

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SYNAFFIX B.V.

Petitioner

v.

HANGZHOU DAC BIOTECH CO., LTD.,

Patent Owner

Patent No. 10,131,682

Ex Parte Reexamination Certificate Issued: January 4, 2021

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

Inter Partes Review No. IPR2022-01531

**PETITIONER'S PRELIMINARY REPLY TO PATENT OWNER'S
PRELIMINARY RESPONSE**

As authorized by the Board's July 3, 2023 Order (Paper 10), Petitioner files this Preliminary Reply to Patent Owner's Preliminary Response ("POPR").

I. Institution Should Not be Denied Under 35 U.S.C. §325(d)

Patent Owner's arguments that all references cited in the Petition are either identical to or cumulative of those considered by the Office and overcome are neither accurate nor sufficient to support a §325(d) denial of institution. Harris and Snow are new references, containing features not found in Lees that underpin unpatentability grounds for claims other than the single claim considered by the Examiner. The remaining references were listed on an IDS but were not applied against the claims, nor did the Examiner ever discuss the specific disclosures relied upon in the Petition. Pet. 78-79. Such facts weigh against a §325(d) denial.

Under the *Becton Dickinson* factors, even a single non-cumulative reference in combination with references discussed during prosecution is sufficient to avoid a §325(d) denial. *Oticon Medical AB v. Cochlear Ltd.* IPR2019-00975, Paper 15, 16, 19-20 (PTAB, Oct. 16, 2019). Harris and Snow more than meet this standard when compared to Lees. In the 3/8/18 Office Action (EX2025), the Examiner cited only the heterobifunctional linker on p. 22 of Lees, noting that it anticipated formula 55 in Figure 6. EX1018, 42. Rather than argue (as the POPR does) that the vinyl sulfone of Lees' structure cannot meet both Z and Q (or T), Patent Owner narrowed claim 1 to require that when Q or T is -S(O)₂-, m and n are not zero. *Id.*, 45.

However, Lees' homobifunctional sulfone (POPR, 25) was never discussed, yet it anticipates claim 1/formula (I) (Pet., 38-39), thus disfavoring §325(d) denial here.

Volkswagen v. Michigan Motor Techs. LLC, IPR2020-00452, Paper 12, 32-33 (PTAB Sept. 9, 2020) (finding §325(d) denial unwarranted where examiner “fail[ed] to fully consider” specific embodiment relied upon in the petition).

Moreover, Harris and Snow contain additional disclosure supporting new §102/103 unpatentability grounds as to formulas (II) and (IV) (claims 3-17, 20-21, 24-26, 29-31, and 32-34). The Petition explains how Harris discloses that (i) PEG bis vinyl sulfones form stable thioether linkages with **pharmaceuticals** as well as proteins, (ii) **haloethylsulfones** are groups meeting Y or Z and Q/T, and (iii) the PEG/sulfone derivatives are highly water soluble and can **solubilize** “otherwise insoluble molecules” conjugated to the derivatives. Pet., 6-7, 38-40. Snow's vinyl sulfone derivatives also contain a sulfone group **not adjacent** to a vinyl group. *Id.*, 74-76. Lees discloses none of this, while each of Grounds 2-5 makes use of one or more of the above features in explaining the unpatentability of formulas (II) and (IV), demonstrating how Harris and Snow are noncumulative. *Id.*, 40-43, 50.

The Petition also explains how Harris anticipates or renders obvious formula (IV) of claims 20 and 29-30, which, unlike claim 1, include a Drug and can have only a single sulfone. Pet., 6, 38-43, 49, 69. By contrast, Lees discloses a vaccine using a polysaccharide antigen, which is not a drug (*see, e.g.*, EX1001, 24:1-3, 10-

16 and 29:42-36:19). EX2026, 7:11-22. Further, the Petition cites Harris’ disclosure of the solubilizing effect of the PEG/sulfone combination and the stability of chloroethyl sulfone as motivations to incorporate sulfones and related sulfone functionality into Singh’s ADC linkers. Pet., 50, 67. Also, Snow’s derivative in which one sulfone is not adjacent to a vinyl group differs from Lees’ bis vinyl sulfone derivative, yet maps to “T” (*id.*, 74-76) even under Patent Owner’s flawed claim construction (discussed *infra*). *Id.*, 74-76. In view of these additional disclosures, Harris and Snow are new, non-cumulative references that do not meet any of *Becton Dickinson* factors (a), (b), or (d). Pet., 78-79.

