

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SYNAFFIX B.V.,
Petitioner

v.

HANGZHOU DAC BIOTECH CO., LTD.,
Patent Owner

IPR2022-01531
Patent No 10,131,682

DRAFT PATENT OWNER PRELIMINARY RESPONSE

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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.
2009	Daugherty, A.L., et al., <i>Formulation and Delivery Issues for Monoclonal Antibody Therapeutics</i> , Advanced Drug Delivery Reviews (2006) 58:5-6, 686-706.
2010	Pappanaicken, R.K., et al., <i>Evaluation of Ketone-Oxime Method for Delivering Therapeutic On-Demand Cleavable Immunoconjugates</i> , Bioconjugate Chemistry (2016) 19:6, 1313-1318.
2011	Jeffrey, S.C., et al., <i>Expanded Utility of the β-Glucuronide Linker: ADCs That Deliver Phenolic Cytotoxic Agents</i> , ACS Medicinal Chemistry Letters (2010) 1, 277-80.
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2015	Hamblett, K., et al., <i>Effects of Drug Loading on the Antitumor Activity of a Monoclonal Antibody Drug Conjugate</i> , Clinical Cancer Research (2004) 10:20, 7063-7070.
2016	Junutula, J., et al., <i>Site-specific Conjugation of a Cytotoxic Drug to an Antibody Improves the Therapeutic Index</i> , Nature Biotechnology (2008) 26, 925–932.
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)
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
2029	WO2012/145112 (Fishkin)
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)

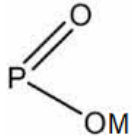
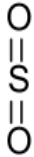
I. INTRODUCTION

HANGZHOU DAC BIOTECH CO., LTD. (“DAC”) is the owner of U.S. Patent No. 10,131,682 (Ex. 1001, “the ’682 Patent”). DAC submits this preliminary response to SYNAFFIX B.V.’s (“Petitioner”) Petition, which challenges the patentability of claims 1–17, 20–21, 24–26, and 29–34 of the ’682 Patent (the “Challenged Claims”). The Board should deny institution because Petitioner fails to establish a reasonable likelihood of prevailing as to any Challenged Claim.

The Challenged Claims are directed to linker structures used in therapeutic protein-drug conjugates, such as antibody drug conjugates (“ADCs”), which target specific cell populations to treat disease. The challenged independent claims fall into the following three classes based upon 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 '682 Patent specifically claims linkers with advantageous hydrophilic properties achieved as a result of incorporating specific polar phosphate- or sulfur-based moieties (such as phosphinate, sulfone (also called sulfonyl), and/or sulfoxide groups as shown in Fig. 1 below) into the backbone of the linker as what are known in the art as “spacer elements” and designated within the claims as “Q” and “T”:

Fig. 1		
Phosphinate	Sulfone	Sulfoxide
		

See EX1001, 2:53-55, 48:30-43. The Formula I claimed linkers also contain what is known in the art as a “conjugation moiety” located at each end (designated within the claims as “Y” and “Z”), which is a chemical functional group possessing specific reactivity that enables formation of a covalent bond between the linker and a cell-binding agent (*e.g.*, an antibody) and a covalent bond between the linker and a cytotoxic drug, respectively. EX.2001, ¶¶36-37, 40-43, 82-84, 95-9. The Formula IV claims are linkers conjugated to a drug on one end, with a conjugation moiety (“Y”) on the other end for attachment to a cell-binding agent. The Formula II claims are linkers conjugated to a drug on one end and a cell-binding agent (“Cb”) on the other end. As explained below, the unique use of the claimed spacer elements Q and

T, including in combination with the conjugation moieties Y and Z, was not disclosed, taught, or suggested in the prior art. The Petition should be denied.

At the outset, Petitioner's cited art and arguments are identical or substantially similar to prior art disclosing the same structures that have already been considered **twice** by the Patent Office—first during prosecution and second during reexamination. Petitioner seeks a redo of the Patent Office's patentability findings, but in so doing, relies on the same alleged prior art linker structures that the Patent Office already considered without identifying any evidence to suggest the Office's two previous considerations erred in any way. The Board should therefore invoke Section 325(d) and decline to revisit such challenges a third time.

The Petition also fails on the merits. Each of Petitioner's Grounds is flawed because Petitioner misreads the claims and incorrectly attempts to map the teachings of its alleged prior art onto the claimed linker structures of the '682 Patent. For Formulas I and IV, Petitioner conflates the distinct functional Y and structural Q/T claim elements into a single claim element and argues that the use of vinyl sulfone ($\text{CH}_2=\text{CH}_2-\text{SO}_2$)—a well-known functional conjugation moiety (designated within the claims as Y)—represents both the claimed Y conjugation moiety and the claimed Q or T spacer element. More specifically, Petitioner separates vinyl sulfone into two components (vinyl or $\text{CH}_2=\text{CH}_2$) and sulfone (SO_2), and argues that they map onto Y and Q/T, respectively. As explained below, this argument ignores, as Petitioner

admits, that vinyl alone cannot “enable[] reaction of the hydrophilic linker with a cell-binding agent,” which is the recited functional requirement of claim element Y. Moreover, if Q is folded into a Y/Q hybrid structure, as Petitioner contends, then the structure as a whole is identical to the very art that it overcame during prosecution. Indeed, it was the recitation of the independent Q and T structural spacer elements that led to the novelty of the Challenged Claims. Additionally, for Formulas I and IV, Petitioner fails to show the structures it maps to claim element Z “enable[] linkage of the hydrophilic linker to a **cytotoxic drug**” as required by the claim language.

With respect to Formula II, Petitioner does not demonstrate that the alleged prior art discloses a “cell-binding agent” or “drug,” which are necessary elements of the claims. Petitioner’s obviousness arguments also fail because Petitioner does not identify why a person of ordinary skill in the art (“POSITA”) would have allegedly been motivated to modify or combine prior art linkers to arrive at the claimed inventions. Instead, Petitioner’s arguments rely on unsupported and conclusory expert testimony which simply parrots the Petition’s arguments and, therefore, should be given no weight.

Ultimately, each of Petitioner’s Grounds contains a fatal flaw and institution of *inter partes* review of the ’682 Patent should be denied.

II. THE '682 PATENT

The '682 patent, entitled "Hydrophilic Linkers and Their Uses for Conjugation of Drugs to Cell Binding Molecules" issued from U.S. Application No. 14/432,073 (the '073 Application), a national stage entry of PCT/IB2012/056700 that was filed on November 24, 2012. The '682 Patent is therefore entitled to a priority date of November 24, 2012, which Petitioner does not dispute. *See, e.g.*, Pet. 19.

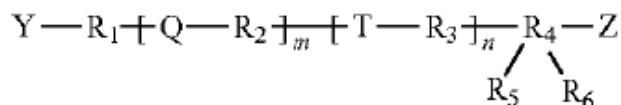
A. Claims

Relevant to the present challenge, the '682 Patent claims three types of linker structures in Formulas I, II, and IV shown in Table 1 below.

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

Claim 1 of the '682 Patent is representative. It recites, 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 $-\text{P}(=\text{O})(\text{OM})-$, or $-\text{S}(\text{O}_2)-$, or $-\text{S}(\text{O})-$;

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 $-\text{P}(=\text{O})(\text{OM})-$; when $n=1$, $m=0$, T is not $-\text{P}(=\text{O})(\text{OM})-$; and when Q or T is $-\text{S}(\text{O}_2)-$, 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; [...]

As shown above, the other independent claims are directed to structures of Formulas II and IV, wherein the linker is conjugated to a drug, (Formula IV: Claims 20, 29, 30), or a cell-binding agent and a drug (Formula II: Claims 3, 24, 26).

The challenged dependent claims are generally directed to the structures comprising the conjugation moiety Z (Claim 2), spacer elements (Claims 9, 31), the cell-binding agent (Claims 6, 7), or drug (Claims 4, 5, 8, 10, 14, 21). Dependent claims 16 and 17 are directed to a pharmaceutical composition containing the

claimed linker structure. Other dependent claims are directed to functional properties of the conjugate containing the linker, such as possessing cell killing activity (Claim 11) and being cleavable by a protease (Claim 13).

B. Specification

The '682 Patent describes the goal of targeting and treating specific cell populations, such as cancer cells, using a selective cell-binding agent such as an antibody attached to a drug compound. *See, e.g.*, EX1001, 1:19-2:3 (discussing, *e.g.*, “[t]issue-selective drug delivery” and “selective permeation” of anticancer agents into a tumor); 1:26-49; 2:53-67; EX.2001, Section II, ¶¶98-100. The '682 Patent also describes attempts to achieve this goal through various prior art antibody-drug conjugates in which targeting agents are connected to a drug with a linker. EX1001, 2:4-24. The '682 Patent recognizes, however, that the “nature of the linker significantly affects the potency, selectivity and the pharmacokinetics of the resulting conjugates.” EX1001, 1:53-61. The '682 Patent then discloses that its novel linkers are desirable to address such concerns and achieve therapeutic goals. EX1001, 1:45-67; EX.2001, ¶¶87-89.

The components of the claimed linkers are distinct and serve different purposes. EX.2001, ¶¶90-97, 110-129. They are not interchangeable or overlapping. *Id.* For example, in the hydrophilic linker of Formula I, Y and Z are conjugation moieties that enable reaction with a targeting domain (*e.g.*, cell-binding

agent) and a therapeutic domain (*e.g.*, cytotoxic drug), respectively. EX1001, 3:11-23; EX.2001, ¶91. Indeed, the Y and Z groups are described and claimed in terms of their **function**. Specifically, Y “represents a functional group that enables reaction with a cell-binding agent.” EX1001, 8:21-22; *see also id.*, 8:61-67, 13:51-63; EX.2001, ¶¶95, 110-116. Similarly, Z “represents a functional group that enables linkage of a cytotoxic drug via” certain groups. EX1001, 8:28-29; *see also id.*, 9:1-7, 14:14-34; EX.2001, ¶¶97, 117-124. As DAC’s expert (Dr. Nathan Tumey¹) explains, at the time of invention of the ’682 Patent, a POSITA would have been very familiar with the concept of “conjugation moieties” on linker structures. EX.2001, ¶¶40-43, 125.

