of the claimed formula including the claimed Q element.

Thus, Petitioner’s Ground 2 arguments fail for essentially the same reasons discussed above for Ground 1. EX2038, ¶¶205-207. Petitioner’s arguments also fail for two other reasons. EX2038, ¶¶208-214.

First, a POSA would not “at once envisage the claimed arrangement or combination” of the elements of Formula I from Harris’ disclosure of R-(OCH₂CH₂)_n-Y, which allows R to be a wide variety of different activating groups. *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015)

(quotes and citation omitted). Harris states that in the above structure:

Y represents $-\text{SO}_2\text{-CH=CH}_2$ or $-\text{SO}_2\text{-CH}_2\text{-CH}_2\text{-X}$ where X is a halogen. R represents a group that *may be the same or different from Y*. R can be H-, $\text{H}_3\text{C-}$, $\text{CH}_2=\text{CH-SO}_2\text{-}$, $\text{Cl-CH}_2\text{-CH}_2\text{-SO}_2\text{-}$, or *a polymer activating group other than $\text{CH}_2=\text{CH-SO}_2\text{-}$, $\text{Cl-CH}_2\text{-CH}_2\text{-SO}_2\text{-}$, such as is referred to with respect to the above patents and published patent applications.*

EX1007, 19:24-30.

Thus, Harris discloses a broad genus in which R can be “a polymer activation group other than” vinylsulfone or haloethyl sulfone. *Id.*; EX2038, ¶¶209-211. Notably, regarding linking two different molecules to the linker, Harris states that “*more typically*, a heterobifunctional PEG derivative” with an active sulfone moiety on one end and a different activating moiety on the other end are used “to produce a molecule having two different activities,” teaching that R being different from Y is “more typical[.]” EX1007, 17:24-18:4; EX2038, ¶210. Harris also discloses that “[o]ther active groups for heterobifunctional sulfone-activated PEGs can be selected from among *a wide variety of compounds*.” EX1007, 18:5-30; EX2038, ¶211. As Petitioner’s expert Dr. Chari admitted, Harris’ disclosure is broad, and Dr. Chari did not calculate the total number of possible linkers disclosed by Harris. EX2037, 35:11-36:7, 40:15-22, 43:7-44:1. Harris’ broad genus of $\text{R-(OCH}_2\text{CH}_2)_n\text{-Y}$ does not anticipate the claimed formula with specific combination of claimed elements.

Second, Harris does not disclose any “cell-binding agent” as required by claim 1, and Petitioner does not even attempt to demonstrate otherwise. EX2038, ¶¶212-213. As discussed in Section VI.A.3, the asserted prior art must disclose or identify “a cell-binding agent” that can react with Y.¹² Absent such disclosure, the claim limitation is not fully met by the asserted prior art. Here, Harris at best discloses unspecified biologically active molecules and proteins, not any antibodies or cell-binding agents. *See, e.g.*, EX1007, 17:28-34; EX2038, ¶¶212-213.

For at least the foregoing reasons, Petitioner's anticipation arguments fail.

Obviousness. Petitioner's cursory obviousness arguments also fail. Pet. 39-40; EX2038, ¶¶215-216. For example, Petitioner provides **no** analysis whatsoever on the “differences between the prior art and the claim[],” nor whether the claim would have been obvious in view of such differences. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Petitioner provides **no** detailed analysis of how combining any particular structures in Harris achieves the specific combination of elements recited in the claimed formula. *ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1327 (Fed. Cir. 2012). To the extent Petitioner's obviousness

¹² This applies equally to claims 20-21 and 29-31 that each recite “Y” as “a functional group that **enables reaction** of the compound **with a cell-binding agent.**” EX2038, ¶213.

argument is substantively co-extensive with its anticipation argument above, it is defective for the same reasons. EX2038, ¶215.

Petitioner's cursory obviousness analysis in a single paragraph is deficient for additional reasons. EX2038, ¶216. As discussed above, the Y conjugation moiety and the Q spacer element are separate and distinct components of the linker. Petitioner must explain how any alleged prior-art teachings of Y (*e.g.*, vinylsulfone or haloethyl sulfone) and Q (*e.g.*, sulfone) would be combined to achieve the claimed linker. *ActiveVideo*, 694 F.3d at 1327. Petitioner has failed to do so. EX2038, ¶216.