While Morales-Sanfrutos, Strauss and Singh were cited in an IDS to the Office, the Board has previously recognized that §325(d) “does *not* require any particular outcome” even where the same or substantially the same prior art and arguments were presented to the Office. *Microsoft Corp. v. Parallel Networks Licensing, LLC*, IPR2015-00483, Paper 10, 15 (PTAB July 15, 2015). As in *Microsoft*, each of these references were cited in an IDS but their teachings were never applied against the claims. Though Patent Owner tries to characterize Morales-Sanfrutos as the same as Harris (POPR, 24), this is false as well because, at a minimum, compounds 2, 4 and 5 of Morales-Sanfrutos are hetero-bifunctional bis-sulfones in which one of the two reactive groups is an alkyne, not adjacent to either sulfone, while its HRP-11 conjugate has both a drug and cell-binding agent. *See* Pet., 27-30, 33-36. Thus, the

Petition points to various aspects of Morales-Sanfrutos and Singh (as well as Harris) never discussed or applied by the Examiner, constituting relevant but overlooked disclosure that disfavors denial under §325(d). *Microsoft*, Paper 10, 15.

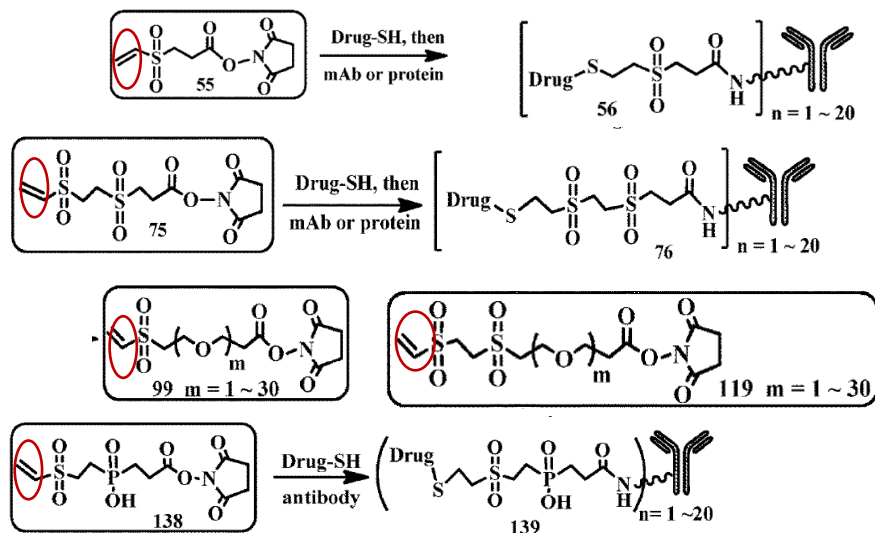
II. The POPR's Constructions are Unsupported and should not be Adopted

"Z," "Y," and "Q/T" (Claims 1, 3, 20, 24, 26 and 29-30)

Patent Owner asserts constructions for Z, Y, and Q/T that would require that the Z and Y groups *independently enable* reaction to a drug or cell-binding agent ("CBA"), without resort to the T-Z or Q-Y groups together enabling such reaction. POPR, 32-37. Thus, the POPR asserts that a terminal vinyl sulfone cannot satisfy the T-Z or Q-Y groups as claimed, allegedly because the vinyl group is only reactive by virtue of being adjacent to a sulfone group. *Id.* However, these proposed, interrelated constructions are flatly contradicted by both the specification and the file history.

Figures 1-19 of the specification disclose "hydrophilic cross linkers as well as the preparation of the conjugates of drugs to a [sic] cell binding molecules of the present invention" (EX1001, 7:55-58, 8:5-10), with Figs. 6 and 8-10 providing specific examples of vinyl-sulfone-containing linkers that meet formula (I). *Id.*, 9:15-19. As seen in those figures (excerpted below), at least compounds 55, 75, 99, 119 and 138 contradict Patent Owner's position here, since the vinyl group of the terminal vinyl sulfone moiety corresponds to Z for all five compounds, and the sulfone group corresponds to Q in all five compounds (and/or T in compounds 55 and 99). The

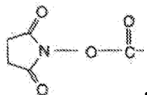
terminal vinyl groups adjacent their respective sulfone groups are highlighted below:



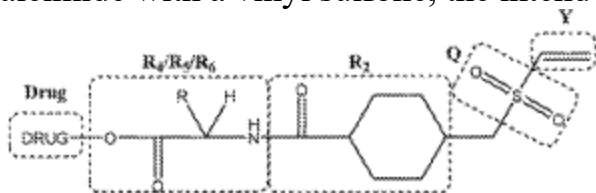
Figures 6-7 and 10 further show compounds 55, 75, and 138 being subsequently linked to a “Drug” via the vinyl group of the terminal vinyl sulfone moiety (and to a CBA at the other end of the linker) to produce compounds 56, 76, and 139, which fall under formula (II) of the patent. *Id.*, 9:31–11:57; *see also* 14:28-31 (noting that drugs with thiol (-SH) groups can be reacted with vinyl sulfones). Thus, compounds 75, 119 and 138 fall within the scope of formula (I) in challenged claim 1, while compounds 56, 76 and 139 fall within the scope of formula (II) in challenged claim 3. Consequently, any argument that terminal vinyl sulfones cannot constitute both the Z and T groups of formula (I) is flatly contradicted by at least the compound pairs 55-56, 75-76, and 138-139. Because constructions that read disclosed embodiments out of the claims are rarely correct (*National Steel Car. Ltd. v. Canadian Pacific Railway, LTD.*, 357 F.3d 1319, 1336 n.19 (Fed. Cir. 2004); *see*,

e.g., *Oatey v. IPS Corp.*, 514 F.3d 1271, 1276-77 (Fed. Cir. 2008) (rejecting construction that excluded a disclosed embodiment absent evidence of disclaimer)), Patent Owner’s proposed constructions for Y, Z, and Q/T should be rejected.

Patent Owner’s interpretations of Y, Z and Q/T are also diametrically opposed to its statements made during prosecution. In response to the 3/8/18 OA (EX1018, 36-43), Patent Owner said this about the N-hydroxysuccinimide vinyl sulfone

disclosed in Lees: “This compound corresponds to
$$Y-R_1-Q-R_2-\text{---}_m-\text{---}_n-T-R_3-\text{---}_n-R_4-Z$$
 (I)  , **Q (or T) is S(O₂)-**, m (or n) is 1, n (or m) is 0, R₂(R₃) and R₄-R₆ are absent, and **Z is **.” *Id.*, 62 (emphasis added). Thus, prior to this proceeding, Q or T were expressly identified as being a sulfone (i.e., S(O₂)-), R₂-R₆ as being absent, and Z as being vinyl, such that the resulting T-Z group in formula (I) is **vinyl sulfone**.

Similarly flawed is Patent Owner’s assertion that Y must “independently enable” reaction of the linker with a cell-binding agent (POPR, 32). In the response to the 6/12/20 reexamination OA (EX1019, 1-44), Patent Owner asserted that if the linker disclosed in US 2004/0185053 (“Govindan”) was modified to substitute the maleimide with a vinyl sulfone, the intended structure was presumed to be:



, where Y is a vinyl. EX1019, 72. Thus,

during prosecution Patent Owner likewise identified vinyl sulfone as satisfying the

Q-Y combination, again directly contradicting its positions here. Patent Owner's proffered constructions for Z, Y, and Q/T run afoul of both express statements made during prosecution and the specification and should not be adopted.

"Cell-binding Agent" (Claims 3, 24, 26)

"Cell-binding agent" appears in formula (II) to functionally describe a part of the claimed conjugate. Functional claim language not limited to a specific structure is interpreted to cover all structures capable of performing the recited function. *See Revolution Eyewear, Inc. v. Aspex Eyewear, Inc.*, 563 F.3d 1358, 1369-70 (Fed. Cir. 2009) (finding that an infringing device need only be capable of performing the claimed function). Thus, here, any agent that binds to, reacts with, or complexes with cells meets this limitation.

However, Patent Owner attempts to read additional limitations into this claim term, asserting that the CBA term should be construed 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*," and suggests that it must be "used to *target* (modify) a *specific* population of cells, *including for therapeutic purposes*." POPR, 17-18, 37-38 (emphasis added). However, the highlighted language (in addition to ignoring the phrase "...or otherwise biologically modified") refers to the *intended use* of the claimed conjugate, not the function of CBA itself, and, as such, has no place in the claims. *See In re Schreiber*, 128 F.3d

1473, 1477 (Fed. Cir. 1997) (“It is well settled that the recitation of a new intended use for an old product does not make a claim to that old product patentable.”); *IPXL Holdings, L.L.C. v. Amazon.com, Inc.* 430 F.3d 1377, 1384 (Fed. Cir. 2005) (holding that claims cannot simultaneously be directed to structures and uses).