In contrast, the ’682 Patent defines and claims the intervening elements between the Y and Z groups in terms of their specific **structures**. The patent describes and claims Q and T as phosphinate, sulfonyl, and/or sulfoxide groups.

¹ See EX.2001, ¶¶7-12 (Dr. Tumey is currently an Assistant Graduate Director and Associate Professor in the School of Pharmacy and Pharmaceutical Sciences at Binghamton University, where he leads a team of research scientists specializing in the application of ADCs and related modalities for the treatment of cancer and autoimmune disorder. For more than a decade before that, Dr. Tumey led several ADC drug-discovery teams at Pfizer).

EX1001, 3:14-15, 7:58-60; *see also id.*, 2:53-55. R₁, R₂, R₃, R₄, R₅, and R₆ are described and claimed as various atoms or branched alkenyl or alkynyl structures. EX1001, 3:24-65. A POSITA would recognize that these intervening elements—“spacer elements,” as Dr. Tumey explains—are separate and distinct structures from the Y and Z groups and serve different roles in the linker than the conjugation moieties. EX.2001, ¶¶36-48; 92-97, 110-129.

Indeed, the '682 Patent inventor recognized the benefits of using specific spacer elements—“phosphinate, sulfonyl, and/or sulfoxide groups”—in therapeutic linkers. EX1001, 2:53-55. When combined with other linker components, these groups yield hydrophilic linkers that advantageously “minimize the amount of aggregation” *in vivo* to “allow for as high [of] drug loading as possible” in therapeutic applications. *See* EX1001, 2:47-49. Moreover, the incorporation of hydrophilic spacer elements confers beneficial properties to the overall cell-binding drug conjugate, including improving stability, decreasing aggregation, reducing immunogenicity, and improving *in vivo* therapeutic safety and efficacy. EX1001, 2:60-67; *see also* EX.2001, ¶94.

To this end, the patent teaches “cell-binding agents” that are used to modify specific populations of cells (*e.g.*, targeting cancer cells using an antibody-drug conjugate). EX1001, 14:38-15:32. The patent defines a cell-binding agent as “a molecule that binds to, complexes with or reacts with a moiety of a cell population

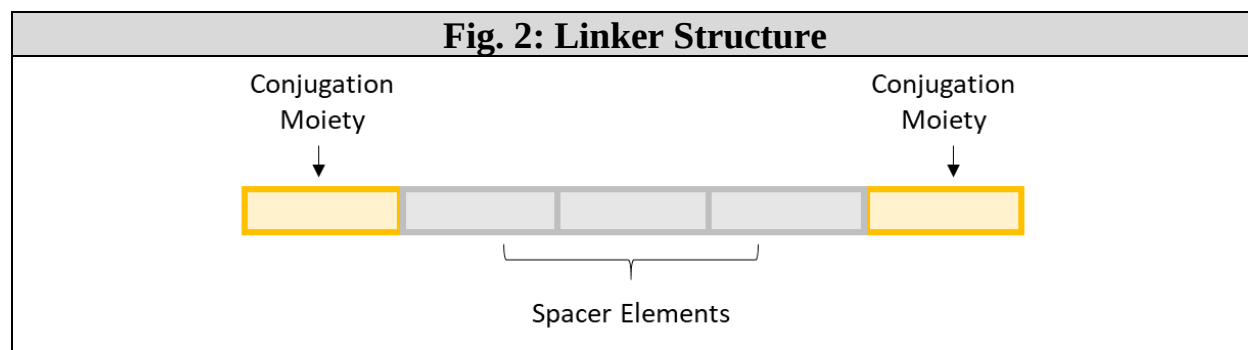
sought to be therapeutically or otherwise biologically modified.” EX1001, 14:42-44. Cell-binding agents include large molecular weight proteins such as, *e.g.*, full length antibodies (polyclonal antibodies, monoclonal antibodies, dimers, multimers, multi-specific antibodies), single chain antibodies, and antibody fragments that selectively target and bind a specific cell surface antigen. EX1001, 14:45-15:32. The patent teaches different options for this agent. EX1001, 14:39-28:5. Accordingly, a POSITA reading the '682 Patent would recognize that the cell-binding agent is intended to target (modify) a particular cell population (*e.g.*, by binding a cell-specific receptor for that particular cell population). EX.2001, ¶¶130-133. In contrast, the claimed “cell-binding agent” does not indiscriminately bind cell populations that are not targeted, as this would undermine the purpose of the linker (and the entire conjugate). EX.2001, ¶132.

III. TECHNICAL BACKGROUND

As noted above (Section II), the '682 Patent relates to linkers for therapeutic conjugates. *See, e.g.*, EX.2001, Section VIII.B, ¶87. Protein-drug conjugates, particularly antibody-drug conjugates (ADCs), have been used as drug delivery vehicles for the treatment of cancer. *Id.*, Section VI.A, ¶¶29-36. These conjugates typically contain three building blocks: a targeting domain that can bind a specific cell population, a therapeutic domain (*e.g.*, a cytotoxic drug), and a linker that covalently connects these two domains. *Id.*, ¶31. Typically, these conjugates are

used to selectively target cancer cells because they contain moieties (*e.g.*, antibodies) that recognize and bind cancer-specific cellular markers. *Id.*, ¶¶30-32. These conjugates, which are also bound to chemotherapeutic drugs, selectively deliver the drugs to the targeted cancer cells. *Id.*, ¶¶30-32, 89. The conjugate platform significantly increases the potency and efficacy of chemotherapies while minimizing off-site toxicity. *Id.* As a POSITA would understand, the design of the linker impacts the efficacy of protein-drug conjugates as it can affect both the stability of the conjugate in the bloodstream and efficient release of the drug in diseased cells. EX.2001, ¶¶33, 48.

A linker is a polymer composed of discrete components, as depicted in Fig. 2 below. EX.2001, ¶36.

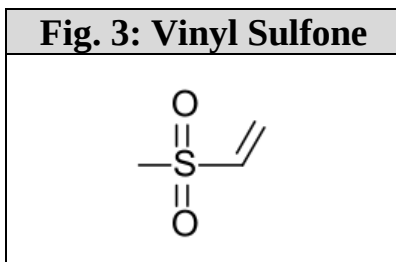


At each end of the linker are “conjugation moieties,” which are used to bind the cell-targeting moiety and the drug, respectively. EX.2001, ¶¶37, 40-43; EX.2010, 13. Conjugation moieties are specifically reactive chemical functional groups that enable formation of a covalent bond with the targeting domain (*e.g.*, an

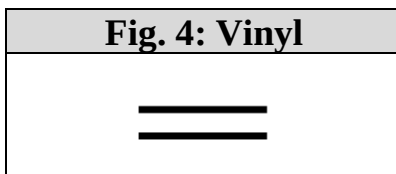
antibody) on one end of the linker and the therapeutic domain (*e.g.*, a cytotoxic drug) on the other end of the linker. EX.2001, ¶40; EX.2012, 523. To drive these attachment reactions and form the covalent bond in both cases, the conjugation moiety must have specific electrophilic (electron accepting) reactivity, while the functional groups on the antibody or drug must have specific nucleophilic (electron donor) reactivity. *Id.*, ¶¶40-42. Absent this reactivity of the conjugation moiety, a covalent bond will not form and the linker will not attach to the antibody or drug, respectively. EX.2001, ¶40.

In between the conjugation moieties are “spacer elements,” another well-known term of art. EX.2001, ¶¶38, 44-48; EX.2011, 277. Spacer elements can affect the linker’s properties. For example, spacer elements function to impart stability to the overall protein-drug conjugate both during synthesis and in the bloodstream, as well as offset steric effects that arise from bulky antibody and drug components. EX.2001, ¶44; EX.2012, 523.

Vinyl sulfone ($-\text{CH}_2=\text{CH}_2-\text{SO}_2-$), *see* Fig. 3 below, can act as a conjugation moiety to enable connection of an antibody to a linker. EX.2001, ¶¶49-51, 96.



The ability to form this connection is due to an electrophilic (electron withdrawing) substituent, sulfone, being ***directly bonded*** to vinyl without any intervening atoms, facilitating the shift of electrons toward the sulfone, thereby creating an electron deficiency at the terminal carbon of the vinyl. *Id.*, ¶¶ 50-51; EX.2012, 488-89; EX.2013, 303-307. This electron void enables the ***vinyl sulfone moiety as a whole*** to become reactive and attracted to a nucleophilic (electron donor) substituent (such as a cysteine) on an antibody, thus serving as a conjugation moiety on the linker. EX.2001, ¶¶ 50-51. In contrast, vinyl (C=C), as shown in Fig. 4 below, alone (without being directly connected to an electron withdrawing group) cannot act as a conjugation moiety to attach a linker to an antibody and create a new covalent linkage. *Id.*, ¶¶ 51-53; EX.2012, 488-89, 491; EX.2019, 933.



Instead, vinyl requires the presence of sulfone or another strong electron withdrawing group linked to the vinyl to become reactive and enable a conjugation reaction with an antibody. EX.2001, ¶¶ 51-53.

IV. THE ASSERTED PRIOR ART

Petitioner asserts five Grounds against the Challenged Claims relying on one or more of the following references for each Ground: Morales-Sanfrutos (EX1005); Straus (EX1006); Harris (EX1007); Singh (EX1008); Snow (EX1010); and Bhakta

(EX1011). Petitioner's arguments concerning each of these references ignore or mischaracterize the teachings of the prior art as explained below.