For example, Petitioner does not identify any reason from the prior art to use sulfones (or other claimed spacer structures) as spacer elements. Besides pointing to sulfone-based ***conjugation moieties*** of the prior art, Petitioner has not identified any motivation to incorporate sulfone groups (or any other claimed Q/T groups) as ***spacer elements*** in the linker. *Id.* In fact, Petitioner's expert admitted there would be no reason to add sulfone-based spacers when PEG was already present. EX2037, 39:14-40:5, 41:16-42:2. Petitioner has failed to carry its burden to explain why a POSA would have been motivated to combine prior-art elements ***as claimed***. EX2038, ¶216; *Hopkins*, Paper 9 at 17 ("It is important to identify a reason that would have prompted a [POSA] ***to combine the elements in the way the claimed invention does.***"). As in *Hopkins*, the Board should reject this approach.

3. Claims 20-21 and 29

Claims 20 and 29 recite a compound of Formula IV, identical to Formula I except for the substitution of a “Drug” for the Z. Claim 21 depends from claim 20.

Structure	Formula
$Y - R_1 - \text{---} Q - R_2 - \text{---}_m \text{---} T - R_3 - \text{---}_n \text{---} R_4 - \text{Drug}$ $\begin{matrix} R_5 & R_6 \end{matrix}$	IV

Petitioner's arguments with respect to claims 20-32 and 29 fail for similar reasons discussed above for claim 1. EX2038, ¶¶217-222.

First, Petitioner maps “Y” of Formula IV to only vinyl or haloethyl of the active sulfone moieties of Harris. Pet. 41. But neither vinyl nor haloethyl is “a functional group that enables reaction of the compound with a cell-binding agent.” EX2038, ¶218. Petitioner's analysis is deficient for the same reasons discussed above for claim 1.

Second, a POSA would not “at once envisage” the claimed combination of the elements of Formula IV from Harris' disclosure of R-(OCH₂CH₂)_n-Y, which allows R to be a wide variety of activating groups. EX2038, ¶¶219-220.

This deficiency applies not only to Petitioner's arguments regarding PEG derivatives having two sulfones (Pet. 41), which fail for the same reasons discussed above for claim 1, but also to Petitioner's arguments regarding Harris' purported teachings of heterobifunctional PEG derivatives having an active sulfone moiety on

one end and an NHS ester on the other end (Pet. 42). EX2038, ¶¶219-220.

Petitioner's analysis regarding heterobifunctional PEG derivatives with an active sulfone moiety and an NHS ester is legally flawed. Pet. 42. As discussed above for claim 1, Harris discloses a wide variety of activating groups that may be used in heterobifunctional PEG derivatives. EX1007, 18:5-30; EX2038, ¶¶209-211, 220. From Harris' broad disclosure of numerous possible activating groups, a POSA would not "at once envisage" a PEG derivative having an active sulfone moiety on one end and an NHS ester on another end, as Petitioner asserts. EX2038, ¶¶219-220.

Third, for the same reasons discussed above for claim 1, claims 20-21 and 29 require a "cell-binding agent" that can react with "Y", but Harris does not disclose any "cell-binding agent" that can react with Y, as required by the claims. EX2038, ¶221.

For at least the foregoing reasons, Petitioner's anticipation arguments fail.

Lastly, Petitioner argues, in a single cursory and conclusory paragraph, that claims 20 and 29 would have been obvious over Harris, relying on similar rationales as for claim 1. Pet. 42-43. Those arguments fail for the same or similar reasons provided above for claim 1. EX2038, ¶222.

4. Claims 30-31

Harris does not anticipate or render claims 30-31 obvious for the same reasons

provided for claims 20-21 and 29, and for additional reasons below. EX2038, ¶¶223-224.

Claim 30 requires that “m and n are integers from 1 to 5.” EX1002, 11:6. Claim 31, depending from claim 30, also includes that requirement. Claims 30-31 require that Q and T must both be present.

Petitioner overlooks this limitation in its analysis regarding Harris’ purported teachings of heterobifunctional PEG derivatives having an active sulfone moiety and an NHS ester. In its mapping, Petitioner admits that “Q and R₂ are absent and m is 0.” Pet. 42. The purported NHS-ester-containing heterobifunctional PEG derivatives do not anticipate or render obvious claims 30-31, for the additional reason that they lack the requisite Q and R₂ moieties required by claims 30-31. EX2038, ¶224. Petitioner does not demonstrate otherwise.

C. Ground 3: Petitioner Fails to Show Singh in View of Harris Renders Obvious Claims 1-8, 10-12, 14-17, 20-21, 24, 26, and 29-31.