Patent Owner applies its construction to try to distinguish the HRP cell-binding agent of Morales-Sanfrutos (as evidenced by Straus (Pet., 36)), arguing that HRP is not a “therapeutic” conjugate and only “may” be able to bind to the surfaces of “some” cells. POPR, 18, 47. While Patent Owner suggests that binding must always occur under all conditions (or must be done with a specific therapeutic purpose in mind), no such limitations appear in the claims and none should be read into the claims. *Parkervision, Inc. v. Qualcomm Inc.*, 903 F.3d 1354, 1361 (Fed. Cir. 2018) (noting that anticipation is not required under all modes of operation). Neither the claims nor the alleged “definition” Patent Owner identifies (POPR, 37 (citing EX1001, 14:42-44 (referring to “cell-binding molecules”))) includes the words “target” or “specific” population of cells.

To the contrary, the specification identifies numerous exemplary CBAs, such as smaller molecular weight proteins, poly-peptide, peptides, cell nutrient-transport molecules, bioactive polymers, and nanoparticles (EX1001, 14:45-15:22), which all may bind to a moiety on a cell population under only some conditions, and without necessarily “target[ing] a ‘specific’ cell population.” Lastly, even if Patent

Owner's proposed construction were adopted, Straus teaches that HRP-11 binds to specific cell populations such as "macrophages, fibroblasts, mast cells and endothelial cells" (EX1006, 1), which at a minimum biologically modifies those cells. Thus, Patent Owner's attempted construction for "cell-binding agent" both is contradicted by the intrinsic evidence, and fails to distinguish Ground 1.

III. Patent Owner's Non-analogous Art Assertions are Erroneous

A reference may be directed to a different problem than the one addressed by the inventor or may be from a different field of endeavor than the claimed invention, yet still be anticipatory if it discloses every limitation recited in the claims. *State Contracting & Eng'g Corp. v. Condotte America, Inc.*, 346 F.3d 1057, 1068, (Fed. Cir. 2003). Accordingly, Patent Owner's assertions that Morales-Sanfrutos, Straus and Harris are non-analogous art are legally erroneous and irrelevant with regards to anticipation of claims 1-3, 6, 24-25 and 33 by Morales-Sanfrutos (evidenced by Straus), and of claims 1, 20-21, and 29-31, by Harris. *See Pet.*, 25-44.

Regarding the Petition's reliance on Harris for obviousness, a reference is analogous art if it is (1) from the same field of endeavor, regardless of the problem addressed, or (2) reasonably pertinent to the particular problem with which the inventor is involved. *In re Clay*, 966 F.2d 656, 658–59 (Fed. Cir. 1992).

Patent Owner argues that Harris is not analogous art because it does not "relate to the field of therapeutic protein-drug conjugates" or "therapeutic targeting." POPR,

20. However, therapeutic targeting is at most an intended use of the claimed structures, not a claim limitation. *Supra*, 7-8. The actual focus of the '682 patent is the hydrophilic linkers themselves that can be used to conjugate drugs and cell-binding agents (including proteins, such as antibodies). EX1001, 1:7-9, 14:45–15:11. Indeed, the specification admits that therapeutic ADCs were already known, with the goal of the invention being to develop linkers exhibiting less aggregation in water (*id.*, 2:25-49, 60-62), while noting other advantages of linkers with improved water solubility, specifically including, *inter alia*, sulfones (*id.*, 13:7-12).

Harris is clearly analogous art. First, it is within the same field of endeavor: “PEG/sulfone derivatives as useful for conjugating two different biologically-active moieties such as proteins [and] pharmaceuticals.” Pet., 6. Second, Harris is pertinent to the problem addressed via its teaching of sulfone linkers having infinite water solubility that bring otherwise insoluble molecules into solution. *Id.*, 6. *Innovation Toys, LLC v. MGA Entm’t, Inc.*, 637 F.3d 1314, 1321 (Fed. Cir. 2011) (“If a reference disclosure has the same purpose as the claimed invention, the reference relates to the same problem.”). The Petition further explains how a POSA would recognize Harris’ linkers as reducing aggregation when used with Singh’s conjugates. Pet., 52, 66-67. Thus, Harris is analogous art under both prongs of *Clay*.

Respectfully submitted,

Dated: July 11, 2023

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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing
PETITIONER'S PRELIMINARY REPLY TO THE PATENT OWNER'S
PRELIMINARY RESPONSE is being served on counsel for Patent Owner by
electronic mail this 11th day of July, 2023 as follows:

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