A. Morales-Sanfrutos (EX1005)

Petitioner does not argue that its Ground 1 reference, Morales-Sanfrutos (EX1005), is analogous art to the '682 Patent. Nor could Petitioner do so, which is ultimately its burden. *See Sanofi-Aventis Deutschland GmbH v. Mylan Pharmaceuticals*, No. 2021-1981, 2023 WL3311549 at *6 (Fed. Cir. May 9, 2023) (reversing invalidity holding because patent challenger did not meet its burden to establish analogousness of prior art reference). Morales-Sanfrutos is not from the same field of endeavor as the '682 Patent's inventions, as Morales-Sanfrutos does not relate to the field of therapeutic protein-drug conjugates. EX.2001, Section VII.A, ¶54. For example, Morales-Sanfrutos does not disclose antibody-drug conjugates, cytotoxic drugs, a functional group capable of attachment to a cytotoxic drug, or even drugs generally. *Id.*, ¶54. Rather, it discloses a reporter system, which is a platform used to visualize the potential activity of biomolecules. *Id.* Nor is Morales-Sanfrutos reasonably pertinent to the problem facing the inventors of the '682 Patent. 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

Morales-Sanfrutos is not directed to and does not teach therapeutic linkers, much less linkers that solve the identified need in the '682 Patent, it is not reasonably pertinent to this problem.

Moreover, as Petitioner admits, Morales-Sanfrutos was before the Examiner during re-examination of the '682 Patent. Pet. 79 (admitting Morales-Sanfrutos was listed in an IDS). The Examiner did not raise any rejections over Morales-Sanfrutos), which further supports that Morales-Sanfrutos does not expressly or inherently teach all elements of the '682 Patent claims arranged as in the claim. EX.2033 (citing file history excerpt where Examiner signed the IDS listing Morales-Sanfrutos).

Morales-Sanfrutos teaches that vinyl sulfone—not vinyl alone—has the ability to functionally react for protein conjugation. Specifically, it “report[s] on the synthesis of bifunctional tag single-attachment-point reagents (BTSAP) bearing both biotin (affinity tag) and a fluorophore (fluorescent tag) and ***a vinyl sulfone function as a reactive linking group.***” EX1005, 4040. Morales-Sanfrutos further clarifies that “***vinyl sulfone is an appealing function for protein conjugation***”—*e.g.*, conjugation to a “cell-binding agent”—“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.” EX1005, 4040. Thus, Morales-Sanfrutos teaches that vinyl sulfone—not vinyl alone—is a functional group that

enables reaction of a linker with a protein (*e.g.*, a cell-binding agent). EX.2001, ¶57. A POSITA would recognize that PEG structures in Morales-Sanfrutos' linkers serve as spacer elements and that Morales-Sanfrutos does not teach the use of phosphate- or sulfur-based moieties as spacer elements, such as in the '682 Patent's claim element Q. EX.2001, ¶57. And Petitioner fails to identify any other alleged Q group in Morales-Sanfrutos besides the sulfone that it attempts to extract from the vinyl sulfone disclosed therein.

Moreover, Morales-Sanfrutos does not disclose a "cell-binding agent," as claimed. Instead, Morales-Sanfrutos' linkers are conjugated to horseradish peroxidase ("HRP"). While Petitioner contends that HRP is a "cell-binding agent" based on a reference other than Morales-Sanfrutos (Pet. 36), a POSITA would not understand HRP to be a cell-binding agent; rather a POSITA would understand HRP to be a reporter as expressly disclosed by Morales-Sanfrutos and discussed below. EX.2001, ¶¶54, 56; EX1005, 4041. Specifically, HRP is an enzyme that catalyzes oxidation of certain organic substrates by hydrogen peroxide, and a POSITA would have understood that HRP is widely utilized in cell-free biochemistry assays (*e.g.*, western blotting, ELISA) to detect proteins, not as a cell-binding agent. EX.2001, ¶58.

Indeed, consistent with the familiar use of HRP in the art—and not as a molecule that can target specific cell populations—Morales-Sanfrutos teaches that

HRP is used in its linker conjugates as a reporter. For example, it states that “because [of] its biotechnological relevance (HRP has been coupled to other molecules to use the peroxidase activity as a reporter).” EX1005, 4041; EX.2001, ¶56. Accordingly, Morales-Sanfrutos does not expressly or inherently teach that HRP is a cell-binding agent. EX.2001, ¶¶54, 56, 58. Petitioner fails to show otherwise and instead relies on Straus for this purported property of HRP (Pet. 36), which fails as explained *infra* (Section IV.B).

Petitioner also states that Morales-Sanfrutos’ linkers are conjugated to biotin, which Petitioner argues is a “drug.” Pet. 36. But Morales-Sanfrutos expressly discloses that biotin is a “tag,” not a “drug” (EX1005, 4040 (disclosing that biotin is “among the tags most commonly used in *omic* sciences”))), which makes sense given that Morales-Sanfrutos does not relate to the field of therapeutic protein-drug conjugates and, instead, discloses a reporter system. EX.2001, ¶54. Petitioner therefore fails to show any disclosure of a “drug” in Morales-Sanfrutos.

B. Straus (EX1006)

Petitioner does not argue that Straus (EX1006), also asserted in Ground 1, is analogous art to the ’682 Patent. Nor could Petitioner do so. Straus is not from the same field of endeavor as the ’682 Patent’s inventions, as Straus does not relate to the field of therapeutic protein-drug conjugates. EX.2001, Section VII.B, ¶59. For example, Straus does not disclose a therapeutic cell-binding agent that can be used

to modify (target) a specific cell population unlike the '682 Patent. See EX1001, 14:39-44; EX.2001, ¶59. Instead, as explained *infra*, Straus merely purports to show that HRP *may* be able to bind to the surfaces of *some* cells, under undetermined and poorly defined conditions. EX.2001, ¶¶60-62; EX1003, ¶36. Nor is Straus reasonably pertinent to the problem facing the inventors of the '682 Patent. See *supra* Section IV.A (Morales-Sanfrutos); EX1001, 2:45-49. For example, Straus does not teach any therapeutic cell-binding agent (*e.g.*, a cancer-specific antibody). EX.2001, ¶59. Petitioner therefore has not met its ultimate burden to qualify Straus as prior art. See *Sanofi*, 2023 WL3311549 at *6.

Moreover, as Petitioner admits, Straus was before the Examiner during re-examination of the '682 Patent. Pet. 79 (admitting Straus was listed in IDS). The Examiner considered Straus and did not issue any rejections over it, which further supports that Straus does not expressly or inherently teach the claimed “cell-binding agent.”

As explained herein (Section VI.B.4), 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; EX.2001, ¶130. Straus neither teaches nor suggests—much less inherently discloses—the use of HRP to target specific cell populations, such as in a therapeutic conjugate. EX.2001, ¶¶59, 133. Petitioner fails to show otherwise.

For example, Straus does not teach nor suggest—much less inherently disclose—that HRP possesses the ability to target specific cell populations or that it could be used for such purpose. EX.2001, ¶60. Instead, Straus merely states that “[b]inding sites for horseradish peroxidase (HRP) with unusual properties, were detected on the surface of cultured and isolated cells,” EX1006, 277, indicating that, in fact, HRP’s ability to bind cells is atypical or poorly characterized. EX.2001, ¶61. Nor does Straus identify a specific cellular target bound by HRP. *Id.* Rather, it suggests “the possibility may be considered” that HRP binds to a cellular protein (e.g., glycosyltransferase), but it caveats that such binding is inhibited by compounds containing carbohydrates (*e.g.*, UDP, CDP, GTP, NAD, and ribose 5-phosphate), which are all present *in vivo*. EX1006, 284; EX.2001, ¶61. Straus also notes that calcium plays a role in binding HRP to cell surfaces, indicating that HRP lacks cell-binding functionality when calcium is absent. EX.2001, ¶61. Straus also describes various limitations of its study, including the presence of artifacts, which further underscore the uncertainty of its purported conclusions. EX.2001, ¶61.

Indeed, Straus’s teachings regarding HRP’s purported cell-binding activity are not mainstream, well-known, or relied upon. EX.2001, ¶59. Rather, HRP is routinely used (*e.g.*, in **cell-free** assays) to detect the presence of a protein. *Id.*, ¶58.

C. Harris (EX1007)

Petitioner does not argue that its Ground 2 reference, Harris (EX1007), is analogous art to the '682 Patent. Indeed, 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 protein-drug conjugates. EX.2001, Section VII.C, ¶63. 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 (emphasis added); EX.2001, ¶¶64-68. Harris's disclosure about pharmaceuticals is general and explains that "almost any substance could be modified." EX1007, 18:34-19:2; EX.2001, ¶63. Yet it does not specifically teach conjugation of a drug to an antibody or other protein for use in therapeutic targeting. EX.2001, ¶63. Accordingly, Harris relates to a different field of endeavor and Petitioner has failed to show otherwise.

Nor is Harris reasonably pertinent to the problem facing the '682 Patent inventors. See Section IV.A; 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. See, e.g., EX.2001, ¶63. Petitioner has not met its ultimate burden to qualify Harris as prior art. See *Sanofi*, 2023 WL3311549 at *6.

Moreover, Harris teaches that that vinyl sulfone—not vinyl alone—has functionality when attached to PEG linkers. For example, Harris teaches:

Specific sulfone moieties for the activated polymers of the invention are those having at least two carbon atoms joined to the sulfone group -S02 - 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. . . . The derivatives of the vinyl and ethyl sulfones can include other substituents, ***so long as*** the water solubility and ***the thiol-specific reactivity of the reactive site on the second carbon are maintained.***

EX1007, 7:3-22 (emphasis added). The use of vinyl itself is not separately taught in Harris to achieve the desired functionality. EX.2001, ¶64. Petitioner fails to identify a different alleged Q group in Harris besides the sulfone it attempts to extract from the vinyl sulfone (or similar sulfone-containing groups) despite bearing the burden to do so.