In Ground 3, Petitioner’s challenges are based on the same misunderstanding of the claims and art as in Grounds 1-2. They fail for similar reasons. EX2038, ¶¶225-242. None of the challenged claims is rendered obvious by Singh and Harris. Petitioner admits that Singh was previously considered during reexamination of the ’682 patent, and no rejections were issued over this reference. Pet. 10, 79.

1. Singh (EX1008)

Singh discloses PEG linker structures that may be conjugated to maytansinoid drugs. EX2038, ¶¶92-97, 225-226. In a single sentence, Singh states that vinylsulfone may serve as a “reactive functionality,” among others, without mentioning vinylsulfone again elsewhere. *Id.*, ¶225. As Petitioner admits, “Singh discloses bifunctional PEG cross-linkers containing each element of claim 1, *save Q and T* (which must be $-P(=O)(OM)-$, or $-S(O_2)-$, or $-S(O)-$.” Pet. 44. Petitioner therefore expressly concedes that Singh fails to teach either Q or T.

None of the exemplified compounds disclosed in Singh contains any sulfone group. *See, e.g.*, EX1008, Figs. 1-54; EX2038, ¶225. Indeed, Petitioner's expert Dr. Ravi Chari, one of the named inventors of Singh, testified that Singh “doesn't include sulfones.” EX2037, 38:15-39:1. Dr. Chari also testified that the purported inventors of Singh found that polyethylene glycol (PEG) led to increased hydrophilicity of the linker, *id.*, 36:12-21, the inventors found it sufficient to use PEG alone to achieve the hydrophilicity, and “there was no reason to add anything else,” *id.*, 39:14-40:5, 41:16-42:2. Petitioner's obviousness arguments in Ground 3 regarding modifying Singh's compounds to incorporate one or two vinylsulfone groups are based on impermissible hindsight. EX2038, ¶226.

2. Claim 1

Petitioner's Ground 3 obviousness arguments fail for several reasons.

EX2038, ¶¶227-236.

First, as in Grounds 1-2, Petitioner misreads the challenged claims and the art and improperly maps a single vinylsulfone reactive group purportedly taught by Singh and/or Harris onto both Y and Q. EX2038, ¶¶228-232; *Hopkins*, Paper 9 at 12.

Petitioner's obviousness arguments are based on Singh's disclosure of certain PEG linkers, which Petitioner admits do not contain the claimed Q or T spacer element. Pet. 44, 46 ("Singh discloses bifunctional PEG cross-linkers containing each element of claim 1, *save Q and T*."). Because Singh does not disclose the Q or T spacer element, Petitioner resorts to arguing that a POSA would modify one or both of Singh's reactive functionalities with vinylsulfone.

Petitioner points to Singh's disclosures of vinylsulfone as one of *several* "reactive functionalities" and argues that a POSA would be motivated to incorporate vinylsulfone in Singh's linkers. Pet. 48-49 (citing EX1008, ¶[0134]). Petitioner argues that Singh "expressly suggests the use of vinylsulfones as a thiol-reactive functionality and teaches their equivalence to maleimide and haloacetamides for this purpose." Pet. 48. Singh defines "reactive functionality" as set forth below:

As used herein, the term "reactive functionality" refers to an amine-, a thiol- or a hydroxyl-reactive functionality. In other words, the *reactive functionality can react with* amine,

sulphydryl(thiol), or hydroxyl group *present on cell binding agent*. For example ... for thiol-reactive functionality, *the functionality could be* a maleimide, a halo acetamide, or *a vinyl sulfone to give a thioether bond* ...

EX1008, ¶[0134].

According to Petitioner, “a POSA would have been motivated to replace one or both of the reactive functionalities in Singh’s bifunctional PEG cross-linkers 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.” Pet. 48-49. This mapping of vinylsulfone should be rejected as explained above for Grounds 1-2.

Specifically, as Petitioner admits, vinylsulfone groups possess the “reactive functionality” because it includes the sulfone, which Dr. Char admits is what enables the linker’s reaction to other molecules such as a cell-binding agent—the claimed function of the “Y” group. Pet. 48; EX2037, 22:1-3. Petitioner does not argue, nor does Singh or Harris teach, that vinyl alone has this capability. Once again, Petitioner’s mapping strategy is contrary to the meaning of the “Y” claim term and flouts the principle that a single prior-art structure should not be mapped to multiple separate, discrete claim elements. EX2038, ¶¶228-232; *Hopkins*, Paper 9 at 12. The Board should reject Petitioner’s improper mapping for Ground 3.

Second, Petitioner argues that it would have been obvious to modify Singh’s linkers to incorporate “vinyl sulfones and related sulfonyl functionality” taught in

Harris. Pet. 44. This argument fails for the same reasons discussed above for Harris in Ground 2. EX2038, ¶233.

Additionally, Petitioner admits that “Harris’ vinyl sulfone-containing PEG derivatives are *nearly identical* to the bifunctional PEG cross-linkers of Singh and serve the same purpose.” Pet. 49. Petitioner does not argue why it would be obvious to modify the Singh structure with the “nearly identical” Harris structure, or what additional benefits that including Harris’ active vinylsulfone groups (conjugation moieties) would confer to a Singh linker that already comprises vinylsulfone (conjugation moieties). EX2038, ¶234.

Third, even accepting Petitioner’s characterization of benefits of using vinylsulfone in linkers, Petitioner fails to show any motivation to achieve the claimed invention. EX2038, ¶¶235-236.

The claimed invention comprises separate and distinct Y and Q elements (among others). As argued throughout this Response, vinylsulfone was recognized in the art—including in Morales-Sanfrutos, Harris, and Singh—as being a reactive functional group. Therefore, even if a POSA were motivated to add vinylsulfone to a linker to serve as a Y group (*e.g.*, as a conjugation moiety enabling reaction with a cell-binding agent), Petitioner wholly fails to show any motivation in Singh or Harris to add sulfonyl groups to *a different part of the linker to achieve Q or T*, the novel claimed spacer elements. EX2038, ¶235. Petitioner merely points to Harris’

methods of synthesizing linkers that comprise sulfone groups at the ends of linkers—*i.e.*, to serve as conjugation moieties. Pet. 51 (“Examples 1 and 2 of Harris describe how to synthesize a PEG linker comprising a **terminal** vinyl sulfone or chloro-ethyl sulfone group...”), 52 (“modifying ... Singh to include vinyl sulfones ... as a reactive functionality that can form a thioether bond with a cell-binding agent or drug”). As explained repeatedly above, these substitutions do not achieve a linker with sulfone group(s) as the Q or T spacer element. EX2038, ¶235.

Similarly, Petitioner argues that the vinyl group is Y. Pet. 49. But Petitioner fails to identify any motivation whatsoever to add **vinyl** alone to a linker to serve as a separate, distinct functional group that enables the linker to react with a cell-binding agent. EX2038, ¶236. As discussed above, and as Petitioner and its expert admit, vinyl cannot enable reaction. The sulfone in the vinyl sulfone is what enables the reaction. EX2037, 22:1-3. Adding vinyl alone would be ineffective as Petitioner and its expert acknowledge. *See supra*; EX2038, ¶236.

3. Claim 2

Singh and Harris do not render claim 2 obvious for the same reasons provided for claim 1, and for additional reasons below. EX2038, ¶¶237-238.

Petitioner argues that “Singh and Harris teach that Z can be maleimide or haloacetyl ... as required by claim 2.” Pet. 53. But keeping Z as maleimide or haloacetyl as Petitioner argues for claim 2 is inconsistent with its arguments for

claim 1 to substitute the Z conjugation moiety with vinylsulfone in order to supply a sulfone moiety to be mapped to T. EX2038, ¶238. Petitioner inconsistent invalidity theory should be rejected.

4. Claims 3-8, 10-12, 14-17, 24, and 26

For these claims, Petitioner similarly argues that “Singh in combination with Harris is relied on for the reasons given” “to teach or suggest all variables in common between formulas (II) and (IV) of the ’682 patent, including sulfonyl groups meeting the definition of Q and T.” Pet. 63-64. Petitioner’s obviousness analysis for these claims is deficient for the reasons provided above for claim 1-2.

5. Claims 20-21 and 29

Petitioner’s arguments for these claims are based on the same rationale as claims 1-2. Pet. 54-55 (arguing vinylsulfone is “a reactive functionality that forms thioether bonds” while mapping vinylsulfone to Y and Q); 56 (“For at least the same reasons discussed above ... a POSA would have been motivated to ...”), 60 (“For the same reasons given above ... a POSA would have been motivated to ...”). These arguments should be rejected for the same reasons provided above.

6. Claims 30-31

Singh in view of Harris does not render claims 30-31 obvious for the same reasons provided above for claims 1-2, and for additional reasons below. EX2038, ¶¶241-242.