D. Singh (EX1008)

Petitioner admits Singh was considered by the Examiner during reexamination of the '682 Patent and no rejections were issued over this reference. See Pet. 79 (admitting Singh was listed in IDS).

Singh discloses various PEG linker structures that may be conjugated to maytansinoid drugs. EX.2001, Section VII.D, ¶¶69-73. Singh also teaches that vinyl sulfone may serve as a conjugation moiety. *Id.*, ¶70. Notably, however, Petitioner

admits that “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 (emphasis added). Petitioner therefore expressly concedes that Singh fails to teach either Q or T.

E. Snow (EX1010)

Snow discloses various polyoxyalkylene linkers. EX.2001, Section VII.E, ¶¶74-77. Petitioner relies on Snow (EX1010), a secondary reference in Ground 5, 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 elements of any Formula claimed in the ’682 Patent.

F. Bhakta (EX1011)

Bhakta discloses ADCs containing antibodies engineered with reactive cysteine residues for linker attachment and cleavable linkers. EX.2001, Section VII.F, ¶¶78-81. Petitioner relies on Bhakta—a secondary reference in Ground 4—only for its purported showings of a “well-known val-cit-PAB linker.” Pet. 71-72. Petitioner does not assert that Bhakta discloses any of the other elements of any Formula claimed in the ’682 Patent.

V. INSTITUTION SHOULD BE DENIED UNDER § 325(D)

At the outset, the Board should deny institution under 35 U.S.C. § 325(d) because Petitioner relies on identical or substantially the same prior art and

arguments previously considered by the Office, and Petitioner fails to show that the Office materially erred in its previous consideration of those materials.

A two-part analysis applies to the Board’s authority to deny institution under § 325(d). *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GMBH*, IPR2019-01469, Paper 6 at 9-10 (precedential). First, the Board considers whether “the same or substantially the same” art or arguments were previously presented to the Office. *Id.*, 8. If either is met, the Board then considers whether the Petitioner demonstrates that the Office “erred in a manner material to the patentability of the challenged claims.” *Id.* In applying the two-part framework, the Board considers several nonexclusive factors set forth in *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17-18 (PTAB Dec. 15, 2017) (precedential as to § III.C.5, first paragraph).

Petitioner admits that Morales-Sanfrutos, Straus, and Singh were before the Examiner during reexamination (Control No. 90/014,390). Pet. 8, 10, 79. Accordingly, under *Becton, Dickinson* Factors (a) and (b), these references—which include two of the three lead references in Petitioner’s Grounds—are identical to art considered by the Examiner and overcome during prosecution. EX.2001, Section VIII.C, ¶¶102-108. Petitioner does not attempt to argue otherwise. Pet. 78-79. *See, e.g., Ecofasten Solar, LLC v. Unirac, Inc.*, IPR2021-01379, Paper 11 at 38–39 (PTAB Feb. 8, 2022) (“Petitioner does not present any evidence or argument to

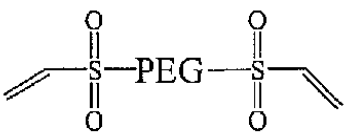
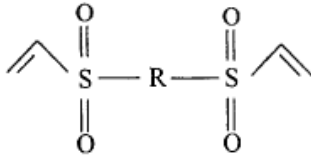
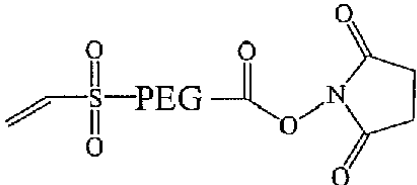
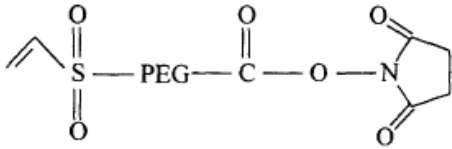
persuade us that [asserted references] are not the same or substantially the same as the prior art raised during the original prosecution or reexamination. Petitioner has the burden of proof to establish that it is entitled to the relief requested.”).

The remaining lead reference (Harris), as well as a secondary reference (Snow), are then cited by Petitioner for essentially the same teachings as Morales-Sanfrutos—*e.g.*, linkers containing vinyl sulfone groups. Pet. 5-9, 17; *see infra* Sections IV.A. IV.C, IV.E (explaining how Petitioner’s arguments concerning Harris and Snow fail for the same reasons as for Morales-Sanfrutos). Petitioner asserts “that none of the claims have been examined in view of prior art disclosing ADC and ADC precursors comprising acyclic bis-sulfonyl linkers.” Pet. 21. Petitioner thus contends that Harris and Snow are non-cumulative because they disclose PEG linkers comprising bis-vinyl sulfone. Pet. 78-79.

Petitioner is incorrect. During prosecution of the ’073 Application (which matured into the ’682 Patent), the Examiner issued three Office Actions and relied on the following references in making rejections under 35 U.S.C. § 102: U.S. Patent No. 5,094,848 (Brixner) (EX.2023) (*see* Non-Final Office Action dated August 15, 2017 (EX.2022)); WO1997/41897 (Lees) (EX.2026) (*see* Non-Final Office Action dated March 8, 2018 (EX.2025)); and WO2012145112 (Fishkin) (EX.2029) as evidenced by Kovtun et al., Cancer Research (2010), 70: 2528-2537 (EX.2005) and Widdison et al., Journal of Medicinal Chemistry (2006), 49:4392-4408 (EX.2030)

(see Final Office Action dated July 10, 2018 (EX.2028)). The claims were amended to overcome these rejections and subsequently allowed by the Examiner. (EX.2031-EX.2032).

The Lees reference cited by the Examiner discloses structures identical to the structures from Harris on which Petitioner relies on for Grounds 2-3. Pet. 38-42, 49; EX.2001, ¶¶103-106. Fig. 5 below depicts a comparison between the linkers in Harris that Petitioner relies on in its Petition and those in Lees that were before the Examiner during prosecution of the '682 Patent:

Fig. 5: Identical Linkers Disclosed in Harris and Lees	
Harris	Lees
 Homobifunctional sulfone linker structure	 Homobifunctional sulfone linker structure
 Heterobifunctional linker structure comprising vinyl sulfone and NHS	 Heterobifunctional linker structure comprising vinyl sulfone and NHS

In Lees' homobifunctional sulfone linker structure shown in Fig. 5 above, "R may be polyethylene glycol." Ex. 2026, 20:10-19. As Patent Owner's expert explains, Lees' homobifunctional sulfone is the same structure as Harris' bifunctional variation of a linear PEG derivative with bis vinyl sulfone that Petitioner

relies upon in Grounds 2-5. EX.2001, ¶105; Pet. 38-42, 49; *see e.g.*, EX1007, 16:37-17:5 (“A linear PEG with active hydroxyls at each end can be activated at each end with vinyl sulfone ... to become bifunctional. The bifunctional structure, PEG bis vinyl sulfone, for example, is sometimes referred to as a dumbbell structure...”). This structure is also identical to Snow’s polymeric bis vinyl sulfone linker shown below in Fig. 6 where A represents PEG PEG and B represents a sulfone group. EX.2001, ¶107; Pet. 17; EX1010, 7:14-27.

Fig. 6: Snow’s Polyalkylene Oxide Bis (Vinyl Sulfone) Linker
$\text{CH}_2=\text{CH}-\text{SO}_2-\text{A}_a\text{B}_b-\text{CH}=\text{CH}_2$

Moreover, as shown in Fig. 5 above, Lees also teaches a heterobifunctional vinyl sulfone PEG linker containing N-hydroxysuccinimide (NHS) on one end and vinyl sulfone on the other end, which is the same structure as Harris’ heterofunctional variation of a linear PEG derivative with vinyl sulfone that Petitioner relies upon in Ground 2. EX.2001, ¶106; Pet. 42; *compare* Ex. 2026, 23:9-15 *with* Ex. 1007, 18:11-15.

During reexamination of the ’682 Patent (Control No. 90/014,390), Morales-Sanfrutos and Straus were cited in an IDS form and appeared on the list of considered references by the Examiner. EX.2033. Additionally, Singh substantially overlaps with WO2009/134976 (Singh ’976) (EX.2034), which was cited in an IDS form and appeared on the list of considered references by the Examiner (EX.2033). EX.2001,

¶108. Lees' PEG linker structure comprising bis vinyl sulfone structure is also the same as compound 1 disclosed by Morales-Sanfrutos (EX1005, 4041, Fig. 2). EX.2001, ¶108.

Under at least *Becton, Dickinson* Factors (c) and (d), Petitioner's arguments concerning Harris's and Snow's bis vinyl sulfone linkers are, therefore, cumulative of art expressly considered and overcome by the Examiner during prosecution.

In light of the above, it is clear that Petitioner merely seeks to rehash the same structures and arguments that were already overcome during prosecution. Petitioner does not show that this is warranted—it is not—as Petitioner wholly fails to establish that the Office committed any error with respect to its prior two considerations of the art. While Petitioner asserts that the Examiner merely gave “cursory consideration” to the references (Pet. 79), Petitioner provides no factual basis to support its position. *See Intervet America, Inc. v. Kee-Vet Laboratories, Inc.*, 887 F.2d 1050, 1054 (Fed. Cir. 1989) (“The presumption of validity under 35 U.S.C. § 282 carries with it a presumption the examiner did his duty and knew what claims he was allowing.) Additionally, Petitioner presents no new evidence, or even argument, suggesting that its asserted references include teachings that were unavailable to the Office when the Challenged Claims were found and confirmed to be patentable in prior examination or re-examination. Thus, Petitioner fails to satisfy *Becton, Dickinson* Factors (e) or (f) and has not met its burden to show that the

Office committed error. *See, e.g., Xilinx, Inc. v. Analog Devices, Inc.*, IPR2021-00294, Paper 9 at 29 (PTAB June 10, 2021) (“Petitioner does not provide any indication that the Examiner’s prior art analysis in the prosecution history was error.”). The identical and cumulative references available and considered by the Patent Office during prosecution and reexamination, coupled with Petitioner’s failure to identify any error in this Office’s two prior patentability determinations, renders Grounds 1-5 redundant and the Board should exercise its discretion to deny institution.

VI. INSTITUTION SHOULD BE DENIED ON THE MERITS

Petitioner asserts five Grounds against the Challenged Claims. In Ground 1, Petitioner alleges that Morales-Sanfrutos as evidenced by Straus anticipates Claims 1-3, 6, 24-25, and 33. Pet. 24. In Ground 2, Petitioner alleges anticipation or obviousness of claims 1, 20-21, and 29-31 in view of Harris. *Id.*, 37. In Ground 3, Petitioner alleges obviousness of claims 1-8, 10-12, 14-17, 20-21, 24, 26, and 29-31 over Singh in view of Harris. *Id.* 44. In Ground 4, Petitioner alleges obviousness of claims 9 and 13 over Singh in view of Harris and Bhakta. *Id.*, 70. In Ground 5, Petitioner alleges obviousness of claims 2, 25 and 32-34 over Singh in view of Harris and Snow. *Id.*, 73. Petitioner bears the burden of demonstrating a reasonable likelihood that it will prevail in showing the unpatentability of at least one Challenged Claim. 35 U.S.C. §§ 314(a), 312(a)(3).

Regarding alleged anticipation in Grounds 1 and 2, Petitioner must show a reasonable likelihood of proving that “the four corners of a single, prior art document describe every element of the claimed invention” in the same specific “arrange[ment] as in the claim.” *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369-71 (Fed. Cir. 2008). Petitioner fails to do so because each Ground contains the same fatal flaw at the outset. Among other arguments, the Grounds identify a single prior art conjugation moiety—*e.g.*, vinyl sulfone—and contend that pieces of that structure—vinyl and sulfone—map to **both** a conjugation moiety claim term (Y or Z), and, separately a spacer element (Q or T).

While a prior art structure might be permissibly parceled into substructures for an invalidity argument in certain circumstances, this is not one of those times. The claimed linkers in the '682 Patent are a combination of separate and distinct elements: functional conjugation moieties on the ends (Y or Z), and structural spacer elements in the middle (Q, T, R groups). As this Office twice recognized, the claimed polar spacer elements in the '682 Patent linkers are separate and distinct from the claimed conjugation moieties (including the individual pieces of conjugation moieties). None of Petitioner's cited references teach these novel spacers. Indeed, Petitioner's attempt to draw a line between vinyl and sulfone in order to find the missing spacer element fails because, when vinyl is not connected to sulfone, vinyl is ineffective as a conjugation moiety. And when vinyl is connected

to sulfone in Petitioner's cited art, then Q and T are absent. Either way, Petitioner's challenge falls short.

Additionally, Petitioner's Ground 1 anticipation challenge also fails because Petitioner does not demonstrate that the prior art discloses a "cell-binding agent" or "drug," which are necessary elements of those Challenged Claims.

Petitioner's obviousness arguments in Grounds 2-5 fare no better. Petitioner must show a reasonable likelihood of proving that "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made" to a skilled artisan. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). Petitioner must "articulate specific reasoning, based on evidence of record, to support the legal conclusion of obviousness." *U.S. Well Servs., LLC v. Halliburton Energy Servs., Inc.*, IPR2022-01163, Paper 9 at 10 (PTAB Dec. 20, 2022) (quoting *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016)).

Petitioner does not identify why a POSITA would have allegedly been motivated to modify or combine prior art linkers to arrive at the claimed inventions—namely, linkers with conjugation moieties and, separately, the claimed spacers. Similar to its Section 102 arguments, Petitioner contends that it would be obvious to add vinyl sulfone (a conjugation moiety) to prior art linkers and that the sulfone in that conjugation moiety should be considered the novel claimed spacer.

Like Petitioner's 102 arguments, Petitioner's 103 arguments in Grounds 2-5 fail because they distort the true scope of the '682 Patent claims and misinterpret the teachings of the prior art. Petitioner's expert merely parrots the Petition and fails to shed further insight, including any alleged reason to combine or modify the asserted references.

Accordingly, institution should be denied.

A. Level of Ordinary Skill in the Art

According to Petitioner, a POSITA for the '682 Patent would have had highly specialized knowledge in the field of linkers and conjugates for biologically-active molecules, which would entail (1) a Ph.D. degree in organic chemistry, biochemistry, medicinal chemistry and/or pharmacology, along with 1-2 years of relevant applied research and/or industry experience in the field of linkers and conjugates for biologically-active molecules or (2) alternatively, a Masters or Bachelor's degree in one of these fields with, respectively, at least 3-5 or 5-7 years' work experience. Pet. 18-19.

DAC adopts Petitioner's proposed level of skill in the art solely for the purposes of this Preliminary Response. DAC reserves the right to address the level of ordinary skill and/or propose a different level of ordinary skill, *e.g.*, should Petitioner amend its proposed definition or if the Board institutes trial.

B. Claim Construction

Petitioner states that it “does not currently believe that any claim terms require construction for purposes of deciding this Petition.” Pet. 24. Yet in light of Petitioner’s mischaracterization of the Challenged Claims and prior art as explained herein, Patent Owner disagrees and believes that the following terms of the ’682 Patent claims warrant construction.

1. “Y” (Claims 1, 20, 29, 30)

“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)). As a matter of law, the claimed “Y” term should be interpreted as a component distinct and separate from the other recited components, including “Q” and “T”, of the claimed linkers of Formula I (claim 1) and Formula IV (claims 20, 29, 30). *See also* EX.2001, Section IX.A, ¶110.

Additionally, the “Y” term should be construed as requiring that Y, as a functional group distinct from Q/T (and other claimed elements of the linker), ***independently enable*** the reaction of the linker with a cell-binding agent. EX.2001¶¶110-116.

The plain language of the claims supports DAC's interpretation of "Y". *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (*en banc*). For example, claim 1 recites that "Y" "represents **a functional group that enables reaction** of the hydrophilic linker with a cell-binding agent." Similarly, claims 2, 29, and 30 recite that "Y" "represents **a functional group that enables reaction** of the compound with a cell-binding agent." The terminology "enables reaction" means that the Y structure by itself allows for the reaction between the linker (compound) and cell-binding agent to occur. EX.2001, ¶111. Petitioner does not point to anything in the '682 Patent demonstrating otherwise.

Moreover, as explained above, other structures of the claimed Formulas, including Q and T, are recited as separate and distinct elements from Y. For example, the claims do not recite that Q and Y together "enables reaction" with the cell-binding agent; rather, as discussed above, the intrinsic evidence defines Q and T to be three particular structures and Y as the functional element. *Id.*, ¶112. Further supporting DAC's position is that the claims recite that an optional intervening structure, "R1," can be located between and therefore physically separate Y from Q. *Id.* Thus, in some embodiments of the claimed linkers, the Q structure is not directly adjacent to Y and any effect of Q on Y would be attenuated or eliminated. *Id.*

The specification also supports DAC's construction; it reiterates that Y is defined as a structure that is specifically attracted to and independently reactive with

certain chemical groups present on a cell-binding agent. EX1001, 8:61-67, 13:51-63; EX.2001, ¶¶113-115. For example, the '682 Patent 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. Additionally, cell-binding agents bearing a carbonyl substituent can react with cross linkers bearing a hydrazide or a hydroxylamine.” EX1001, 13:54-60. “One skilled in the art can readily determine which linker to use based on the known **reactivity of the available functional group** on the cell-binding agent.” EX1001, 13:61-63 (emphasis added). Y, not Q or T, is claimed as “a functional group.” EX1001, 48:30-43; EX.2001, ¶115.

2. “Z” (Claim 1)

As with “Y” above, the claimed “Z” term should be interpreted as a component distinct and separate from the other recited components, including “Q” and “T”, of the claimed linkers of Formula I (claim 1). EX.2001, Section IX.B, ¶117.

Additionally, the “Z” term should be construed as requiring that Z, as a functional group separate from Q or T (and other claimed elements of the linker), **independently enable** the reaction of the claimed linker with a **cytotoxic drug**. EX.2001, ¶¶117-124.

The plain language of the claims supports DAC's interpretation of "Z". *Phillips*, 415 F.3d at 1313. For example, claim 1 recites that "Z" "represents a **functional group that enables linkage** of the hydrophilic linker **to a cytotoxic drug**." The limitation "cytotoxic drug" requires that Z enable attachment of the linker to a particular class of cell-killing compounds. EX.2001, ¶119. Additionally, the terminology "enables reaction" means that the Z structure by itself allows for the reaction between the linker (compound) and cytotoxic drug to occur. *Id.* The claim language further specifies the type of chemical linkage between the claimed linker and cytotoxic drug, which must occur "via a disulfide, thioether, thioester, hydrazone, ether, ester, carbamate, carbonate, secondary, tertiary, or quaternary amine, imine, cycloheteroalkane, heteroaromatic, alkoxime or amide bond." *Id.* Petitioner does not point to anything in the '682 Patent demonstrating otherwise.