As discussed in Section VI.B.4, claims 30-31 require that Q and T must both be present. As also discussed above, “Y” in claims 30-31 must be mapped to a reactive functional group, such as vinylsulfone, not just vinyl. Petitioner overlooks these limitations in its analysis regarding claims 30-31. EX2038, ¶242. Even assuming a POSA were to modify Singh's linker to incorporate *two* vinylsulfone conjugation moieties, one vinylsulfone must be mapped entirely to Y (as discussed above). *Id.* That leaves only one sulfone group (from the second vinylsulfone) for potential mapping to Q and T. Thus, one of Q and T would be missing. *Id.* And, as discussed above, Petitioner fails to demonstrate that Singh in view of Harris would have motivated a POSA to incorporate any Q or T spacer element, without its flawed reliance on vinylsulfone. *Id.*

D. Ground 4: Petitioner Fails to Show Singh in View of Harris and Bhakta Renders Obvious Claims 9 and 13.

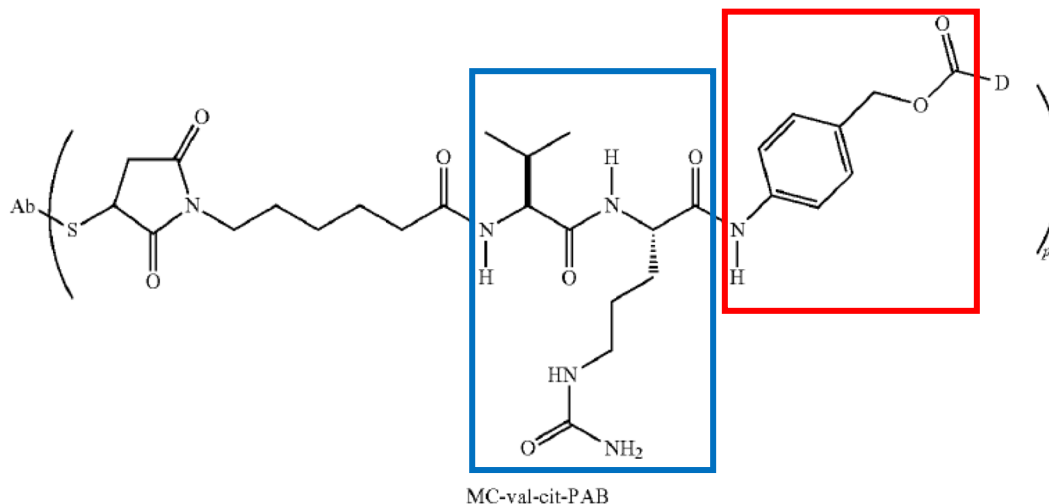
Ground 4 fails for the same reasons discussed above for Ground 3 and also fails for the following reasons. EX2038, ¶¶243-245.

1. Bhakta (EX1011)

Petitioner relies on Bhakta only for its purported showings of a “well-known val-cit-PAB linker.” Pet. 71-72; *see* EX2038, ¶¶102-105. Petitioner does not assert that Bhakta discloses any of the other claim elements of the '682 patent.

2. Claims 9 and 13

Petitioner argues Bhakta discloses the following structure with a dipeptide val-cit (highlighted in blue box) and a para-aminobenzylcarbamoyl (PAB) group (highlighted in red box). Pet. 71-72.



Petitioner also argues that “[a] POSA would have been motivated to use the well-known val-cit-PAB linker of Bhakta to replace, e.g., the disulfide linkage of Singh.” Pet. 72. Petitioner, however, does not explain which “disulfide linkage of Singh” is being replaced, which specific compound of Singh it is referring to, and whether the modified compound would still meet all the elements of claim 9 and 13, including the Q, T, m, n, and R₁ through R₆ elements in the claimed Formula II. EX2038, ¶245. Petitioner’s cursory analysis also does not demonstrate *how* a POSA would have allegedly combined the prior-art teachings to arrive at the claimed conjugate and whether a POSA would have had a reasonable expectation of success