Moreover, as explained above, other structures of the claimed Formula I, including Q and T, are recited as separate and distinct elements from Z. EX.2001, ¶120. For example, the claims do not recite that T and Z together "enables reaction" with a cytotoxic drug; rather as discussed above, the intrinsic evidence defines Q and T to be three particular structures and Z as the functional element. *Id.* Further supporting DAC's position is that the claims recite that optional intervening structures, such as "R3" and "R4," can be located between and therefore physically separate Z from T. *Id.* Thus, in some embodiments of the claimed linkers, the T

structure is not directly adjacent to Z and any effect of T on Z would be attenuated or eliminated. *Id.*

The specification also supports DAC's construction; it reiterates that Z is defined as a structure that is specifically attracted to and independently reactive with certain chemical groups present on a cytotoxic drug. EX1001, 8:61-67, 13:51-63; EX.2001, ¶¶121-123. For example, the '682 Patent teaches various cytotoxic drugs that can be attached to the claimed linkers, including "analogs of tubulysins, calicheamicins, maytansinoids, auristatins, doxorubicin, daunorubicin, CC-1065, [and] pyrrolobenzodiazepine dimmers." EX1001, 5:59-63; *see also id.*, 28:6-20; 33:39-36:19. The specification further states that cytotoxic drugs bearing thiol, amino, or hydroxyl substituents can react with Z structures, including "thiol, disulfide, amino, carboxy, aldehydes, maleimido, haloacetyl, hydrazines, and hydroxy" functional groups. EX1001, 9:1-7; 14:15-34. Z, not Q or T, is claimed as "a functional group." EX1001, 48:30-43. Finally, the specification teaches the type of resulting covalent bond formed between the claimed cytotoxic drug and linker consistent with the claim language. *Id.*, 14:15-34.

3. "Q" and "T" (Claims 1, 3, 20, 24, 26, 29, and 30)

To the extent not covered by the construction of the "Y" claim element above, as a matter of law, "Q" and "T" each must also be construed as being a claim element separate from Y and Z (as well as other claimed elements of the linker) and should

not be construed to allow for overlap with other structures in the claim, including Y. *See e.g., Becton, Dickinson*, 616 F.3d at 1254; EX.2001, Section IX.C, ¶¶125-129.

DAC's proposed construction of "Q" and "T" is supported by the claim language itself, which recites that Q and T are distinct claim elements from others (*e.g.*, Y and Z). EX.2001, ¶126. And, unlike Y, the claims define Q and T in terms of specific structures (*i.e.*, —P(=O)(OM)—, —S(O2)—, or —S(O)—), not in terms of their function. *Id.* Indeed, as noted above, Y, not Q or T, is recited to be "a functional group." *Id.* The specification likewise defines Q and T in terms of these specific structures. EX1001, 3:14-15, 8:23-24; EX.2001, ¶127. As taught in the '682 Patent, and as a POSITA would recognize, Q and T serve a different purpose in the claimed linker than Y (for example)—*i.e.*, Q and T are each spacer elements, not a conjugation moiety. EX.2001, ¶¶125, 128.

4. "cell-binding agent" (Claims 3, 24, 26)

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, 14:42-44 (emphasis added); EX.2001, Section IX.D, ¶¶130-133; *Phillips*, 415 F.3d at 1316. Put differently, the "cell-binding agent" is a molecule that is used to target (modify) a specific population of cells, including for therapeutic purposes. EX.2001, ¶130. The

inventor described the “cell-binding agent” in terms of 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 linker conjugate (*e.g.*, “sought to be therapeutically or otherwise biologically modified”). EX1001, 14:43-44; *see also id.* 14:45-15:32 (listing “large molecular weight proteins” and a variety of other biological and chemical molecules, preferably monoclonal antibodies). The inventor’s definition should be given effect. *Phillips*, 415 F.3d at 1316.

The claims only further support the inventor’s definition. In particular, the use of the claim term “agent” is significant. EX.2001, ¶¶131-132. A POSITA would recognize from the term “agent” that the cell-binding “agent” is a molecule that is intended to be used to achieve a specific purpose—*e.g.*, binding a specific cell population as taught in the patent. *Id.*

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 of the ’682 Patent. *Phillips*, 415 F.3d at 1324. The patent teaches that the linkers of its invention are linkers that target specific cell populations, particularly for therapeutic purposes. *See generally* EX1001, 1:5-2:67; 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”). Thus, a “cell-binding agent” should not be interpreted, as Petitioner suggests, to

encompass any structure that could have the property of binding to other molecules that may be on the surfaces of cells. EX.2001, ¶132. Such interpretation effectively eliminates the “agent” term and reduces the cell-binding agent to a moiety that is not used to target cell populations, contrary to the plain language of the claim and intent of the inventor. *Id.*

Indeed, such a broad interpretation untethered to the patent’s definition and context is reflected in Petitioner’s reliance on Straus. EX.2001, ¶133. As explained above, Straus teaches “unusual binding sites” on cells 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 patent. *See supra* Section IV.B; EX.2001, ¶133. Petitioner’s contrary interpretation of “cell-binding agent” stretches far beyond how the inventor defined this term and should be rejected.

C. The Alleged Grounds Lack Merit

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

As explained below, claims 1-3, 6, 24-25 and 33 of the ’682 Patent are not anticipated by Morales-Sanfrutos as evidenced by Straus. Indeed, both references were previously considered by the Examiner during reexamination of the ’682 Patent and the claims were deemed patentable over this art. *Supra* Sections IV.A-IV.B.

(a) Claims 1-2

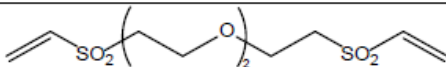
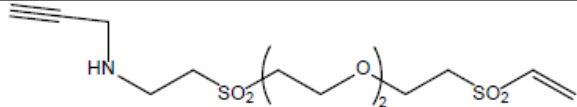
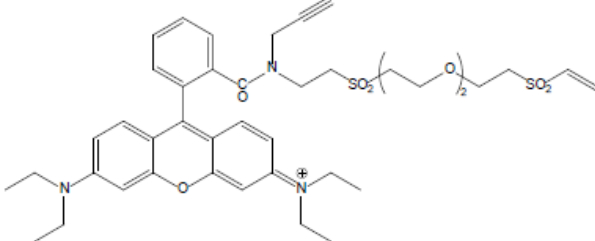
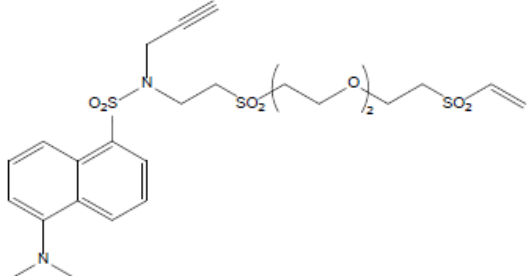
Independent claim 1 of the '682 Patent recites a hydrophilic linker of Formula I with specific limitations on the individual components of Formula I. Formula I is reproduced below.

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

For Petitioner to prevail on these arguments, Petitioner must show (*inter alia*) that both the separate and distinct structures (Y, Q, T, and Z) are expressly or inherently disclosed in the prior art. *Net MoneyIN*, 545 F.3d at 1369-71; *Hopkins Mfg. Corp. v. Cequent Performance Prods., Inc.*, IPR2015-00613, Paper No. 9 (P.T.A.B. Aug. 7, 2015). “The inherent result must **inevitably result** from the disclosed steps; ‘[i]nherency ... **may not be established by probabilities or possibilities.**’” *In re Montgomery*, 677 F.3d 1375, 1380 (Fed. Cir. 2012) (internal citation omitted) (emphasis added). Petitioner must also show that each of these distinct structures are arranged in the prior art as each element is arranged in the claims of the '682 Patent. *Net MoneyIN*, 545 F.3d at 1369.

Petitioner asserts that each of four linker embodiments—Compounds 1, 2, 4, and 5—disclosed in Morales-Sanfrutos anticipate claim 1. See Pet. Table B1, reproduced below. To do this, Petitioner splits the vinyl sulfone disclosed in

Morales-Sanfrutos in half—mapping the vinyl component to Y and the sulfone component to Q. But as explained above, the '682 Patent does not claim Y conjugation moieties that are vinyl alone. See *supra* Section VI.B.1. Additionally, Morales-Sanfrutos does not disclose either (1) a Q/T group (*e.g.*, sulfonyl) separate and apart from vinyl sulfone or (2) a Z group as claimed by the '682 Patent.

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

Compound 1 does not anticipate claim 1. As shown above, the compound 1 linker is a PEG linker with vinyl sulfone groups at each terminus. Petitioner maps vinyl to Y and Z and the sulfones to Q and T. See *e.g.*, Pet. 28-29 (Table B2). Petitioner's arguments fail for several reasons.

First, as explained above in Section VI.B.1, Y should be construed to mean a functional group that independently enables reaction of the hydrophilic linker with a cell-binding agent. 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” based on the specification. *Hopkins*, Paper No. 9 at 11-12. Here, too, the claim terms Y and Q (for example) are separate and distinct. See *supra* Sections VI.B.1, VI.B.3. It would therefore be improper to map a single prior art structure—Morales-Sanfrutos’ singular vinyl sulfone structure—onto both as Petitioner has done.

By Petitioner’s own admission, when vinyl is not part of vinyl sulfone, vinyl lacks the ability to enable reaction with a cell-binding agent and cannot satisfy the functional requirement of Y. In fact, Petitioner repeatedly states the “vinyl sulfone” group as a whole is the “reactive functionality.” See, e.g., Pet., 52; see also *id.*, 54 (“Singh discloses vinyl sulfone—a reactive functionality. . . .”); *id.*, 64 (arguing that “a POSA would have been motivated to prepare ADCs with one or two sulfones using vinyl sulfones as the reactive groups”); EX1003, ¶¶103, 107 (Petitioner’s expert relying on disclosures of “vinyl sulfone” groups in the alleged prior art). Thus, Petitioner recognizes what a POSITA would: **a vinyl must be part of a vinyl sulfone group** to enable reaction with functional groups present in cell-binding agents; vinyl alone will not suffice. See also *supra* Section III. Accordingly, as in

Hopkins, the single prior art structure vinyl sulfone cannot be separated into its individual components vinyl and sulfone to map on to Y and Q, respectively. Here, Y can only be satisfied by vinyl sulfone.