in doing so. *Id.*

E. Ground 5: Petitioner Fails to Show Singh in View of Harris and Snow Renders Obvious Claims 2, 25, and 32-34.

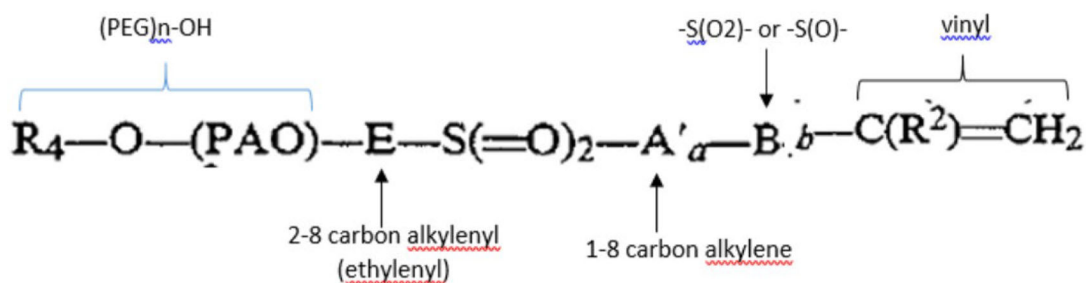
Claims 2, 25, and 32-34 each respectively depend from claims 1, 24, 30, 3, and 20. Ground 5 fails for the same reasons as discussed for Ground 3 and also fails for the following reasons. EX2038, ¶¶246-253.

1. Snow (EX1010)

Snow, a decades-old patent from 1995, discloses certain polyoxyalkylenes. *See* EX2038, ¶¶98-101. Petitioner relies on Snow only for its purported showings of “vinyl sulfone linkers containing PEG polymers” and “the bis-vinyl sulfone group.” Pet. 73-75. Petitioner does not assert that Snow discloses any of the other claim elements of the '682 patent.

2. Claims 2, 25, and 32-34

Petitioner argues that Snow allegedly discloses the following structure:



Pet. 73-74 (citing EX1010, 7:51-65). Petitioner argues that “a POSA 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 because such substitution would further enhance the hydrophilicity of the PEG linkers” Pet. 74. Petitioner’s obviousness arguments are infected with impermissible hindsight. EX2038, ¶¶249-253.

First, while Snow discloses the above genus structure, it defines the elements of that structure as broad genus groups, not the limited choices Petitioner depicts above. EX1010, 7:51-65 (defining R₄ as broad genus (not just H), and E, A, a B, b, and R₂ as “defined above”); *see also id.*, 5:61-6:10, 6:12-35, 6:56-57 (defining each of E, A, B, and R₂ as broad genus); EX2038, ¶249. Petitioner does not explain how and why a POSA would have selected the specific structural elements depicted above from the broad genus groups actually disclosed by Snow. EX2038, ¶250.

Second, Petitioner does not explain why a POSA would have selected the above genus structure over other structures disclosed in Snow. EX2038, ¶251. Indeed, Snow discloses a series of “preferred,” “more preferred,” and “even more preferred” embodiments. EX1010, 7:66-9:48. Petitioner does not explain why a POSA would not have instead looked to the more preferred embodiments of Snow. EX2038, ¶251.

Third, Petitioner argues, without support, that “bis-vinyl sulfone linkers of Snow impart higher water solubility.” Pet. 75. But Snow does not say anything about solubility or hydrophilicity. EX2038, ¶252. Indeed, the reason Petitioner has

to rely on Snow for these dependent claims is because when it mapped Singh's compounds to the claimed formula, many of the R₁ through R₄ groups are "absent." Pet. 57-59, 65-66. Petitioner's hindsight-driven combination of Singh and Snow allows it to assemble a compound with the R groups being alkyl, rather than absent, to meet the limitations of the dependent claims. Such structural changes to *add* several alkyl groups to a molecule would *decrease* the hydrophilicity of the molecule. EX2038, ¶252.

Lastly, for claim 2, Petitioner argues that it "specifies that Z comprises a maleimido group" Pet. 73. As discussed above in Section VI.C.3, keeping Z as maleimide as Petitioner argues for claim 2 is inconsistent with its arguments for claim 1 to substitute Z with vinylsulfone to supply a sulfone to be mapped to T. EX2038, ¶253.

VII. CONCLUSION

Patent Owner respectfully submits that Petitioner has not carried its burden and that patentability of the challenged claims should be confirmed.

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CERTIFICATE OF LENGTH (37 C.F.R. § 42.24)

The undersigned hereby certifies that, according to the word-processing system used to prepare the foregoing document, this document has 13,975 words and thus complies with the applicable word limit.

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CERTIFICATE OF SERVICE (37 C.F.R. §§ 42.6(E), 42.105(A))

The undersigned hereby certifies that the foregoing document was served in its entirety on December 6, 2024 upon the following parties via Electronic Mail:

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