Petitioner's argument that claim 1 "does not require actual conjugation to a cell-binding agent; rather it requires only that Y be a functional group that enables reaction of the formula I compound with a cell-binding agent" (Pet. 31), does not remedy the deficiency in Petitioner's invalidity challenge. By Petitioner's own admission ***vinyl alone does not enable reaction of the formula I linker***. Pet. 31. Instead, the vinyl must be part of a vinyl sulfone group. But Petitioner does not map vinyl sulfone to Y. If Petitioner did, then Petitioner would fail to demonstrate that Q and T were disclosed in the alleged prior art because Petitioner would then not have the separate sulfone group to match with those separate claim elements.

Second, to the extent Petitioner argues that claim 1 does not require *Morales-Sanfrutos* to demonstrate a cell-binding agent—*e.g.*, because the claim "does not require actual conjugation" to this agent (Pet. 31)—Petitioner's interpretation should be rejected. Claim 1 recites that Y is "a functional group that enables reaction of the hydrophilic linker with a cell-binding agent." Petitioner tacitly concedes that this language is limiting; Petitioner does not argue otherwise. Thus, this limitation must be shown in the prior art, as in the claim. *Net MoneyIN*, 545 F.3d at 1371.

Regardless, Morales-Sanfrutos (and Straus) fail to teach a cell-binding agent for reasons explained below with respect to claim 3.

Third, Claim 1 requires that Z is “a functional group that enables linkage of the hydrophilic linker to a cytotoxic drug.” Petitioner argues that vinyl as Z should merely enable reaction with a cytotoxic drug. Pet. 31. But Petitioner fails to show that Morales-Sanfrutos has any disclosure of cytotoxic drugs, much less a functional group, particularly vinyl, that enables linkage to a cytotoxic drug. Thus, Morales-Sanfrutos does not disclose Z and Petitioner fails to show otherwise.

Compound 2 does not anticipate claim 1. As shown above, the compound 2 linker is a PEG linker with, *inter alia*, a vinyl sulfone group at one end. Again, Petitioner’s splitting of the vinyl sulfone group into vinyl and sulfone and subsequent mapping of that split structure to Y and Q, respectively, or Z and T, respectively, fails for the same reasons as discussed above for Morales-Sanfrutos’ compound 1.

First, Petitioner fails to meet the Z limitation. As explained above, Z is “a functional group that enables linkage of the hydrophilic linker to a cytotoxic drug.” Vinyl sulfone is that functional group. For example, the ’682 Patent teaches that Z can be a vinyl sulfonyl moiety as a whole but not vinyl alone. EX1001, 14:28-31 (“**A drug bearing a thiol group can be reacted with a cross linker bearing a malimido or a vinylsulfonyl, or a haloacetyl group, to give a modified drug bearing thioether link.**”). If Petitioner splits Morales-Sanfrutos’ vinyl sulfone in half and

maps vinyl alone to Z, Petitioner's arguments fail for similar reasons as explained above with respect to compound 1. Additionally, Petitioner fails to show that Morales-Sanfrutos discloses vinyl as enabling linkage to a **cytotoxic drug**.

Second, compound 2 does not anticipate claim 1 because both Q and T groups must be present, yet are not. Specifically, claim 1 of the '682 Patent recites that, when Q or T is sulfonyl (-S(O₂)-), "m and n are not 0," which means that both Q and T must be present. See Pet. 20. As explained above, the vinyl sulfone of compound 2 is either Z or Y. Thus, only one of Q or T is satisfied by the other sulfonyl group in the compound 2 linker.

Compound 4 does not anticipate claim 1 for the same reasons as provided above for compound 2. As shown above, the compound 4 linker is a PEG linker with, *inter alia*, a vinyl sulfone group at one end and a sulfone group in the linker structure. Again, Petitioner fails to meet the Z limitation because it does not show that Morales-Sanfrutos discloses vinyl as enabling linkage to a cytotoxic drug. Additionally, because Q and/or T are sulfonyl groups, both Q and T must be present. This limitation is not satisfied, however, because one of the two sulfonyl groups is part of vinyl sulfone (Y or Z).

Compound 5 does not anticipate claim 1 for the same reasons as provided above for compounds 2 and 4. As shown above, like compound 4, the compound 5 linker is a PEG linker with, *inter alia*, a vinyl sulfone group at one end and a sulfone

group in the linker structure.² Again, Petitioner fails to meet the Z limitation because it does not show that Morales-Sanfrutos discloses vinyl as enabling linkage to a cytotoxic drug. Additionally, because Q and/or T are sulfonyl groups, both Q and T must be present. This limitation is not satisfied, however, because one of the two sulfonyl groups is part of vinyl sulfone (Y or Z).

(b) Claim 2

Morales-Sanfrutos and Straus do not anticipate Claim 2 at least for the same reasons provided with respect to Claim 1.

(c) Claims 3 and 24

Independent claims 3 and 24 recite cell-binding agent-drug conjugates of Formula II as shown below. Petitioner argues that a particular structure, HRP-11—a linker conjugated to biotin and HRP—teaches every limitation of this formula.

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

Morales-Sanfrutos does not disclose the claimed “cell-binding agent” as it does not teach that HRP binds cells. EX.2001, ¶58. Petitioner therefore attempts to rely on a different reference (Straus) for this claim element. Pet. 36. But Petitioner

² 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.

fails as a matter of law to establish that Straus necessarily teaches that HRP is a “cell-binding agent” as claimed. Petitioner relies only on two paragraphs of its expert’s declaration—paragraphs 59 and 90. Pet. 36. Paragraph 90 identifies no factual basis for this proposition and is entirely conclusory. See EX1003, ¶90. Consequently, it is entitled to no weight. *Xerox*, Paper No. 9 at 15.

Paragraph 59 of Petitioner’s expert’s declaration states that “Straus discloses that the horseradish peroxidase (HRP) enzyme **may** bind to the surface of a variety of cells, including macrophages, fibroblasts, mast cells and endothelial cells.” EX1003, ¶59. Petitioner’s expert does not assert that HRP **necessarily** binds to cells. Because Morales-Sanfrutos does not expressly disclose the HRP therein as a cell-binding agent, Petitioner’s anticipation argument requires more than the mere possibility of HRP binding—HRP **must** necessarily and inherently bind cells. Inherency is established when the “prior art necessarily functions in accordance with, or includes, the claimed limitations.” *Bettcher Indus., Inc. v. Bunzl USA, Inc.*, 661 F.3d 629, 639 (Fed. Cir. 2011). “Inherency, however, may not be established by probabilities or possibilities.” *Id.* The “mere fact that a certain thing may result from a given set of circumstances is not sufficient.” *Id.* Therefore, Petitioner’s

proffered evidence is inadequate to support either express or inherent anticipation by Morales-Sanfrutos and Straus.³

Morales-Sanfrutos and Straus also do not anticipate Claims 3 and 24 for similar reasons as provided above with respect to Claim 1. Petitioner's efforts to map both sulfonyl groups of the HRP-11 conjugate to both Q and T is improper, as one sulfonyl mediates conjugation to the HRP (the alleged "cell-binding agent") and would therefore be part of a different structure (Y). As a result, Q is absent from Petitioner's mapping. Indeed, Morales-Sanfrutos teaches that HRP-11 is generated by conjugating HRP via vinyl sulfone. EX1005, 4046 ("Labeling of HRP with Vinyl Sulfone Based BTSAP Reagents 9 11 and 17. HRP ... was incubated with vinyl sulfone derivatized bifunctional tags ...The resulting labeled proteins (... HRP-11, ...)); EX.2001, ¶57.

(d) Claim 6

Morales-Sanfrutos and Straus do not anticipate Claim 6 for the same reasons provided with respect to Claim 3. *E.g.*, HRP is not a "cell-binding agent."

³ Independently, DAC's expert identifies many reasons to doubt Straus's proffered teachings. *See supra* Section IV.B.

(e) Claims 25 and 33

Morales-Sanfrutos and Straus do not anticipate Claim 25 and 33 for the same reasons provided with respect to Claims 3 and 24. *E.g.*, HRP is not a “cell-binding agent.”

2. 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 as explained above for Ground 1.

(a) Claim 1

Claim 1 recites a Formula I linker, reproduced below.

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

Anticipation. Petitioner argues that claim 1 is anticipated by Harris’s disclosure of the structure $R-(OCH_2CH_2)_n-Y$, where R and Y are vinyl sulfone and/or halo-ethyl sulfone. Pet. 38. Thus, according to Petitioner, Harris teaches a linker comprising two sulfonyl moieties. Petitioner refers to this as the “basic” structure of Harris’s linkers.

Petitioner's argument is a simple one. Petitioner merely argues that attaching vinyl sulfone and/or halo-ethyl sulfone conjugation moieties to the ends of Harris's "basic" PEG-based linker results in the claimed Formula I linker. Pet. 38-39.

Once again, Petitioner misreads the Challenged Claims and art and improperly maps a single prior art element to two separate and distinct claim elements. *Hopkins*, Paper No. 9 at 11-12. Like vinyl sulfone, Harris teaches that halo-ethyl sulfone is a conjugation moiety. Harris teaches that coupling these sulfone groups to the linker allows the linker to attach or "coupl[e]" to other structures. EX1007 6:8-14 ("The invention provides ... poly(ethylene glycol) ("PEG") polymers ... having one or more active sulfone moieties ... [which] are highly selective for coupling with thiol moieties ... on molecules and on surfaces ..."); EX.2001, ¶64.

Petitioner even concedes this. Petitioner states that "the ***vinyl and halo-ethyl groups located adjacent to sulfone moieties***"—i.e., vinyl sulfone and halo-ethyl sulfone—"in Harris ***are equivalent to Y or Z*** of formula I because they are known in the art as functional groups that react with thiol moieties ..." Pet. 39. It is therefore undisputed that Harris's sulfone moieties are part of a larger "Y" group (vinyl sulfone and halo-ethyl sulfone) and necessary to enable that group's reactivity.⁴ Because the sulfone structures are necessary to achieve the functionality

⁴ Petitioner's admission here contradicts its Ground 1 argument, wherein it asserts vinyl and halo-ethyl alone are Y and Z. Pet. 38.

of the Y and Z groups, they cannot map to the separate, distinct spacer elements Q and T. Petitioner makes no other attempt to argue that Harris teaches the claimed spacer elements. Indeed, Harris merely teaches PEG groups as spacer elements. EX.2001, ¶65. Therefore, Harris does not teach all elements of the claimed invention as it does not teach the separate and distinct Q and T elements.

Thus, Petitioner's Ground 2 arguments fail for essentially the same arguments set forth for Ground 1.

Obviousness. Petitioner argues that claim 1 is obvious over Harris's basic structure because Harris purportedly teaches advantages of certain PEG bis vinyl sulfones. Pet. 39-40. Petitioner provides no detailed analysis of how combining any particular structures in Harris achieves the specific combination of elements recited in the claimed Formula I linker. *ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1327 (Fed. Cir. 2012) (affirming non-obviousness when expert "failed to explain how specific references could be combined [or] which combination(s) of elements in specific references would yield a predictable result"). To the extent Petitioner's obviousness argument is substantively co-extensive with its anticipation argument above, it is defective for the same reasons.

Petitioner's obviousness analysis—a single paragraph—is deficient for additional reasons. Y, Q, and other elements are separate and distinct components of the linker. *See supra* Sections VI.B.1, VI.B.3. Thus, Petitioner must explain how

specific teachings of Y, Q, and other elements would be combined to achieve the claimed Formula I linker. *ActiveVideo*, 694 F.3d at 1327.

But Petitioner does not provide any motivation to combine vinyl or haloethyl—**alone** and not part of a sulfone group—to achieve a Y/Z group in the claimed linker. Nor does Petitioner identify any reason to use sulfones (or other claimed spacer structures) as spacer elements. Accordingly, besides pointing to sulfone-based conjugation moieties, Petitioner has not identified any motivation to incorporate sulfone groups (or any other claimed Q/T groups) as spacer elements in the linker. Petitioner has therefore failed to carry its burden to explain why a POSITA would be motivated to combine individual prior elements **as claimed**. *Hopkins*, Paper No. 9 at 17 (“A patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art”—rather, “[i]t is important to identify a reason that would have prompted a person of ordinary skill in the relevant field **to combine the elements in the way the claimed invention does.**”) (emphasis added). As in *Hopkins*, the Board should reject this approach.

(b) Claims 20-21 and 29-31

Claims 20-21 and 29-31 recite a linker of Formula IV, reproduced below. Its structure is identical to Formula I except for the substitution of a “Drug” for the former’s Z group.

Structure	Formula
$Y - R_1 - \text{---} Q - R_2 - \text{---} T - R_3 - \text{---} R_4 - \text{Drug}$ $\swarrow \quad \searrow$ $R_5 \quad R_6$	IV

Petitioner asserts that claims 20-21 and 29-31 are invalid based on its mapping of Harris’s prior art structures to the ’682 Patent’s Formula IV linker “for the same reasons” provided with respect to claim 1. Pet. 41. Petitioner’s analysis is therefore deficient for the same reasons identified above.

Petitioner also relies on Harris’s purported teachings of heterobifunctional PEG derivatives having a sulfone moiety. Petitioner does not point to any specific support, structures, or disclosures in Harris for this argument. Pet. 42. To the extent Petitioner purports to map Harris’s “basic” structure comprising sulfone groups on to the separate and discrete elements recited in the claimed Formula IV, this argument fails for the same reasons as explained above for Formula I. Indeed, Petitioner and its expert do no more than point to Harris’s use of vinyl sulfone as a conjugation moiety. *See e.g.*, EX1003, ¶50 (with respect to heterobifunctional linkers, Harris “expressly recommends use of vinyl sulfones and other active sulfones ... on either end of its PEG-based linkers”), ¶109 (citing ¶50). To the extent Petitioner purports to map Harris’s “basic” structure comprising sulfone groups on to the separate and discrete elements recited in the claimed Formula IV, this argument fails for the same reasons as explained above for Formula I.

Petitioner also argues that it would be obvious to achieve these claims over Harris relying on the same rationale for claims 20, 29, and 30 as for claim 1. Pet. 42-43. These arguments fail for the same reasons provided above for claim 1.

3. Ground 3: Petitioner Fails To Establish That 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 challenges claims 1-8, 10-12, 14-17, 20-21, 24, 26, and 29-31 of the '682 Patent as obvious over Singh in view of Harris. These challenges are premised on the same misunderstanding of the prior art and distortion of the claimed invention as explained above for Grounds 1-2. Thus, they fail for similar reasons.

(a) Claims 1-2

First, in Ground 3 as in Grounds 1 and 2, Petitioner misreads the Challenged Claims and asserted prior art and improperly attempts to map a single group from an alleged prior art structure from Singh onto multiple separate and distinct claim elements. *Hopkins*, Paper No. 9 at 12.

Petitioner's obviousness arguments are based on Singh's disclosure of certain linkers, which Petitioner admits do not contain the claimed spacer elements. Specifically, Petitioner states that "Singh discloses bifunctional PEG cross-linkers containing each element of claim 1, **save Q and T**." Pet. 44; *see also* Pet. 46. Because Singh does not disclose these structures, Petitioner resorts to arguing that a

POSITA would modify one or both of Singh's reactive functionalities with vinyl sulfone.

To this end, Petitioner points to Singh's disclosures of vinyl sulfone and argues that a POSITA would be motivated to combine them in Singh's linkers. Pet. 48-49. But as Petitioner notes, Singh "expressly suggests the use of vinyl sulfones as a thiol-reactive functionality and teaches their equivalence to maleimide and haloacetamides for this purpose." Pet. 48 (citing EX1008, ¶[0134]). Singh defines "reactive functionality" as set forth below (¶[0134], emphasis added):

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, sulfhydryl(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*** ...

Thus, Singh expressly teaches that vinyl sulfone is a "reactive functionality" that "can react" with a "cell binding agent"—*i.e.*, the claimed "Y" functional group, not the claimed Q or T structural claim elements.

According to Petitioner, a POSITA 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"—*i.e.*, the vinyl sulfones taught in Singh or Harris—"resulting in Q or Q and T each being a sulfone group, and Y, or Y and Z, each being

a vinyl group,” and “[s]uch substitutions ... would thereby fully satisfy claim 1’s formula I.” Pet. 49. This approach should be rejected as explained above for Grounds 1 and 2.

Specifically, as Petitioner admits, vinyl sulfone groups possess the “reactive functionality” that would enable the linker’s reaction to other molecules such as a cell-binding agent—the claimed function of the “Y” group. Pet. 48. Petitioner does not argue, nor does Singh or Harris teach, that vinyl alone has this capability. Once again, Petitioner’s mapping strategy flouts the principle that a single prior art structure should not be mapped to multiple separate, discrete claim elements. *Hopkins*, Paper No. 9 at 12. The Board should reject Petitioner’s improper mapping strategy 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 set forth above for Harris in Ground 2.

Additionally, Petitioner admits “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 the Harris vinyl sulfones (conjugation moieties)

would confer to a Singh linker that already comprises vinyl sulfones (conjugation moieties). Petitioner's motivation-based arguments merely recite general purported benefits of vinyl sulfone conjugation moieties, which are already disclosed in Singh.

Third, even accepting Petitioner's characterization of benefits of using vinyl sulfones in linkers, Petitioner fails to show any motivation to achieve the claimed invention.

The claimed invention comprises separate and distinct elements Y and Q (among others). *See supra* Sections VI.B.1, VI.B.3. As argued throughout this Response, vinyl sulfone was recognized in the art—including in Harris and Singh—as having reactive functionality equivalent to the claimed Y or Z groups **alone**. *See also* EX.2001, ¶¶49-51, 68, 70. Therefore, even if a POSITA were motivated to add vinyl sulfone to a linker to serve as a Y or Z group (*e.g.*, as a conjugation moiety connecting the linker to a protein or drug), Petitioner wholly fails to show any motivation in Singh or Harris to add sulfonyl groups (*e.g.*, vinyl sulfone) to **a different part of the linker to achieve Q or T**, the novel claimed spacer elements. Petitioner merely points to Harris's 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...”)(emphasis added), 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) in the Q or T location.

Similarly, Petitioner argues that the vinyl group is Y or Z. 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. As explained above, and as Petitioner admits (*supra* Ground 1), vinyl must be next to a sulfone group in order for this reactivity to occur—*i.e.*, vinyl must be present in the context of a vinyl sulfone group. Adding vinyl alone, separate from a sulfone, would be ineffective as Petitioner acknowledges. Pet. 31.

(b) Claims 20-21 and 29-31

Petitioner’s arguments for these claims are based on the same rationale as claims 1-2, *supra*. See *e.g.*, Pet. 54-55 (arguing vinyl sulfone is “a reactive functionality that forms thioether bonds” provides both Y and Q structures); 56 (“For at least the same reasons discussed above ... a POSA would have been motivated to incorporate vinyl sulfones ...”), 60 (“For the same reasons given above ..., a POSA would have been motivated to substitute thiol reactive groups ... with vinyl sulfone or other sulfones as taught by Harris”). These arguments should be rejected for the same reasons as provided above.

(c) 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. Accordingly, Petitioner’s obviousness analysis with respect to these claims is deficient at least for the reasons provided above and should also be rejected.

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

Claims 9 and 13 depend from claim 3. Thus, Ground 4 fails for the same reasons set forth above with respect to Ground 3.

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

Claim 2 depends from claim 1. Claim 25 depends from claim 24. Claim 32 depends from claims 30-31. Claim 33 depends from claim 3. Claim 34 depends from claim 20. Accordingly, Ground 5 likewise fails for the same reasons set forth above with respect to Ground 3.

VII. CONCLUSION

For the foregoing reasons the Board should deny institution of this petition.

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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 12,789 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 May 26, 2023 upon the following parties via Electronic Mail:

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